SPCG-17

Prostate Cancer Active Surveillance Trigger trial (PCASTt)

STATISTICAL ANALYSIS PLAN

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SUPPLEMENTARY INFORMATION:

1. LIST OF ABBREVIATIONS

ADT	Androgen deprivation therapy
AS	Active surveillance
BCR	Biochemical recurrence
CRF	Case report form
EPIC	Expanded prostate cancer index composite
MRI	Magnetic resonance imaging
PCASTt	Prostate Cancer Active Surveillance Trigger trial
PSA	Prostate-specific antigen
RP	Radical prostatectomy
RT	Radiotherapy
SPCG	Scandinavian Prostate Cancer Group
UK	United Kingdom
WW	Watchful waiting

2. STUDY SYNOPSIS

Study title	Prostate Cancer Active Surveillance Trigger trial (PCASTt)
Short title	SPCG-17
Clinical study phase	Phase III
Study objective	To test the hypothesis that standardized triggers for repeat biopsies and initiation of curative treatment will reduce overtreatment without increasing disease progression and prostate cancer mortality.
Reference arm (1)	Current practice for active surveillance
Intervention arm (2)	Standardized triggers for re-biopsy and curative treatment
Study design	Randomized multicentre open-label clinical trial
Inclusion criteria	• Newly diagnosed men (within 12 months) with untreated ≤T2a prostate adenocarcinoma • PSA <15 ng/ml, PSA density ≤ 0,20 ng/ml/cc • All Gleason 3+3=6 or Gleason 3+4=7 (<3 cores (or <30% of cores if more than ten cores are taken), <10 mm cancer in one core) • Life expectancy >10 years with no upper age limit • Candidate for curative treatment if progression occurs • Signed written informed consent
Study started	3 October 2016
Enrolment ended	30 September 2024
Planned end of study	Planned end of follow-up 2040
Planned data analysis	January 2027 (primary outcome based on randomization and according to intention-to-treat) and thereafter every third year.
Number of patients	2008
Primary variable	Progression-free survival
Power analysis	See *Supplement 1*
Participating countries	This is a multinational study involving the following countries: Sweden, Finland, Denmark, Norway, and the UK.

3. OVERVIEW

Scandinavian Prostate Cancer Group (SPCG) study number 17 (SPCG-17) is a randomised controlled trial investigating standardised triggers for repeat biopsies and initiating curative treatment among men on active surveillance for low-risk and favourable intermediate-risk prostate cancer. The English title for the study is *Prostate Cancer Active Surveillance Trigger trial* (PCASTt). The primary objective for the study is to reduce overtreatment and subsequent side effects in men with low-risk and favourable intermediate-risk prostate cancer. The primary endpoint is progression-free survival. The trial has recruited patients in Sweden, Finland, Norway, Denmark, and the UK (PCASTt-UK). Recruitment closed on 30th of September 2024.

Currently, decisions to re-biopsy and initiate curative treatment are not guided by any set criteria and tend to be at the clinician's discretion. The SPCG-17 trial aims to test the safety of a set of standardised rules around when to undertake a repeat biopsy and when to initiate curative treatment for men on active surveillance.

Briefly, eligible men who are managed with active surveillance at participating hospital sites and who consented to participating in SPCG-17 have been randomised to receive care according to current practice or a standardised set of triggers for initiation of repeat biopsy and curative treatment based on prostate-specific antigen (PSA) density, magnetic resonance imaging and pathological signs of progression. All men in the trial are followed up with PSA test every 6 months, a yearly clinical check-up, and magnetic resonance imaging (MRI) every second year.

Data on clinical outcomes and patient quality of life is collected until 2040, in order to assess the safety and efficacy of a standardised protocol of active surveillance triggers.

4. STUDY OBJECTIVES

With the primary endpoint set to progression-free survival, the aim of this trial is to test the safety of an active surveillance protocol comparing current practice with standardized triggers for initiation of curative treatment. The hypothesis is that standardized triggers will reduce overtreatment and increase the quality of life, without increasing disease progression and prostate cancer mortality.

5. ANALYSIS POPULATION

Men with untreated ≤T2a prostate adenocarcinoma who fulfil the inclusion criteria were selected for the study. The total number of patients randomized in the study is 2008.

The inclusion criteria:

- Recently (within 12 months) diagnosed adenocarcinoma of the prostate
- Tumour stage ≤ T2a, NX, M0 (former MX)
- PSA <15 ng/ml, PSA density ≤ 0.20 ng/ml/cc
- Gleason pattern 3+3=6 (any number of cores, any cancer involvement)
- Gleason pattern 3+4=7 (<3 cores (or <30 % of cores if more than ten cores are taken) for systematic biopsies, and <10 mm cancer in one core (for any biopsy mode))
- Life expectancy >10 years with no upper age limit
- Candidate for curative treatment if progression occurs

- Signed written informed consent

Before inclusion, all patients underwent an MRI with MRI-targeted biopsies towards Prostate Imaging Reporting and Data System (PI-RADS) v.2 score 3, 4 and 5, and systematic biopsies (optional in patients diagnosed by MRI and MRI-targeted biopsy).

6. ANALYSIS SCHEDULE

The first full-scale analysis of primary and secondary outcomes, and randomized design, will be undertaken in January 2027 when all patients have had their first follow-up MRI. This timepoint was chosen based on advice from the *Data Safety and Monitoring Committee* (DMSC) and an extensive power calculation (*Supplement 1*). Assumed statistical power and precision in estimates, as well as the scientific and clinical value of the study, were carefully considered in the decision-making.

Subsequently, analyses of all primary and secondary endpoints will be performed every third year.

7. DEFINITION OF ENDPOINTS

This section outlines the definitions of the primary and secondary endpoints in the study.

7.1 Primary endpoint

The primary endpoint is progression-free survival, due to the low prostate cancer mortality estimated in the study.

Disease progression is defined as a composite endpoint where the participants can be either recurrence-free or reach any of the following states:

- Biochemical recurrence defined as two consecutively rising PSA values >0.20 ng/ml following radical prostatectomy (RP)
- Biochemical recurrence defined as any rise by 2 ng/ml or more above the nadir PSA value, regardless of the serum concentration of the nadir, following radiotherapy (RT) with or without androgen deprivation therapy (ADT)
- ADT in non-curatively treated men (men in active surveillance (AS) or watchful waiting (WW))
- Metastases or prostate cancer mortality without prior ADT

7.2 Secondary endpoints

The secondary endpoints in this study are:

7.2.1 Treatment with curative intent and transition to watchful waiting

Curative treatment will be defined as RP or local RT (with or without neo adjuvant/adjuvant ADT). Transition to watchful waiting is defined as conversion from active surveillance to watchful waiting according to the judgement of the urologist and reported on the study case report form (CRF).

7.2.2 Occurrence of pT3

This endpoint will be defined as the occurrence of pT3 in RP specimens according to the pathology report.

7.2.3 Initiation of ADT

This endpoint will be defined as initiation of ADT, according to the study CRFs, not including neo-adjuvant/adjuvant ADT in men treated with radiation therapy.

7.2.4 Distant metastases

At the assessment after each follow-up examination, the patient will be categorized as having either:

- No distant metastasis
- Suspected distant metastasis (based on PSA level and/or symptoms but without further verification)
- Confirmed distant metastasis (verified by imaging and/or cytology or biopsy)

7.2.5 Prostate cancer mortality

We will analyse prostate cancer mortality at 10 years from randomization, with competing causes of death accounted for. For classification of causes of death, we will rely on blinded assessment of an external expert committee. This committee should attempt to classify death as follows:

- Death from prostate cancer
- Death with locally recurrent or metastatic prostatic cancer, but other main cause of death
- Death without evidence of tumour progression/recurrence
- Death from prostate cancer treatment complications and/or diagnostics complications

7.2.6 Quality of life

Quality of life (QoL) will be assessed from questionnaires at baseline (before randomisation) and every second year. The questionnaire consists of two parts; one part that contains study-specific questions and the other part is the Expanded Prostate Cancer Index Composite (EPIC)-26.

The main parameters that will be included in an analysis are:

- EPIC-26 score
- Incontinence
- Erectile dysfunction
- Self-reported QoL (rated on a scale of 1-7)

8. ANALYSIS OF THE PRIMARY ENDPOINT

Data will be analysed by the intention-to-treat approach. Interpretations of outcomes will be based on the combination of effect size, a 95% confidence interval and p-value (two-sided).

Disease progression, as reported on the study CRFs, will be analysed as cumulative incidence proportions in a competing risk analysis, considering death from other causes as a competing risk event.

Censoring events will be:

- Date of data extraction without prior primary endpoint events

- Date of withdrawal from study (by choice or lost to follow-up)

Comparisons of trial arms will be made using Gray's tests, with a significance level of 0.05.

Date of withdrawal from study and date of death will be extracted from CRF no 8 "End of follow-up in SPCG-17", using the following variables:

Date
PatientChoice
PatientUnable
PatientDeath
Death

Data on biochemical recurrence will be extracted from CRF no 7 "Annual follow-up after ending active surveillance", using the following variables:

LastPSADate
PSAvalue
CurativeProstatectomyDate
CurativeRadiation
CurativeRadiationDate
CurativOtherRelapse
CurativOtherRelapseDate

Data on ADT in non-curatively treated men (ADT in AS or ADT in WW) will be extracted from CRF no 6 "Ending active surveillance" (for men receiving non-curative treatment) and CRF no 7 "Annual follow-up after ending active surveillance" (for men in watchful waiting), using the following variables:

TreatHormone
TreatTotalAndrogen
TreatMonotherapy

Data on metastases without prior ADT will be extracted from CRF no 7 "Annual follow-up after ending active surveillance", using the following variables:

TreatSuspectMetastas
TreatSuspectMetastasDate
TreatMetastas
TreatMetastasDate
PallMetastas
PallMetastasDate
PallSuspectMetastas
PallSuspectMetastasDate
PallTreatmentMe

PallTreatmentMetDate
PallSuspectMet
PallSuspectMetDate

8.1 Further analysis

8.1.1 Disease progression will be subdivided into:

1) Men with biochemical recurrence following RP
2) Men with biochemical recurrence following RT
3) Men with ADT following WW
4) Men treated with ADT when in AS

8.1.2 Biochemical recurrence will be subdivided into low- and high-risk biochemical recurrence as defined by the European Association of Urology (EAU):

- *Low-risk biochemical recurrence* is defined as Gleason score <8 and PSA doubling time >12 months.
- *High-risk biochemical recurrence* is defined as Gleason score ≥8 or PSA doubling time ≤12 months.

9. ANALYSIS OF SECONDARY ENDPOINTS

Data will be analysed by the intention-to-treat approach. Interpretations of outcomes will be based on the combination of effect size, a 95% confidence intervals and p-values (two sided).

The following sub-sections outline secondary endpoint analyses.

9.1 Treatment with curative intent or transition to watchful waiting

Treatment with radical prostatectomy, treatment with radiotherapy and transition to watchful waiting, as reported on the study CRFs, will be analysed as cumulative incidence proportions in a competing risk analysis.

Death from other causes will be considered as a competing risk event.

Cumulative incidence of competing risk events will be compared using Gray's test.

Censoring events will be:

- Date of data extraction without prior records of events
- Date of withdrawal from study (by choice or lost to follow-up)

Date of withdrawal from study and date of death will be extracted from CRF no 8 "End of follow-up in SPCG-17", using the following variables:

Date
PatientChoice
PatientUnable
PatientDeath

Data on treatment with curative intent will be extracted from CRF no 6 “Ending active surveillance”, using the following variables:

ReasonOptions
TreatStartDate
TreatRadicalProstatec
TreatRadio
TreatRadioAndrogen
TreatOtherCurative
TreatOtherCurativeText

Data on transition to watchful waiting will be extracted from CRF no 6 “Ending active surveillance”, using the following variables:

ReasonOptions
TransferalDate

9.1.1 Further analysis

In a further analysis, curative treatment will be subdivided into:

1) pathological stage T2
2) pathological stage T3-T4
3) RT without ADT
4) RT with neo-adjuvant/adjuvant ADT

Cumulative incidence of competing risk events will be compared using Gray’s test.

Censoring events will be:

- Date of data extraction without prior records of events
- Date of withdrawal from study (by choice or lost to follow-up)

Date of withdrawal from study and date of death will be extracted from CRF no 8 “End of follow-up in SPCG-17”, using the following variables:

Date
PatientChoice
PatientUnable
PatientDeath

Data on pT will be extracted from CRF no 6 “Ending active surveillance”, using the following variables:

pT

9.2 **Initiation of ADT** (not including neo-adjuvant/adjuvant ADT in RT)

Initiation of ADT, as reported on the study CRFs, will be analysed as cumulative incidence proportions in a competing risk analysis.

Initiation of ADT will be subdivided into:

1) men in WW receiving ADT
2) men in AS receiving ADT
3) men who have undergone RP and are receiving ADT
4) men who have undergone RT and are receiving ADT (not including neo adjuvant/adjuvant ADT)

Death from other causes will be considered as a competing event.

Cumulative incidence of competing risk events will be compared using Gray's test.

Censoring events will be:

- Date of data extraction without prior records of events
- Date of withdrawal from study (by choice or lost to follow-up)

Date of withdrawal from study and date of death will be extracted from CRF no 8 "End of follow-up in SPCG-17", using the following variables:

Date
PatientChoice
PatientUnable
PatientDeath

Data on initiation of ADT will be extracted from CRF no 6 "Ending active surveillance" and CRF no 7 "Annual follow-up after ending active surveillance", using the following variables:

Table 6

TreatHormone
TreatTotalAndrogen
TreatMonotherapy

Table 7

TreatAndroDepri
TreatAndroDepriDate
PallTreatmentDate
PallTreatmentDate
TreatHormone
TreatTotalAndrogen
TreatMonotherapy

9.3 Distant metastasis

Events of metastases, as reported on the study CRFs (confirmed and suspected, or prostate cancer death without prior confirmed/suspected metastasis), will be analysed as cumulative incidence proportions in a competing risk analysis.

Death from other causes will be considered as a competing event.

Cumulative incidence of competing risk events will be compared using Gray's test.

Censoring events will be:

- Date of data extraction without prior records of events
- Date of withdrawal from study (by choice or lost to follow-up)

Date of withdrawal from study and date of death will be extracted from CRF 8 "End of follow-up in SPCG-17", using the following variables:

Date
PatientChoice
PatientUnable
PatientDeath

Data on distant metastasis will be extracted from CRF no 7 "Annual follow-up after ending active surveillance", using the following variables:

TreatSuspectMetastas
TreatSuspectMetastasDate
TreatMetastas
TreatMetastasDate
PallMetastas
PallMetastasDate
PallSuspectMetastas
PallSuspectMetastasDate
PallTreatmentMe
PallTreatmentMetDate
PallSuspectMet
PallSuspectMetDate

9.4 Prostate cancer mortality

Prostate cancer mortality, as reported on the study CRFs, will be analysed as cumulative incidence proportions in a competing risk analysis.

Death from other causes will be considered as a competing risk event.

Cumulative incidence of competing risk events will be compared using Gray's test.

Censoring events will be:

- Date of data extraction without prior records of events
- Date of withdrawal from study (by choice or lost to follow-up)

Date of withdrawal from study and date of death will be extracted from CRF no 8 "End of follow-up in SPCG-17", using the following variables:

Date
PatientChoice
PatientUnable
PatientDeath

Data on prostate cancer mortality will be extracted from CRF no 8 "End of follow-up in SPCG-17", using the following variables:

PatientDeath
Death

9.5 Quality of life

Prevalence of incontinence and erectile dysfunction at year 0, 2 and 4 will be presented and statistical significance assessed using a Chi-square test. Levels of EPIC-26 score and self-reported quality of life (rated on a scale of 1-7) will be presented and statistical significance assessed using the Wilcoxon rank-sum test. Longitudinal changes will be investigated.

10. ACTIVITY IN MEN AT RISK

Incidence of the following monitoring activities in men at risk (men who has still not experienced any of the primary or secondary endpoints) will be compared between treatment arms:

- PSA measurement
- MRI examination
- Biopsy

The time at risk will be split in time since diagnosis 0-2, 2-4, 4-6, 6+ years and split by calendar time period, prior to 1/1 2020, 1/1 2020-31/12 2021, 1/1 2022-31/12 2023, and later than 1/1 2024. Comparison between treatment arms will be performed by means of Poisson regression.

11. TRIGGERS FOR CURATIVE TREATMENT

Triggers for curative treatment will be analysed and presented in contingency tables with a Chi-square test for all curatively treated men, according to randomisation arm. Possible

triggers in hierarchical order are 1) pathological progression, 2) MRI progression, 3) PSA progression, 4) patient wish and 5) Other.

Data on reasons for initiating curative treatment will be extracted from CRF no 6 “Ending active surveillance”, using the following variable:

ReasonOptions

12. SUBGROUP ANALYSES of the primary endpoint

The following exploratory and hypothesis-generating subgroup analyses are planned. The analyses will be performed using cox regression, censoring for competing events (death from other causes) and tested for interaction between randomisation arm and subgroup:

1) Age ≤ 65 ***versus*** >65
2) Gleason grade group 1 ***versus*** Gleason grade group 2
3) Positive MRI (PI-RADS score 3-5) at inclusion in the study ***versus*** negative MRI (PI-RADS score 1-2) at inclusion in the study

SPCG-17

Prostate Cancer Active Surveillance Trigger trial (PCASTt)

Power Calculation

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Study Registration: https://clinicaltrials.gov/ct2/show/NCT02914873
https://doi.org/10.1186/ISRCTN64382660

Introduction

The SPCG-17 trial aimed to randomise 2000 patients in 4 years. This would give an 85% power to detect an absolute difference in progression-free survival of 1.3% in the intervention arm compared to the standard arm. The assumption then was that 90% of the patients are managed per protocol according to the randomization and that the cumulative progression-free survival in the standard arm would be 98% after five years from randomization [1].

On 30th of September 2024 we had randomized 2008 patients in the SPCG-17 trial and recruitment was stopped. This prolonged inclusion period prompts a new, more detailed, power calculation.

Here, we have used more current and granular data (national Swedish data from PCBaSe5 [2, 3]) than in the original power calculation and included four different scenarios for the assumption of cumulative progression-free survival in the standard arm (1, 2, 3 or 4% risk of progression at five years from randomization). Taking into account that the protocol stipulates the first mandatory follow-up at 6 months (PSA testing) following randomization, we assumed an increased risk proportional to the hazard in the standard arm from 7.2 months and onwards.

We investigated power by calendar time of analysis, to use as an underpinning for a final statistical analysis and publication plan.

When deciding on the best date for analysis, the following questions must be addressed:

1. The most likely 5-year progression-free survival.
2. The power as displayed in Figure 1 (see Summary of results).
3. The upper confidence limit for the difference in progression-free survival at 5 years.
4. The risk that the result from the trial becomes outdated due to new techniques to detect disease progression.

Summary of results from PCBaSe simulations

The simulations show that a power of 85%, when assuming 2% progression after 5 years from randomization in the standard arm, will be achieved later than 2029-12-31 (Figure 1). On the other hand, if the risk for progression is 1%, a power of 85% will be achieved close to February 2028. Our simulations using 3% and 4% progression at 5 years indicate low power.

The lack of data on risk of progression-free survival in active surveillance in the era of MRI makes the assumption of 2% progression at 5 years difficult to verify.

The statistical analysis plan for SPCG-17 states that the difference in progression-free survival at 5 years from randomization should be presented with a 95% two-sided confidence interval. The upper limit of this confidence interval is less influenced by the intended date of analysis than the power, as indicated by Figures 2 and 3.

Both the power and the confidence interval for the difference are heavily dependent on the assumed 5-year progression-free survival following randomization in the standard arm.

Figure 1 below shows the power in the study by calendar time for analysis and median follow-up time for the four different scenarios tested (95-99% progression-free survival in the standard arm).

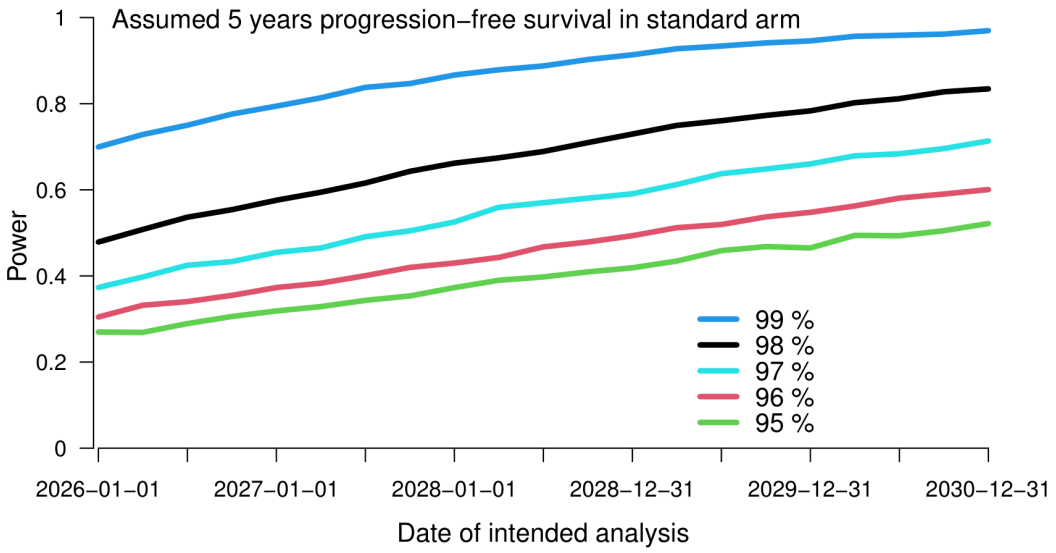

Figure 1. Power in study by calendar time for analysis based on a two-sided Gray's test.

Figure 2 and 3 below shows the 90% and 80% percentile of the upper 95% two-sided confidence, respectively.

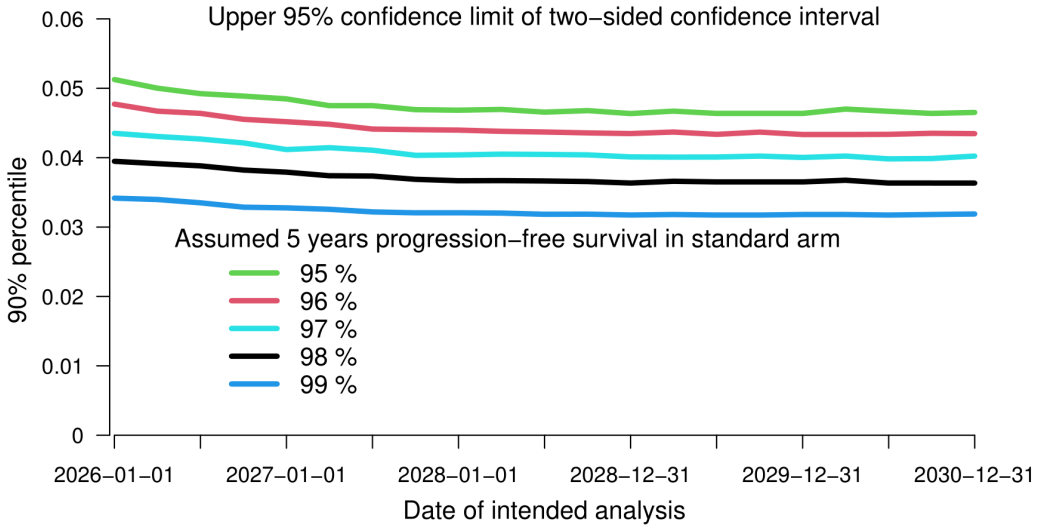

Figure 2. 90% percentile of the upper 95% two-sided confidence of the difference in 5-year progression-free survival in 10 000 simulations of the trial assuming 95%, 96%, 97%, 98% and 99% progression-free survival in the standard arm at 5 years

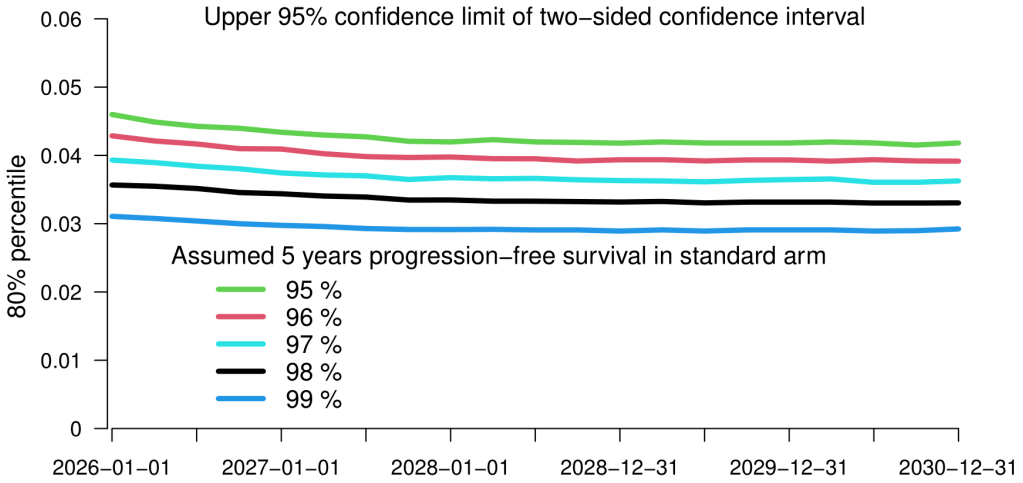

Figure 3. 80% percentile of the upper 95% two-sided confidence of the difference in 5-year progression-free survival in 10 000 simulations of the trial assuming 95%, 96%, 97%, 98% and 99% progression-free survival in the standard arm at 5 years

Methods

To estimate the risk of progression in terms of PSA relapse or initiation of ADT without prior PSA relapse, we used data from PCBaSe5 [2, 3].

From the data, a target population for the calculations was chosen. This target population were men registered as “managed with active surveillance” in the Swedish National Prostate Cancer Registry (NPCR) between 2009 and 2022, and who met the following criteria:

- PSA density satisfying 0<PSA density ≤0.20 ng/ml
- Gleason score 3+3 or 3+4
- T-stage T1c or T2
- Proportion positive cores less than 33%
- Expected remaining lifetime [4] >15 years
- Age at diagnosis ≥55 and ≤75 years

PSA relapse was defined as a PSA level of >0.2 ng/ml after surgery or a PSA level of >2 ng/ml after radiotherapy. Data on initiation of ADT treatment was retrieved from the Swedish National Prescribed Drug Register.

We found 107018 men satisfying these criteria. Of these, 757 men experienced a PSA relapse during follow-up and 309 men received ADT treatment without a prior relapse. No events occurred prior to 7.2 months (0.6 years). We therefore subtracted 0.6 years from all times and estimated progression-free survival and fitted a Weibull survival distribution to the data. The observed event-free survival (black line) and fitted survival (red line) are displayed in Figure 4. The displayed survival was retrieved by adding 0.6 years of event-free survival.

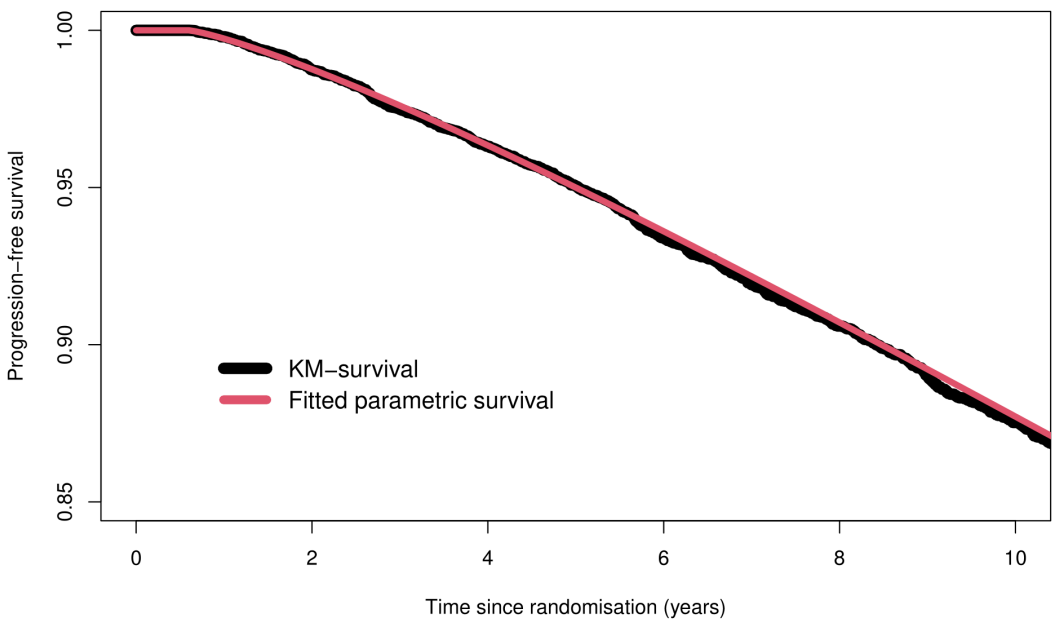

Figure 4. Observed and fitted progression-free survival.

The shape parameter in the Weibull distribution was estimated to a= 1.24 and the scale parameter was estimated to m= 48.6, i.e., the parametrisation of the hazard function $h(x)= a/m*(x/m)^{(a-1)}$

The standard arm of SPCG-17

We tested four scenarios for the standard arm regarding assumption of the risk of progression within 5 years. Firstly, we assumed a 2% risk of progression within 5 years, as also assumed in the original power calculation [1]. To achieve this, we applied a proportional hazards assumption to the fitted Weibull distribution. Using the HR factor 0.491 to and multiplied it with the fitted hazard, the progression-free survival becomes the black survival curve in Figure 5.

We also assumed a 1% risk of PSA relapse within 5 years (blue line in Figure 5) using the HR factor 0.238, a 3% risk of PSA relapse within 5 years (light blue line in Figure 5) using the HR-factor 0.743, and a 4% risk of PSA relapse within 5 years (red line in Figure 5) using the HR factor 1.

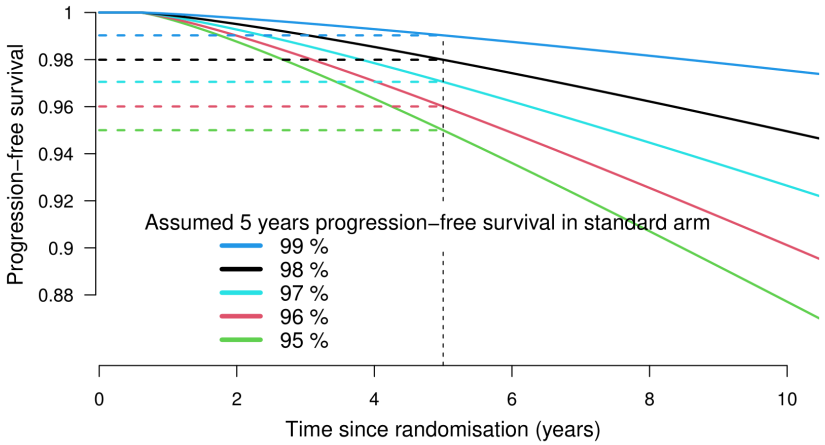

Figure 5. Progression-free survival curves corresponding to 99% (blue), 98% (black), 97% (light blue), 96% (red) and 95% (green) progression-free survival at 5 years.

The intervention arm of SPCG-17

In the original power calculation, we aimed to be able to detect an absolute difference of 1.3% in progression-free survival after five years from randomization in the intervention arm. Here, we assumed that the first difference in occurrence of events could be detected at the earliest 7.2 months after randomization. This fact does not affect the hazard function for the intervention arm.

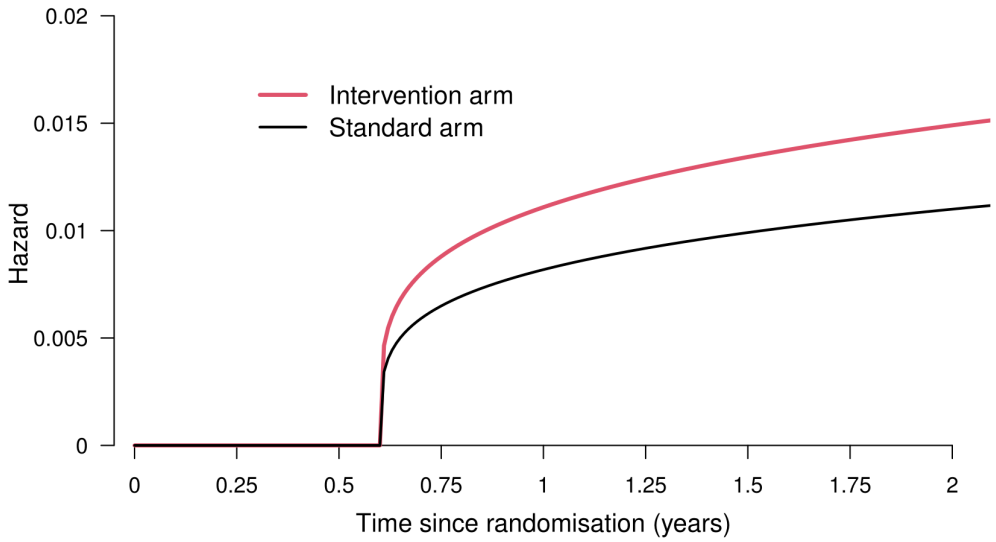

Figure 6. Hazard function for standard arm (black) and intervention arm (red).

The cumulative hazard corresponds to the area under the hazard function and changes with time as illustrated in Figure 7.

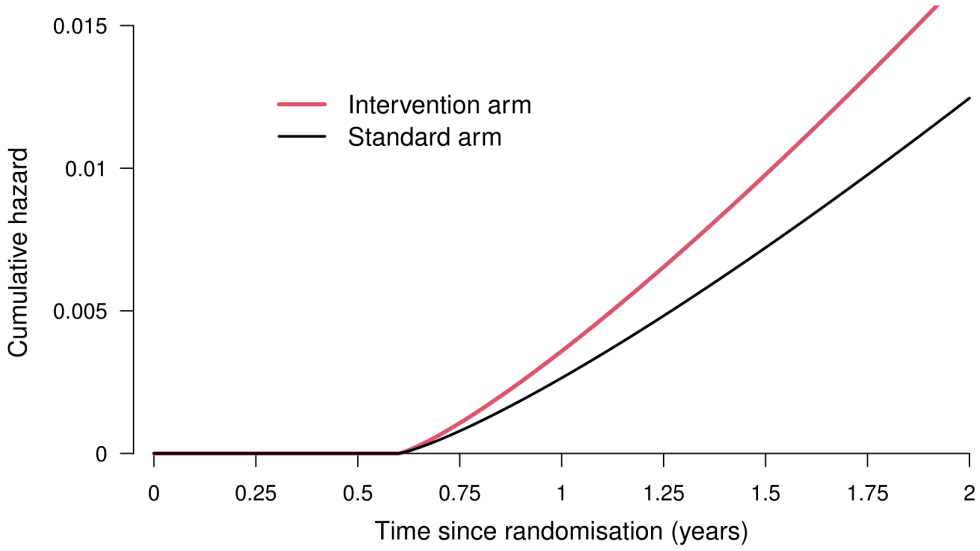

Figure 7. Cumulative hazard function for standard arm (black) and intervention arm (red). The survival curve corresponds to the exponential of the negative cumulative hazard.

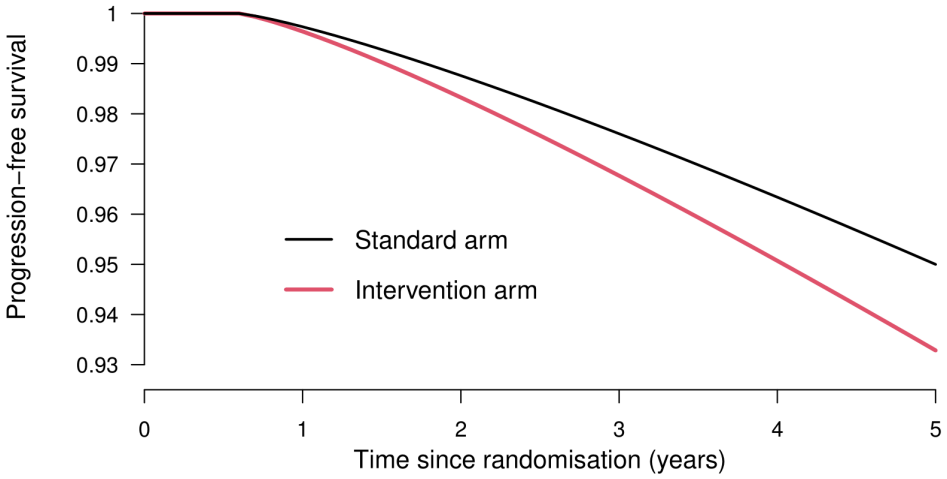

Figure 8. Progression-free survival curves for the standard arm (black) and intervention arm (red).

Competing risks

Death without prior PSA relapse is considered a competing risk. Data on the risk of death is related to age and comorbidities. Rather than taking age and comorbidities into account, we assumed that the risk of death was like that of men aged 50 in Sweden. Such data was retrieved from Statistics Sweden [5].

Simulation

We simulated the SPCG-17 trial using the following approach.

1. We created a cohort of 2000 men with randomization date and randomization arm according to Figure 9, where black dots correspond to arm1 of the study and red dots correspond to arm 2 of the study.

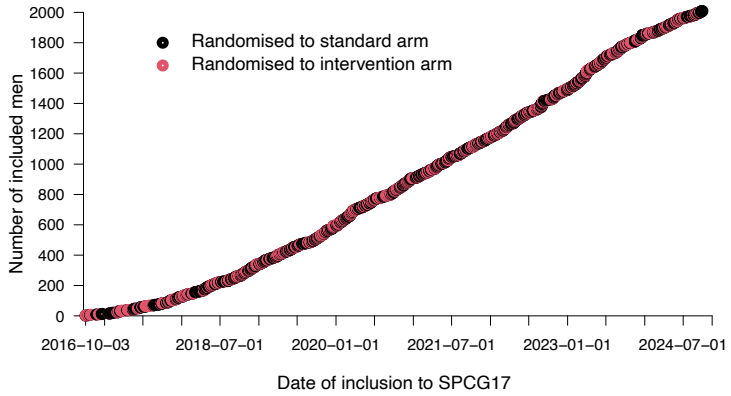

Figure 9. Recruitment to the SPCG-17 trial.

2. In arm 1 and 2, we generated date of death according to the probability distribution for death described above.
3. In arm 1, we generated date of PSA relapse by taking the inverse of the black progression-free survival curve of **Figure 8.**
4. In arm 2, we generated date of PSA relapse according to the inverse of the red progression-free survival curve of **Figure 8.**
5. We determined the last date of follow-up (LDOF).
6. We ignored all events after LDOF.
7. We calculated time to event as the minimum of time to PSA relapse, time to death, and time to LDOF.
8. We calculated the censoring variable, where 0 corresponds to reaching LDOF free of events, 1=an event of progression (relapse or initiation of ADT, and 2=death as first event.

We thereafter ran the simulation 10 000 times and calculated:

1. Number of progression-events in the standard arm
2. Number of progression-events in the intervention arm
3. Number of deaths in the standard arm
4. Number of deaths in the intervention arm
5. 5-year cumulative incidence proportion of progression in the standard arm, considering death as competing risk
6. 5-year cumulative incidence proportion of progression in the intervention arm, considering death as competing risk
7. Difference in 5-year cumulative incidence proportion estimates
8. Upper two-sided 95% confidence limit for the difference

9. P-value of Log-rank test of equal progression in treatment arms

The assumed date of analysis (=LDOF) was set to 2026-01-01, 2026-04-01, 2026-07-01, …., 2029-12-31, i.e., every third month between 2026-01-01 and 2029-12-31. We also varied the assumed risk of progression at 5 years in the standard arm (1%, 2%, 3%, 4% and 5%). For each combination of date of analysis and assumed proportion of progression at 5 years we simulated 10 000 trials.

For each proportion of progression at 5 years in the standard arm the hazard function for the intervention arm was adjusted with a relative hazard to accomplish a difference in absolute risk of progression at 5 years of 1.3%.

The relative hazards used in the intervention arm was set to 2.457, 1.710, 1.475, and 1.355 when risk of progression at 5 years in the standard arm was set to 1%, 2%, 3% and 4% respectively.

The results from the simulations are presented in Figures 1-3. The average number of progression events by date of intended analysis are shown in Figure 10.

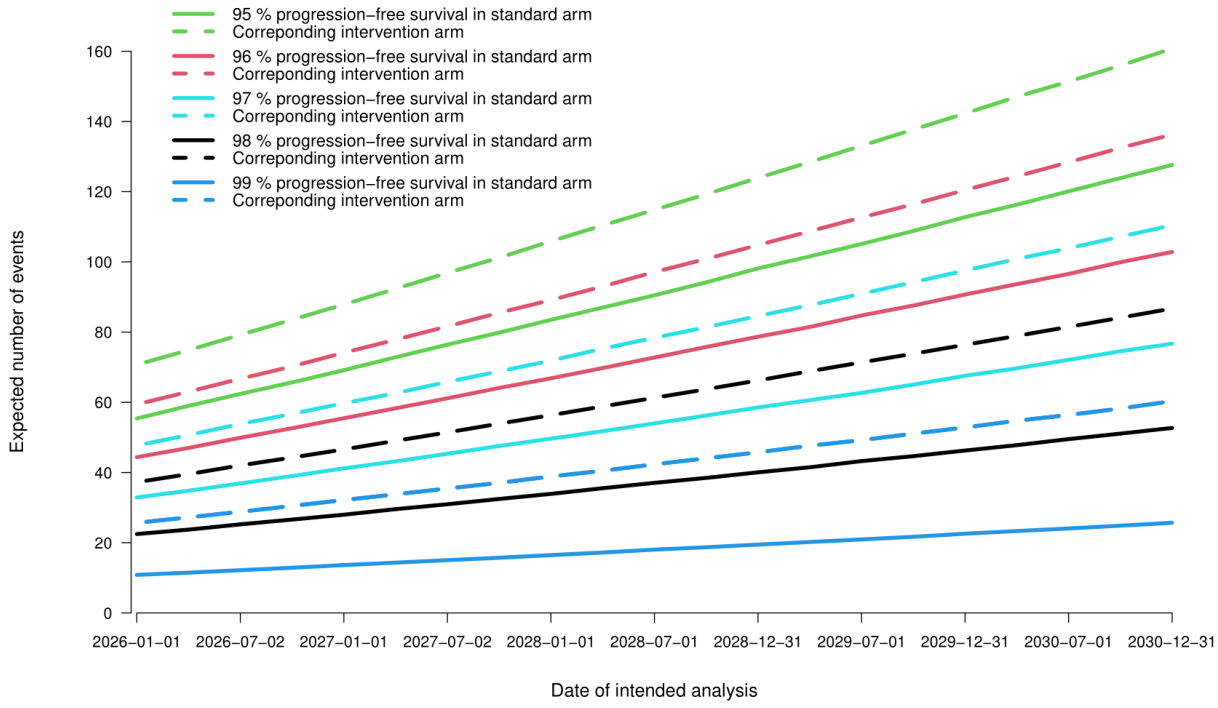

Figure 10. Average number of events by date of intended analysis.

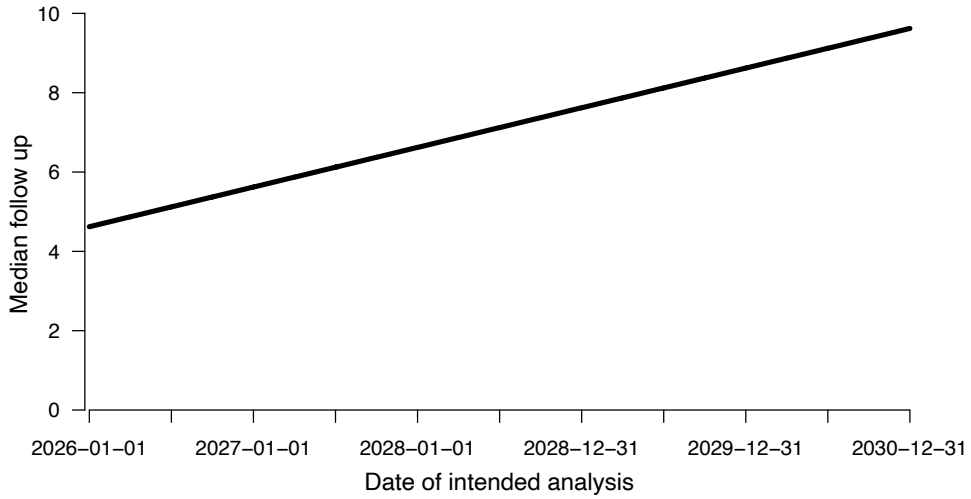

Figure 11. Median follow-up time in SPCG-17 by date of intended analysis.

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