Statistical Analysis Plan

Intestinal function 8 years after radical prostatectomy. A comparison between surgical techniques and postoperative pelvic radiotherapy in the Swedish LAPPRO trial.

Version 3. 2021-11-02

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INTRODUCTION

This statistical analysis plan (SAP) details the statistical and data related aspects of the analyses of urine, sexual and intestinal function after radical prostatectomy. The research objectives and methodologies are hereby specified before accessing data in order to ensure a high scientific integrity and credibility.

The LAPPRO trial, a prospective, controlled, non-randomized trial where robot assisted laparoscopic prostatectomy was compared with open retropubic prostatectomy, is the context for the described study. A detailed description of the trial protocol has been published (Thorsteinsdottir et al 2011). Inclusion took place during September 2008 until November 2011, with a total of 4003 included patients at 14 Swedish Departments of Urology. The primary end-point of the trial was to compare urinary incontinence 12 months postoperatively (Haglind et al 2015). Many secondary and tertiary outcomes have been analysed and duly published. The cohort has been followed for eight years so far. A manuscript including the analyses of urinary incontinence, erectile dysfunction, biochemical recurrence and mortality at 8 years follow-up has recently been submitted to a peer-reviewed journal (Lantz A et al 2020).

The primary aim of this study is to estimate the effect of postoperative pelvic radiotherapy on urinary, sexual, intestinal function, bother due to dysfunction, general quality of life and physical health in men that underwent postoperative pelvic radiotherapy after radical prostatectomy compared to men who did not receive postoperative pelvic radiotherapy.

Secondary aim is to:

- explore the relationship between time and dose of postoperative pelvic radiotherapy and incidence and severity on urinary, sexual and intestinal dysfunction.

This statistical analysis plan was completed and finalized before analyses of data commenced.

DATA COLLECTION

Data was collected through clinical record forms before and during surgery and during hospital stay, and at 6-12 weeks, 12 months and 24 months after the operation and by detailed questionnaires answered by the patients before, 3, 12 and 24 months as well as 8 years after the operation. To the resulting database data was retrieved from the Swedish Cause of Death Register and added (Lantz et al manuscript 2020).

From the National Prostate Cancer Register information regarding radiotherapy at any time following prostatectomy was retrieved and added, including dose and time for radiation.

ANALYSIS OBJECTIVES

The primary objective is to estimate the causal effect of postoperative pelvic radiotherapy on urinary, sexual and intestinal function, bother due to dysfunction, general quality of life and physical health.
Secondary aim is to

- explore the relationship between the relationship between time and dose of postoperative pelvic radiotherapy and incidence and severity on urine, sexual and intestinal dysfunction.

The secondary objective may be presented in separate report or in a supplement to the main report.

ANALYSIS POPLULATION

4003 enrolled patients.

Inclusion criteria:
1) Age <75 years, prostate-specific antigen (PSA) < 20 ng/ml, tumor stage <T4, no metastatic disease, and informed consent.

2) Not received adjuvant radiotherapy between index surgery and 12 month follow-up.

VARIABLES AND ENDPOINTS

Background variables will be used to describe demographics and patient characteristics and adjust for confounding (where applicable).

Background variables

Preoperative questionnaire

1. Body weight Q8,
2. Body height Q9.
3. Smoking Q57.
4. Alcohol consumption Q59- 62.

5. Physical activity Q143.
6. Quality of life Q79.
7. Psychological wellbeing Q84.
8. Feeling depressed Q112 (yes/no).

Clinical characteristics from CRF

Pre-operative CRF:
1. Clinical tumor staging Q6.
2. Gleason Score on biopsy
3. Gleason Score in specimen (pathology)
4. Pathology t-stage
5. Pre-operative PSA
6. Prostate Volume

Additional variables

Surgical method (RRP and ORP)

Exposure variables

Postoperative pelvic radiotherapy up to 8 year follow-up as documented in National Prostate Cancer Register (NPCR) of Sweden. Date of initiation of radiotherapy and dosing is collected.

Outcome variables/endpoints

Primary endpoints

The endpoints used to address the primary objective are presented in Table 1. In the supplementary excel spread sheet additional information is provided.

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Urine function	Erectile function	Bowel function	Additional
How many times do you change pad, diaper or other sanitary protection during a typical 24 hours?'	When you had erections with sexual stimulation, how often was your erection hard enough for penetration during the last 3 months?'	Have you had occasions when you could not control your flatus (wind) in the last month?	How would you like to describe your quality of life in the last month?
How often have you had to urinate again within two hours in the last month?	How often have you, during intercourse, been able to maintain an erection since you had intercourse into your partner in the last 3 months?" (question is similar to IIEF Q3)	Have you had any accidental leakage of liquid stool when awake in the last month?"	How do you assess your physical health in the last month?
How often have you had difficulty postponing urgent urination the last month?		Have you had such a strong urge to open your bowels that you had to rush to the toilet in the last month?"	If you were to live the rest of your life with your overall urinal problems, how would you experience it?
How often, on average, have you gotten up and peed during a typical night? the last month?		Have you had any leakage of red blood when awake in the last month?"	If your erection has deteriorated compared to before and it will persist the rest of your life, what do you think of it?
Have you sought medical attention due to any of the following after the operation: Bleeding from the urinary tract or catheter?		How often do you open your bowels?	If you would live for the rest of your life with your overall gastrointestinal problems, as it has been in the last month, how would you experience it?
		Have you noticed bleeding from the anus during the last month?	
		Have you noticed mucus from the anus during the last month?	
		Do you ever have to open your bowels again within one hour of the last bowel opening?	
		"Have you emptied all the feces in your clothes without warning in the last month?"	

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HANDLING OF MISSING VALUES AND OTHER DATA CONVENTIONS

Categorization/dichotomization of response options

Categorization/dichotomization of variables result in arbitrariness and induce a loss of information where a loss in statistical power may be substantial ([1], [2]), but may aid interpretation if it reflects clinically relevant categories. All outcome variables will be analysed without categorization/dichotomization.

Missing values

In the primary statistical analysis, adjustment for confounders will be made. For the situation with a serious rate of missing values in the confounding variables, this will need to be addressed by characterizing the pattern of the missing values and well as using imputation techniques (multiple imputations).

The variables judged as being confounders (see Section below) are the following seven variables:

1. Age at surgery
2. Pathological tumor staging.
3. Preoperative PAD Gleason Q20
4. Surgical method
5. Smoking (former/current/no)
6. Prostate volume
7. Preoperative PSA

Based on previous publications from the study the degree of missingness of variable 1, 2, 3 and 4 , the rate of missing values is very low (between no missing to approximately 3%). .

STATISTICAL METHODOLOGY

Study design

In order to address the primary objective, the target trial emulation approach of Hernan ([3]) will be used. All patients that has not received adjuvant radiotherapy up to 12 month follow-up will be included. Patients receiving radiotherapy treatment between 12 month follow up and five years later (six years after index surgery) will be defined as having received treatment. Patients receiving no radiotherapy between 12 month and 8 year follow-up will defined as being control group.

A sensitivity analysis will be performed where patients receiving radiotherapy treatment between 12 month follow up and three years later (four years after index surgery) will be defined as having received treatment.

	Summary of protocol of target trial /Target trial	Analysis of data
Eligibility criteria	Patients operated for prostate cancer with no use of adjuvant radiotherapy (salvage therapy)	Patients in **LAPPRO** operated for prostate cancer with no use of adjuvant radiotherapy (salvage therapy) up to 12 month follow-up
Treatment strategies	1. Initiate salvage therapy at baseline and remain until follow-up 2.Refrain from salvage therapy at baseline and remain until follow-up	1. Receive salvage therapy between 12 month follow-up and 5 years later (6 years after index surgery) 2. Do not receive salvage therapy between 12 month follow-up and 8 year follow-up (8 years after index surgery)
Assignment procedures	Participants will be randomly assigned to either strategy at baseline, and will be aware of the strategy they have been assigned to.	Participants will be assigned to respective group according to the definition of treatment strategy.
Follow-up period	The time point where the patient complete the eight year questionnaire	The time point where the patient complete the eight year questionnaire (time zero is 12 month follow-up)
Outcome	1. Urinary function and bother 2. Bowel function and bother 3. Erectile function and bother 4. Quality of life and phycial health	1. Urinary function and bother 2. Bowel function and bother 3. Erectile function and bother 4. Quality of life and phycial health
Causal contrasts	Intention to treat effect	Intention to treat effect of receiving salvage therapy
Analysis plan	Intention to treat analysis	Intention to treat effect of receiving salvage therapy with handling of confounders by regression adjustment and 12 month outcome as covariate ("ANCOVA")

Handling of confounders for causal inference

By means of directed acyclical graphs (DAG) we displayed hypothetical assumptions about the relationship between variables. From the DAG (see Appendix) it was concluded that the following variables should be adjusted for in order to enable a causal assessment:

1. Age at surgery
2. Pathological tumor staging.
3. Preoperative PAD Gleason Q20
4. Surgical method
5. Smoking (former/current/no)
6. Prostate volume
7. Preoperative PSA

The variables will adjusted for by including them as covariates in the regression model. Continuous variables will be standardized and includes as restricted cubic spline to allow for nonlinear relationship. Baseline value of the outcome will be included as covariate (ANCOVA) in the respective emulated trials.

Statistical analysis

Primary analysis

Regression models for ordinal scale variables will be used (that is analysis of data where the ordinal scale is preserved and no dichotomization is performed)[2]. A proportional odds model is the intended model, but the validity of the model will be examined.

Results will be presented as odds ratio estimates, estimated treatment effects, 95% compatibility intervals and p-values. The prevalence estimates will displayed graphically to aid interpretation.

An additional logistic regression analysis may optionally will be performed for dichotomized variables.

Optional exploratory secondary analysis

The relationship between the relationship between the time and dose of postoperative pelvic radiotherapy and incidence and severity of subsequent urine, sexual and intestinal dysfunction will be addressed exploratory using statistical regression modelling and plots.

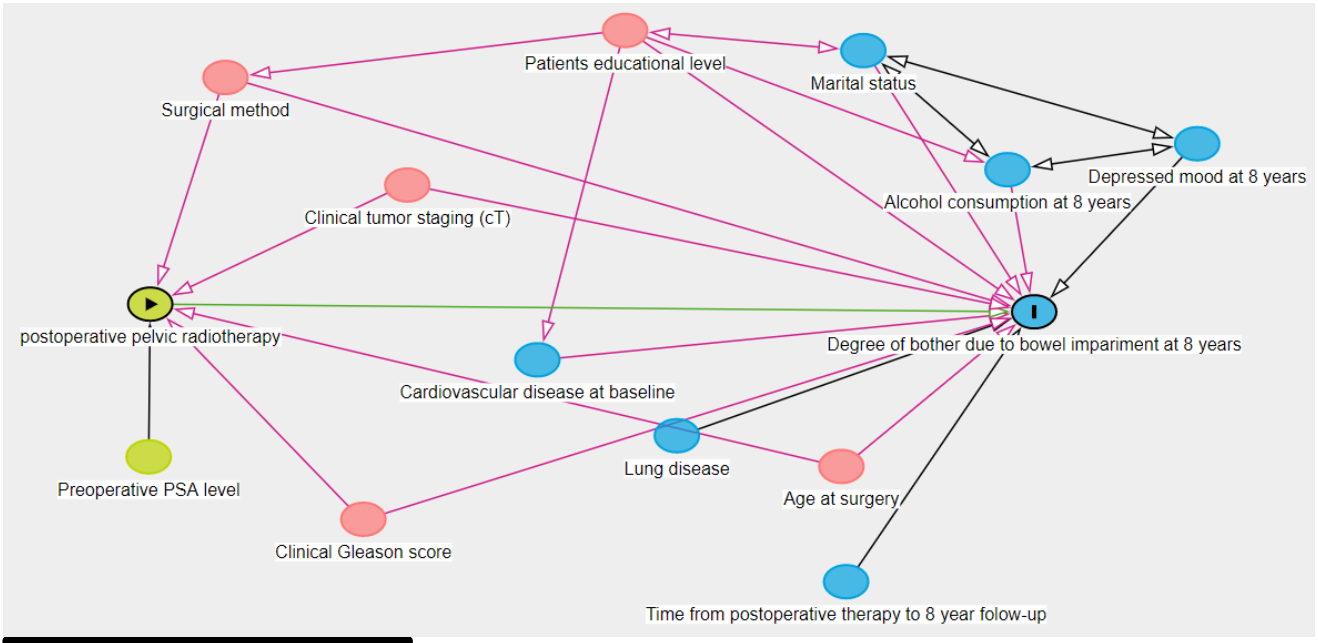
JOURNALS FOR SUBMISSION

Planned (may be subject to change)
1. European Urology (IF 17.947)
4. BJUI (IF 4.806)
2. European Urology Focus (IF 4.827)
3. European Urology Oncology (IF 2.51)
5. Scandinavian Journal of Urology (IF 1.400)

REFERENCES

1. Sankey, S. and L.A. Weissfeld, *A Study of the Effect of Dichotomizing Ordinal Data Opun Modelling.* Commun Statist Simul, 1998. **27**(4): p. 871-887.
2. Harrell, F., *Regression modelling strategies.* 2nd ed. Springer Series in Statistics, ed. P. Buhlmann. 2015: Springer.
3. Hernan, M.A., et al., *Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses.* Clin Epidemiol, 2016. **79**: p. 70.

APPENDIX 1: DAG



Minimal sufficient adjustment sets for estimating the total effect of postoperative pelvic radiotherapy on Degree of bother due to bowel impariment at 8 years:

- Age at surgery, Clinical Gleason score, Clinical tumor staging (cT), Surgical method

Code for dagitty.net

```
dag {
bb="0,0,1,1"
"Age at surgery" [pos="0.695,0.560"]
"Alcohol consumption at 8 years" [pos="0.801,0.251"]
"Cardiovascular disease at baseline" [pos="0.501,0.449"]
"Clinical Gleason score" [pos="0.390,0.615"]
"Clinical tumor staging (cT)" [pos="0.418,0.267"]
"Degree of bother due to bowel impariment at 8 years" [outcome,pos="0.818,0.399"]
"Depressed mood at 8 years" [pos="0.922,0.224"]
"Lung disease" [pos="0.590,0.528"]
"Marital status" [pos="0.709,0.127"]
"Patients educational level" [pos="0.557,0.106"]
"Preoperative PSA level" [pos="0.253,0.550"]
"Surgical method" [pos="0.302,0.155"]
"Time from postoperative therapy to 8 year folow-up" [pos="0.698,0.680"]
"postoperative pelvic radiotherapy" [exposure,pos="0.254,0.391"]
"Age at surgery" -> "Degree of bother due to bowel impariment at 8 years"
"Age at surgery" -> "postoperative pelvic radiotherapy"
```

"Alcohol consumption at 8 years" -> "Degree of bother due to bowel impariment at 8 years"
"Alcohol consumption at 8 years" <-> "Depressed mood at 8 years"
"Alcohol consumption at 8 years" <-> "Marital status"
"Cardiovascular disease at baseline" -> "Degree of bother due to bowel impariment at 8 years"
"Clinical Gleason score" -> "Degree of bother due to bowel impariment at 8 years"
"Clinical Gleason score" -> "postoperative pelvic radiotherapy"
"Clinical tumor staging (cT)" -> "Degree of bother due to bowel impariment at 8 years"
"Clinical tumor staging (cT)" -> "postoperative pelvic radiotherapy"
"Depressed mood at 8 years" -> "Degree of bother due to bowel impariment at 8 years"
"Depressed mood at 8 years" <-> "Marital status"
"Lung disease" -> "Degree of bother due to bowel impariment at 8 years"
"Marital status" -> "Degree of bother due to bowel impariment at 8 years"
"Marital status" <-> "Patients educational level"
"Patients educational level" -> "Alcohol consumption at 8 years"
"Patients educational level" -> "Cardiovascular disease at baseline"
"Patients educational level" -> "Degree of bother due to bowel impariment at 8 years"
"Patients educational level" -> "Surgical method"
"Preoperative PSA level" -> "postoperative pelvic radiotherapy"
"Surgical method" -> "Degree of bother due to bowel impariment at 8 years"
"Surgical method" -> "postoperative pelvic radiotherapy"
"Time from postoperative therapy to 8 year folow-up" -> "Degree of bother due to bowel impariment at 8 years"
"postoperative pelvic radiotherapy" -> "Degree of bother due to bowel impariment at 8 years"