CLINICAL STUDY PROTOCOL

Primary radical prostatectomy versus primary radiotherapy for locally advanced prostate cancer: an open randomized clinical trial

Study Design: Open randomized two- armed, parallel clinical trial

Sponsor short name: SPCG-15

Number of participants: 1200

Sponsor protocol number	SPCG 15, version 1.2 dated March 31, 2016
Clinical study phase	Phase III
Sponsor	Olof Akre Karolinska Institutet/University Hospital
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PROTOCOL SIGNATURE PAGE

Investigator's Statement of compliance

I have read and understood this protocol version 1.2 dated: 2016-03-31 and agree to conduct the study accordingly. I have also understood that this protocol contains information that is confidential. This information is provided to me as an investigator. The content of this protocol may not be disclosed to any other person without prior permission from sponsor. The foregoing shall not apply to disclosure required by governmental regulations or laws. However, I will promptly notify the sponsor of any such disclosure. The study will be carried out in accordance with the Helsinki Declaration and Good Clinical Practice ICH-GCP. I have read and agree to comply with the investigator's obligations stated in this protocol. I have understood that deviations from the protocol are to be made in the form of amendments, which must have prior written approval by the sponsor and the relevant Ethics Committee and medicinal Product Agency. I agree to ensure that all personnel that assist me in the conduct of the study are aware of their obligations. I agree to report any Serious Adverse Events to the sponsor and as required to the relevant Ethics Committee and Regulatory Authorities. This signature below constitutes the approval of this protocol and assurance that the study will be conducted accordingly.

Olof Akre

_____ _____

Coordinating Principal Investigator Name (print)

Date (DD-MM-YYYY)

_____ _____

Coordinating Principal Investigator signature

Date (DD-MM-YYYY)

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_____ _____

Investigator name (print)

Date (DD-MM-YYYY)

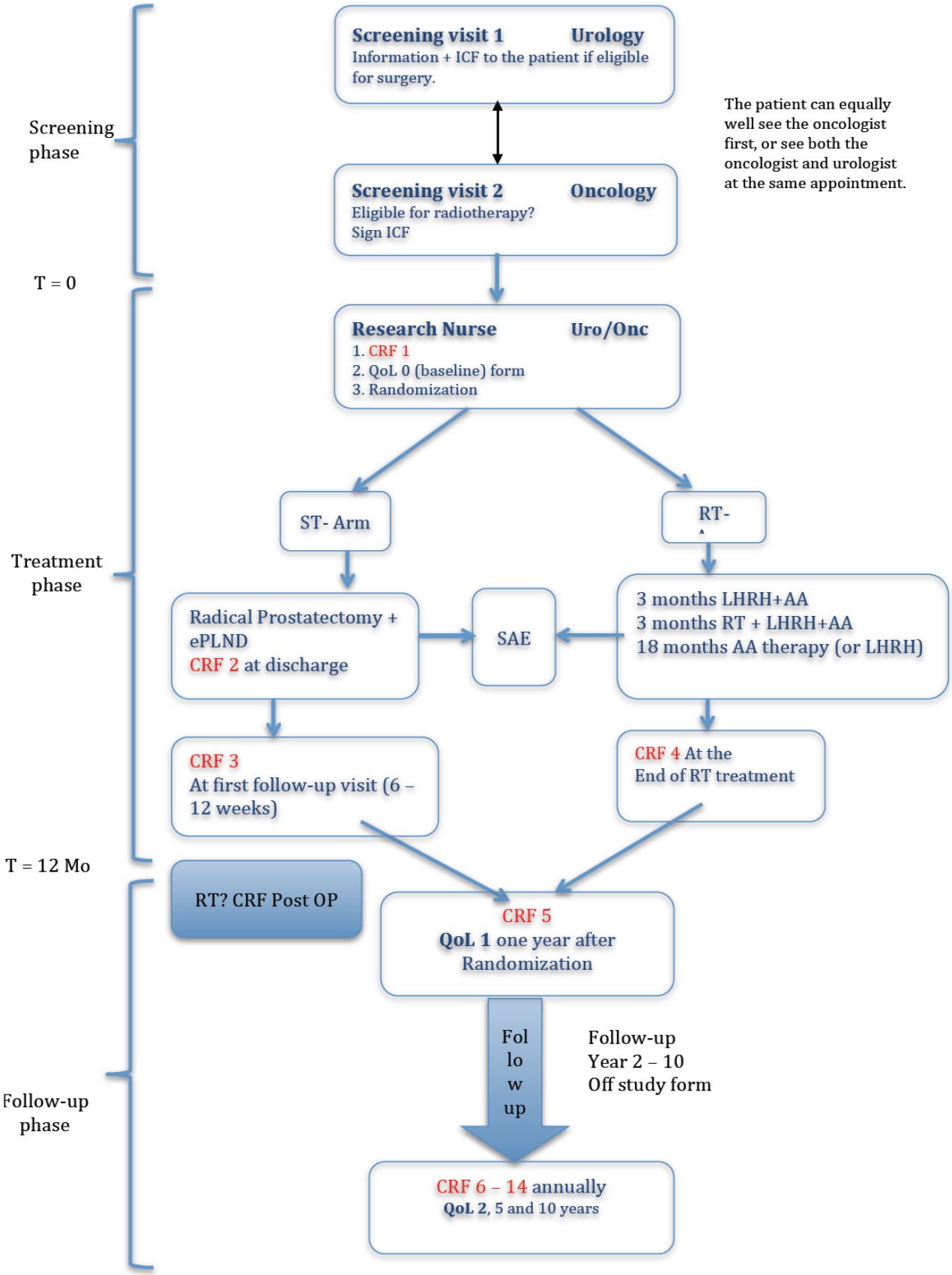
_____ _____

Investigator signature

Date (DD-MM-YYYY)

TRIAL SYNOPSIS AND FLOW CHART

Study Title	Primary radical prostatectomy versus primary radiotherapy for locally advanced prostate cancer: an open randomized clinical trial
Short title	SPCG 15
Clinical study phase	Phase III
Study objective	To compare the efficacy of primary prostatectomy with that of primary radiotherapy with adjuvant endocrine therapy in locally advanced prostate cancer.
Intervention arm (A)	Radical prostatectomy with or without adjuvant/salvage radiotherapy
Reference arm (B)	Primary radiotherapy and endocrine treatment
Study Design	Open prospective, randomized two-armed parallel trial. Estimated study duration 13 years, approximately 13 follow-up contacts and five questionnaires of QoL.
Main patient inclusion criteria	Newly diagnosed with untreated T3 prostate adenocarcinoma. Age ≤ 75 years Eligibility for both treatment arms Signed informed consent Ability to cooperate
Main patient exclusion criteria	PSA value > 100ng/ml
Planned study start	Planned start of screening March 2014
Planned study stop	Planned end of enrolment 2017
Planned End of trial	Planned End of Study 2027
Planned Data analysis	Start of final data analysis and report writing: 2026-2027
Number of patients	1,200
Primary outcome	Cause specific survival
Statistical analysis	Patient flow will be presented according to the CONSORT chart. For demographic variables, the full analysis set(FAS, all subjects randomized) will be presented using descriptive statistics. The data will be analyzed according to the 'intention-to-treat' principle.
Number of Sites	To be determined
Countries	Sweden Finland Norway Denmark Iceland


Screening visit 1 Urology
Information + ICF to the patient if eligible for surgery.
Screening visit 2 Oncology
Eligible for radiotherapy?
Sign ICF
The patient can equally well see the oncologist first, or see both the oncologist and urologist at the same appointment.
Screening phase
T = 0
Research Nurse Uro/Onc
1. CRF 1
2. QoL 0 (baseline) form
3. Randomization
Treatment phase
ST- Arm
RT-
Radical Prostatectomy + ePLND
CRF 2 at discharge
SAE
3 months LHRH+AA
3 months RT + LHRH+AA
18 months AA therapy (or LHRH)
CRF 3
At first follow-up visit (6 – 12 weeks)
CRF 4 At the End of RT treatment
T = 12 Mo
RT? CRF Post OP
CRF 5
QoL 1 one year after Randomization
Follow-up phase
Follow up
Follow-up
Year 2 – 10
Off study form
CRF 6 – 14 annually
QoL 2, 5 and 10 years

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AA	Anti androgens
ADT	Androgen deprivation therapy
ADR	Adverse Drug Reaction
AE	Adverse Event
CRF	Case Report Form
eCRF	Electronic Case Report Form
CSS	Cause specific survival
CRPC	Castration-resistant prostate cancer
CTV	Clinical target volume (CTV-P , CTV-PNV)
CTV-P	Clinical target volume prostate [i.e. the entire prostate and proximal seminal vesicles] (outlined in CT, with MRI support)
CTV-PNV	Clinical target volume pelvic nodes volume, i.e. the vessels, arterial and vein connected, include with a margin of 7mm in all directions, distal common iliac, presacral (S1-S3), external and internal iliac and the obturator vascular structures (outlined in CT, if possible with angio sequence MRI support).
EBRT	External beam radiotherapy
ED	Erectile dysfunction
EPE	Extra Prostatic Extension
FAS	Full analysis set
GTVP	Gross tumor volume prostate, whole prostate gland, (outlined in CT, with MRI support)
GTV-Ves	Gross tumor volume prostate, the proximal part of the seminal vesicules (outlined in CT, with MRI support)
HDR	High Dose Rate
ICH	International Conference Harmonization
IEC	Independent Ethics Committee
ICRU	International Commission Radiation Units?
IMRT	Intensity modulated RT
LAPC	Locally Advanced Prostate Cancer
LHRH	Luteinizing hormone-releasing hormone
LMWH	Low molecular-weight heparin
LND	Lymph node dissection
eLND	Extended lymph-node dissection
MPA	Medical Products Agency
MAB	Maximal Androgen Blockage
OS	Overall survival
OAR	Organ at risk
PC	Prostate cancer
PORT	Prostate only radiotherapy
PSM	positive surgical margins
PLND	Pelvic lymph-node dissection
ePLND	Extended Pelvic lymph-node dissection
PSM	Positive surgical margins
PTV-P	Planning Target Volume - prostate
PTV-PNV´s	Planning Target Volume pelvic node, seminal vesicles
RTQA	Radiation therapy quality assurance
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event
VMAT	Volumetric Modulated Arc Therapy
WPRT	Whole Pelvis Radiotherapy

BACKGROUND AND RATIONALE

OCCURRENCE AND PROGNOSIS OF LOCALLY ADVANCED PROSTATE CANCER (LAPC)

Prostate cancer (PC) is the most common type of cancer and the second leading cause of cancer mortality in Scandinavian men. While the diagnostic means have been improved during recent years, the mortality rates have not been reduced to the same extent(1-5). The prognosis of the disease is related to several clinical factors: The TNM stage, prostate-specific antigen (PSA) and the differentiation of the tumor classified by the Gleason score. Based on these pre-treatment factors the patients are classified in three prognostic risk groups: Low, intermediate and high-risk. High-risk cancers are either PSA > 20 ng/ml, Gleason score >7, or clinical stage T3a or higher. The increasing use of prostate-specific antigen (PSA) testing during the last decades has led to a migration towards a lower grade and stage due to earlier discovery of the disease. However, whilst more than 90% of men are diagnosed with a clinically localized and curable cancer(6-14) approximately 20 to 35% of all patients receiving the diagnosis of PC are still classified as high risk(1-12,15). High-risk PC is associated with an increased risk of post-treatment PSA failure, secondary treatment, metastatic progression and death for the patient. However, there are limited prognostic data for LAPC (defined as non-metastatic prostate cancer stage T3 or higher) to guide in the choice of treatment. Akre et al. reported an 8-year PC specific mortality rate of 41-64%, depending on biopsy Gleason score, among 12 184 Swedish men with locally advanced PC either with local clinical stage T3 or T4 or with T2 with serum levels of prostate-specific antigen (PSA) between 50 and 99 ng/ml and without signs of metastases(16). This high risk of dying from the disease suggests an under-treatment for this group of patients and underscores the need for more studies of treatment with curative intent for locally advanced tumors.

CURRENT STATE-OF-THE-ART TREATMENT FOR LAPC

Huggins and Hodges were first to describe androgen deprivation therapy (ADT) as a means to control growth and progression of PC and ADT has ever since been the treatment of choice in a majority of patients with LAPC. In later years, however, reports from several observational studies as well as randomized trials have supported treatments with curative intents, radical prostatectomy (RP) and external beam radiation therapy (EBRT) with or without adjuvant ADT(1,3-6,8-14).

EXTERNAL BEAM RADIATION THERAPY (EBRT)

For the concept of EBRT added to ADT, an increased long-term survival, both cancer specific (CSS) and overall (OS), has been shown in prospectively randomized trials for patients with locally advanced or high-risk local PC(1,17). The combination of local radiotherapy and endocrine treatment rendered a 10-year cancer specific survival (CSS) of approximately 90% as compared to approximately 70-75% for ADT only. For the opposite concept, i.e. adjuvant ADT for EBRT vs. EBRT alone, the RTOG trial 85-31(6), a phase III randomized trial for adjuvant hormonal therapy with definitive radiotherapy showed improved 5-years disease-free survival (DFS) for patients with Gleason 8-10. The RTOG 86-10 trial (17) applying two months androgen deprivation (ADT) prior and during radiotherapy versus radiotherapy alone has also shown significant improvement of local control, disease progression and survival in patients with localized disease. EORTC 22961 produced improved outcome when 3 years of adjuvant ADT was applied in men with locally advanced cancer(18). However, the radiation dose to the prostate in many of these earlier trials is too low by today`s standards; today the standard dose is ≥74 Gy. Several reports indicate a clinical benefit between applied EBRT dose and tumor control(19-21). Pollack et al. showed that an increase of EBRT dose to the prostate conferred to improved relapse-free interval in patients with PSA >10 ng/mL(22). However, dose escalation increases the risk of toxicity to surrounding soft tissue and organs. Long-term side effects from the urinary bladder and the rectum may thus impair the patients` quality of life.

In summary, the combination of ADT and radiotherapy improves both the relapse-free and overall survival rates as compared to either treatment alone(13). The mechanisms behind the additional effect of ADT may include eliminating occult systemic disease, reducing the prostatic volume for better coverage by the radiated field, decreasing the irradiated volume and thus toxicity, and impairing DNA repair(23-25). Moreover, experimental data have shown increased vascularisation of the gland during ADT, known to reduce hypoxia and probably reducing the radio-resistance of the tumor(26).

In a report by Solberg et al., as many as 22% of prostate biopsies taken after radiotherapy in the SPCG 7 study showed evidence of residual cancer(27). Residual cancer was also associated with PSA recurrence, local tumor progression, clinical recurrence, and cancer-specific death.

EXTERNAL RADIATION VERSUS HIGH-DOSE-RATE BRACHYTHERAPY (HDR-BT) PLUS EBRT

Men with locally advanced prostate cancer are at high risk of relapse, progression and death and may benefit of dose escalation with HDR-BT. There are no randomized trials comparing high-dose modern EBRT and HDR-BT + high-dose EBRT. However, Phan et al demonstrated a 5-year CSS of 98% and an OS of 91% after HDR-BT in addition to EBRT in a group of 133 patients with high-risk PC(28). Lilleby et al published recently their findings with HDR-BT as boost technique combined with ADT in high-risk PC(29). HDR-BT given in combination with RT and ADT was associated with favorable 5-years outcome results. It seems likely that the higher intra-prostatic dose achieved by this technique has the potential of improving the results of RT for LAPC. The effect of ADT in HDR-BT patients has not been shown as of yet and its role with HDR-BT has therefore not been definitely established(30).

Hoskin et al. randomized 220 patients to receive either hypofractionated EBRT alone or hypofractionated EBRT plus HDR-BT(31). The EBRT group received 55 Gy in 20 fractions (EQD2 78 Gy), wheras the combined treatment group was given 35.75 Gy EBRT in 13 fractions plus 17 Gy HDR boost applied in two fractions with a single implant. The mean biochemical failure-free survival in the EBRT-BT arm was 5.1 versus 4.3 years in the EBRT only group (p=0.03) with no considerable increase of Grade 2 or greater toxicity, thus supporting a benefit of adding HDR-BT in patients with LAPC.

SURGICAL TREATMENT OF LAPC

No study has yet compared RP and EBRT with or without ADT for the treatment of LAPC, and high-quality evidence for surgical treatment of LAPC is lacking. A number of studies case series treated with RP have suggested good long-term CSS as well as OS. The absolute survival rates were similar to those of cohorts treated with RT + ADT and surpassing those of cohorts treated with RT alone(32-36). Carver et. al. reported in 2006 a 10-year CSS of 85% after surgery for 176 patients with clinical T3 tumors at their institution(36). In this study there were no survival advantage found when adjuvant ADT was administered. Ward et al. similarly reported a 10-year CSS of 90% in 842 patients with T3 disease who underwent RP at their institution(37). Some indirect evidence of the efficacy of prostatectomy in locally advanced disease does also come from the SPCG-4 study. After 23 years of follow up, radical prostatectomy is associated with a significantly reduced risk of cancer-specific survival (0.56; 95% CI 0.41-0.77) corresponding to a number needed to treat to prevent one death of 8(3). The study did admittedly assess surgery versus watchful waiting in a population of clinical T2 cancer, but did so in the pre-PSA era and the prevalence of postoperative pT3 was 47%(38).

There are no large randomized head-to-head comparisons of radiation treatment versus surgical treatment in prostate cancer overall. Observational comparisons of the two modalities in localized disease have consistently and rather strongly favored surgery(39-41), even after adjustment for known potential confounding factors. However, it cannot be precluded that residual confounding explains much or all of the difference.

THE EXTENT AND EFFECTS OF LYMPH NODE DISSECTION (LND)

The rationale for adding LND to the RP procedure are potentially two: staging and improved survival. For staging purposes it is generally accepted that the number of positive nodes, tumor volume within the node and capsular penetration of the node provides important information on prognosis that no other procedure can match. Such information may be valuable for the evaluation of postoperative disease status, which may be important for further treatment decisions such as the potential benefit of salvage radiotherapy.

Studies on the lymphatic drainage of the prostate indicate that apart from obturator and external iliac lymph node areas, the drainage also goes to internal iliac and pre-sacral areas(42-44). Limiting the LND to the obturator and external iliac vein areas would therefore limit the yield of lymph nodes and thereby also the staging accuracy(45,46). An extended LND (eLND) should therefore be performed including also nodes surrounding the internal iliac artery and the common iliac trunk up to the ureteric crossing. By doing this approximately 75% of the anatomical drainage areas of the prostate are covered(46). A systematical approach to the dissection in robot-assisted surgery was described by Feicke et. al. in an article/Surgery in Motion film sequence published in Eur. J. Urol. in 2009(47).

In addition to being a staging tool the LND may also have a therapeutic function for patients with limited lymph node engagement, for some maybe even curative. There are numerous observational studies evaluating the therapeutic effect of the PLND. In a study of 3463 consecutive patients at their institution who underwent radical prostatectomy and bilateral pelvic lymphadenectomy, Cheng et.al could show an equivalent 5- and 10-year CSS in patients with or without a single lymph node metastasis. The CSS rates decreased with an increasing number of positive nodes(45,48). Joslyn et al. also reported, in a search of 13,020 patients undergoing radical prostatectomy, with or without lymphadenectomy within the Surveillance, Epidemiology, and End Results Program database (SEERS) that the excision of at least 4 lymph nodes (node-positive and node-negative patients) had a higher 10-year CSS than those who did not undergo lymphadenectomy(49). The authors concluded that performing more extensive pelvic lymphadenectomy in patients undergoing radical prostatectomy could reduce the risk of PC-specific death in the long term. Nevertheless, making inference from observational studies on the benefits of a LND is, however, complex mainly for two reasons: confounding by indication and stage migration (also known as the Will Rogers Phenomenon(50). Given these two methodological issues in observational studies and the scarcity of experimental studies assessing the potential benefit of LNDs, evidence to support the performance of a LND is still weak. Nonetheless, in the latest update of the EAU guidelines for PC it is suggested that an extended pelvic lymph node dissection (eLND) should be performed in all patients with high-risk PC treated with radical prostatectomy(51).

MORBIDITY AFTER LYMPH NODE DISSECTION

The reported overall complication rate after eLND ranges from 2% to 22% in various contemporary reports (52-54) and extending the LND involves an increased risk for complications(52,54). The most common complication is lymphocele formation, ranging from 0% to 10.6% after eLND(53). The risk of lymphocele seems to correlate with extent of dissection; eLND has been associated with a two to threefold increase in risk as compared to limited PLND(52,54,55). Another complication closely related to lymphocele is edema of the lower extremity. This is a more rare complication less noted in most reports. However, an incidence of 4% was reported by Clark and co-workers in 2003 in 123 patients randomized to eLND on the right versus the left side of with a LND on the other side (54) and Stone and co-workers reported an incidence as high as 10% in a report from 1997 (56). In both these series the eLND included lymph nodes lateral to the external iliac artery in the specimen and it is likely that such extended dissection increases the risk of developing a post-operative lymphocele. Series including these lymph nodes also report a higher (up to 51%) overall rate of complications (57). Post-operative low molecular weight heparin (LMWH), to minimize the risk of thromboembolic complications, is also suggested to be injected into the upper body (above the diaphragm) instead of the abdomen to minimize the risk of lymphocele.

The incidence of thromboembolic complications, including both deep venous thrombosis and pulmonary embolism, has been lower than 1-5% in most reported series (53,58,59). Whereas a radical prostatectomy

increases the risk of thromboembolism moderately, the performance of a lymph-node dissection appears to strongly increase the risk (58,59). LMWH has been shown to reduce this risk (60) and is therefore recommended. Based on the time dynamics of postoperative thromboembolism (58) the prophylaxis should be administered for at least 4 weeks. Other rare, but documented, complications to eLND is nerve injury, especially of the obturator nerve, ureteral injury and injury to the iliac artery or vein. Most series report rates of less than one percent of these complications.

NEOADJUVANT HORMONAL TREATMENT PRIOR TO SURGERY FOR PROSTATE CANCER

Neoadjuvant hormonal therapy has been used prior to surgery in patients with prostate cancer. This strategy have been demonstrated to reduce intra-operative bleeding, facilitate surgery, reduce the risk of positive surgical margin(61,62), and lower the percentage of patients having extra capsular extension of the tumor (pT3) on final histo-pathological examination. Furthermore initial results suggested, that prolonged endocrine treatment > 3 months of endocrine therapy could reduce the risk of subsequent bio-chemical progression(63).

These finding led to a number of studies to evaluate the long-term effect of endocrine therapy as neo-adjuvant treatment prior to radical prostatectomy. The results of case series and randomized studies, however, came out negative, indicating that the results obtained in the early studies were likely artifacts induced by the tumor-cell-shrinking effect of endocrine therapy rather than a true impact on the prostate cancer(11,64) Therefore, there is at present no role for neo-adjuvant hormonal therapy prior to surgery for prostate cancer.

EBRT TO THE LYMPH NODES

Two randomized trials (GETUG-1 (65)and RTOG 94-13 (66) have evaluated the concept of radiation to the pelvic lymph nodes (whole pelvis radiotherapy, WPRT) vs. prostate only radiotherapy (PORT) both in conjunction with hormonal therapy. Half of the patients included in the GETUG-1 study had an estimated risk of lymph node metastasis less than fifteen percent based on nomograms whereas the RTOG study had 15 percent risk as an inclusion criterion. The four-armed RTOG 94-13 testing both PORT and WPRT as well as neoadjuvant or adjuvant hormone therapy could show a benefit for the group receiving neoadjuvant ADT and WPRT compared to PORT. The study was not powered enough to compare between single arms. The French study possibly included patients not in need of lymph node treatment and could not demonstrate any benefit.

Data from retrospective studies support lymph node irradiation(67,68), but other studies have reported null findings (69) and yet others that irradiation to the lymph-node entails no benefit when the dose to the prostate is escalated(22). All studies used a four-field box radiation technique to the pelvis and the doses to the prostate varied but were generally low, up to 70 Gy. Higher doses to the prostate would allow the potential benefits of lymph node irradiation to show because fewer recurrences would be local.

Side effects of the increased field size include both Genitourinary (GU) and Gastrointestinal (GI) toxicity. In the RTOG study (66) the rate of grade 2 or higher acute toxicity was significantly increased for both GU 30% (WPRT) vs. 22% (PORT) and GI 47% (WPRT) vs. 20% (PORT). Late toxicities were also increased with 4.3% late GI toxicity grade 3 when comparing WPRT with PORT. In contrast, the French study did not report any differences depending on field size. Modern radiotherapy studies using Intensity Modulated Radio Therapy (IMRT) evaluating side-effects report increased acute gastrointestinal toxicity but very modest late side effects (grade 3, 1.3%; grade 2, 6,5%)(70). The irradiated bowel volume is of high importance. With known pelvic lymph-node metastases and boost to positive nodes the acute toxicity can be kept low with only grade 2 gastrointestinal toxicity and 6 % grade 3 genitourinary toxicity(71) A study by Deville (72) could only demonstrate acute GI toxicity to be elevated in the pelvic irradiation arm compared to prostate only irradiation, and there were no differences in late toxicity.

QOL AFTER SURGERY AND RADIATION TREATMENT FOR PROSTATE CANCER

In the recent update of SPCG-4 trial, comparing radical prostatectomy with watchful waiting, a similar proportion of men in both groups reported high quality of life at 12 years follow up(73). Nevertheless, patients in the radical prostatectomy group were more likely to experience treatment-related urinary leakage and erectile dysfunction. In the watchful waiting group, the quality-of-life impairment was mainly due to disease progression and hormone treatment. In a recent population based analysis from Norway it was found that after curative prostate cancer treatments, irritative-obstructive urinary symptoms was associated with low global quality of life while erectile function was not(74). Not only do these results highlight the importance of selecting proper tools for quality of life analysis, they also demonstrate that patients without primary curative treatment will develop high level of urinary and sexual adverse events and subsequently decreased quality of life. The more aggressive the disease, the more likely the patients are to develop quality-of-life impairing adverse events even without treatments.

Generally, in patients with LAPC, nerve-sparing surgery may not be the primary aim and thus ED will develop in the majority of the patients. Instead, close attention should be paid to preservation of continence despite wide excision of the prostate to maximize radicality. In a series of 288 high-risk patients, 92% continence rate was observed after 10 years(75). In another series of 56 high risk patients, generic quality was considered good or better by 81% of the patients postoperatively while 58% reported using 0-1 pads per day(76). In an exploratory analysis of CaPSURE database, surgical treatment of LAPC caused a significant decrease of urinary and sexual function while both physical and mental domains of SF-36 were less affected(77). Generally, data are sparse and published cohorts, besides not being randomized, are often heterogeneous and lack use of validated questionnaires and longitudinal follow-up.

ADJUVANT AND SALVAGE RADIATION THERAPY

There are three randomized controlled trials of adjuvant radiotherapy after radical prostatectomy. EORTC 22911 trial(78), randomized 1005 patient to either adjuvant radiotherapy or salvage therapy with hormones or radiotherapy at relapse. The dose given to the prostate bed was 60 Gy. A pronounced difference in favor of adjuvant therapy is seen for biochemical freedom from relapse with a hazard ratio of 0,48 (0,37-0,62). However, this is not translated into a difference in clinical progression-free survival or overall survival at 10 years. The SWOG 8794 (79) trial also randomized pT3 patients to observation or adjuvant radiotherapy 60-64 Gy to the prostate fossa and periprostatic tissue. Again there was an advantage for the adjuvant group regarding biochemical relapse, HR 0, 43 95%CI (0, 31-0, 58) in addition there was a survival benefit HR 0.72; 95% CI 0.55, 0.96; p = 0.023). The third study from the German group, was not powered to evaluate survival but overall the results points in the same direction with a hazard ratio 0, 53 95%CI (0, 37-0, 79) for biochemical progression. In the two first studies patients were included with a PSA ≥0.2, which by today's standards would be regarded as a salvage situation. In the German study all patients with pT3 tumors were included but if they had detectable PSA at eight weeks they were excluded. None of these studies compared adjuvant to salvage radiotherapy since the control arm did not stipulate what treatment to add at progression or at what PSA level, this question remains open.

There are several retrospective studies of salvage therapy but no randomized trials. King (80) systematically reviewed 41 studies where the selection criteria included length of follow-up, pre-radiotherapy PSA, radiotherapy dose and surgical pathological factors. Assuming the microscopic tumor burden to be proportional to the PSA level and that the tumor control probability also depends on dose he made a model to fit the data. The model indicated an average loss of relapse free survival of 2.6% for each rise in PSA of 0.1ng/ml. Initiating radiotherapy at a PSA of 0.2ng/ml or less would lead to a relapse free survival of 64% or better. Radiation dose was an independent predictor of relapse. Doses ranged from 60 to 74 Gy, and data indicated an association between dose and tumor control.

In a large observational study by Abdollah et al., adjuvant radiotherapy seemed to improve survival among men with low-volume nodal disease up to four positive lymph nodes(81).

There are three ongoing open randomized trials evaluating the timing of salvage radiotherapy, RADICALS(82), GETUG-17 and RAVES from the Trans Tasman Radiation Oncology Group. Unfortunately, results are not expected in the near future and while awaiting their data, each patient need to be individually evaluated in the choice between immediate adjuvant and deferred salvage therapy.

STUDY AIM AND RATIONALE

This prospective, open randomized phase III trial seeks to investigate whether radical prostatectomy with or without adjuvant/salvage external radiation improves prostate-cancer specific survival in comparison with primary radiation treatment and hormonal treatment among patients diagnosed with locally advanced (T3) prostate cancer. Untreated or conservatively treated locally advanced prostate cancer is associated with high mortality(16). Whereas there is evidence that surgery can cure localized prostate cancer, there are no clinical trials of multi-modal treatment of locally advanced prostate cancer that includes surgical removal of the prostate.

One potential advantage of adding prostatectomy to the treatment of LAPC is that removing the prostate enables a full pathological assessment of the tumor characteristics and thus a better estimation of the risk of recurrence. Surgical treatment could thus reduce the numbers of patients in need of second-line treatment, and thus potentially improve quality of life after treatment. In addition, evidence indicate that residual cancer in the prostate occurs in 25% after radiation treatment (27) and surgical removal of the prostate may improve survival beyond what can be achieved by radiation and ADT. A randomized clinical trial comparing two multimodal treatment regimens of which one includes a radical prostatectomy is therefore strongly merited.

STUDY DESIGN

This is a prospective, multi-center, open randomized phase III trial complying with international guidelines for the treatment of locally advanced prostate adenocarcinoma. Subjects will be randomized to either conventional treatment (radiotherapy+ ADT) or intervention treatment (i.e. surgical prostatectomy+ radiotherapy if necessary). Each subject will follow the guidelines regarding the timing of treatment, additional postoperative radiotherapy, the dosing of radiotherapy, and adjuvant treatment such as androgen deprivation therapy. All surgical patients will be managed according to standard operating procedures at each local operating theatre. The total study duration will be 13 years. Each subject will be followed up for 10 years. The enrolment period extend to three years. The amount of visits sums to 14 times. The planned start of screening is March 2014, planned end of enrolment March 2017. The planned end of follow up, start of data analysis and report writing: 2027-2028.

STUDY OBJECTIVES

PRIMARY OBJECTIVE

The main purpose of this study is to evaluate whether cause-specific survival is better after primary radical prostatectomy, with the addition of adjuvant or salvage radiotherapy and endocrine treatment if indicated, than after primary radiation and endocrine treatment.

SECONDARY OBJECTIVES

To compare metastasis-free survival, overall survival, quality of life and health-services requirements (measured has hospitalization rates and analgesic consumption) between the two intervention arms.

ENDPOINTS

PRIMARY ENDPOINT

Cause-specific survival (CSS). Mortality and mortality causes will be ascertained from the nationwide Cause-of-Death Register.

SECONDARY ENDPOINTS

- Metastasis free survival
- Overall survival
- Quality-of-life, assessed through repeated questionnaires
- Time to Castration-Resistant Prostate Cancer (ascertained at follow-up visits)
- Time to biochemical progression (ascertained at follow-up visits)
- Adverse events
- Annual DDD of analgesics, prescription databases
- Annual number of days of hospitalization (patient registers)
- Cardiovascular disease (patient register)

PLAN OF STUDY VISITS

The plan of study visits is schematically depicted on page 24. Case Report Forms (CRFs) are web-based (eCRFs) as are the quality-of-life questionnaires, but paper questionnaires should be available for patients that prefer or have limited access to the internet. Apart from the randomized allocation of treatment, the documentation in eCRFs, and the quality-of-life questionnaires, the study does not entail examinations or visits outside standard clinical routine.

SCREENING, VISIT 1

The first assessment of eligibility is done either by a urologist or an oncologist. After assessment of eligibility for surgery/radiotherapy, the urologist refers to an oncologist, or vice versa, for second opinion and assessment of eligibility for the alternative treatment. It is preferable and beneficial for the inclusion rate if screening visit one and two are combined into one single coordinated visit. All subjects are logged in a ‘screening visits log’ in order to calculate screening failures and the reasons for failure.

SCREENING, VISIT 2

Before the second screening visit, a study nurse may give further study information to the patient. If the patient is considered eligible for either treatment and is willing to participate, the informed consent is signed.

INCLUSION AND RANDOMIZATION

Inclusion and randomization is done as soon as possible after the informed consent is signed, preferably within 24 hours.

1. The patient completes the **baseline quality-of-life questionnaire** (**QoL 0**).
2. The **inclusion form** is filled in to confirm that the inclusion criteria are met
3. The patient is **randomized to treatment A or B**. The randomization will be executed in strict sequence as their eligibility is confirmed. **The date of randomization marks day 0 of follow up.**
4. Clinical characteristics are documented in **eCRF #1**.
5. Anytime before surgery or neoadjuvant hormone treatment is started, blood and urine samples (50 ml each) shall be collected (see separate instructions).

TREATMENT PHASE

If the patient is randomized to radiotherapy, endocrine therapy is initiated as soon as possible. Otherwise, surgery is scheduled with high priority.

- Surgery (**intervention)** arm (A): Perioperative data are registered in **eCRF #2** at discharge from postoperative care. The remaining postoperative data will be added in **eCRF #3** after the first follow-up visit at 6 to 12 weeks postoperatively. Whenever the patient is subjected to postoperative radiotherapy, **eCRF Postop RT is completed**.
- Radiotherapy (**reference**) arm (B): Patients in the radiotherapy group will have frequent visits for their fractioned treatment during a three-month period. Therapy data will be summarized in **eCRF #4** by the end of the treatment period around 6 months after randomization.

Serious adverse events during treatment phase (0 to 12 months after randomization) leading to hospitalization are documented in a specific CRF for SAEs (**eCRF SAE**)

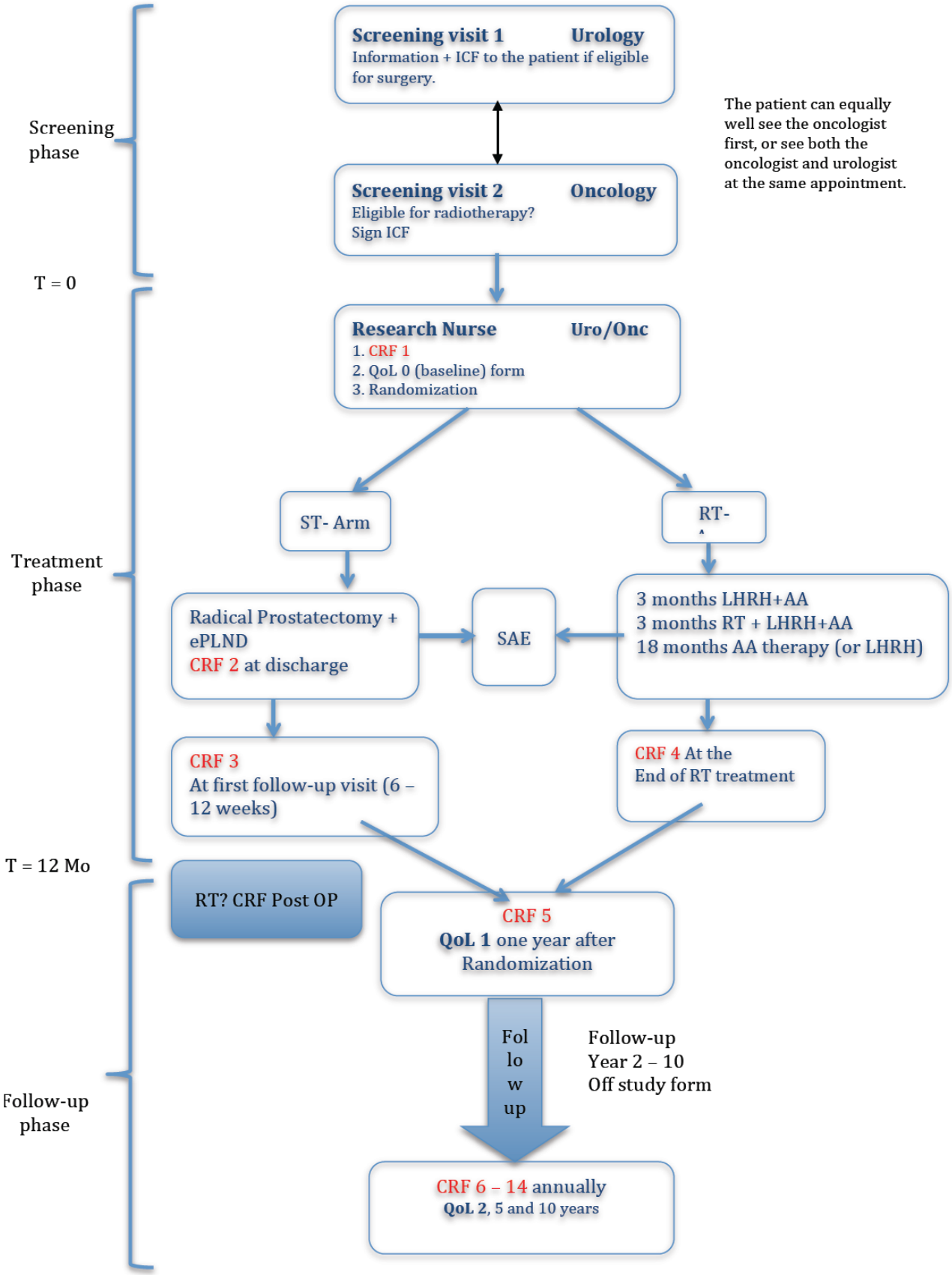
FOLLOW-UP PHASE

The first follow-up visit/contact common for both treatment arms is at 12 months after randomization. The visit/contact follows standard clinical routine. PSA is measured. **eCRF #5** is completed. Patients respond to the one-year QoL questionnaire (QoL 1).

Patients are followed up every 6 months during the second year after randomization, and annually thereafter. **eCRF #5** is then completed annually. Evaluation always includes PSA testing to assess biochemical progression. Before completing **eCRFs #5 at 5 and 10 years after randomization**, a bone scan (or other routinely used imaging method for detection of bone metastases) is performed for those with a PSA that has risen above PSA nadir + 2.0 ng/mL.

An off-study form is completed whenever a patient leaves follow up. For patients dying during follow up, an off-study form is only necessary if the cause of death cannot validly be ascertained through register-based follow up.

SPCG-15 STUDY FLOW CHART



ENROLMENT OF PATIENTS

Participating centers shall aim to include all patients who fulfill the requirements for randomization. No randomization shall be made until all inclusion criteria are met. The total number of patients to be randomized is 1,200.

INCLUSION CRITERIA

Subject will be included in the study if he meets ALL of the following inclusion criteria:

1. Age ≤75, at the time of randomization
2. Newly diagnosed prostatic adenocarcinoma morphologically confirmed and untreated
3. The transrectal ultrasound (TRUS-guided) systematic biopsy with at least 10 cores or alternatively fewer but MR/TRUS fusion guided biopsies.
4. The general condition and mental status of patients shall permit observation in accordance with the study protocol
5. Tumor stage (T, M, N): *T3* stage (as indicated by digital rectal examination or MR imaging or other validated imaging technique). *T4 tumors* can be included if considered resectable/treatable on MR imaging.
   Significant extra-capsular tumor extension (rare, but is also accepted for inclusion)
   M0 (no sign of distant metastases) confirmed by bone scan or MRT of axial skeleton and thorax
   N0 stage, defined in accordance to the RECIST guidelines (83) as no sign of macroscopic retroperitoneal lymph-node metastases ≥1.5 cm (short axis) on CT scan, PET-CT, or MRT or more than one suspected lymph-node metastases.
   Presence of Gleason grade pattern 4 or 5
6. Signed Informed consent.

EXCLUSION CRITERIA

If any of the following criteria are met, the subject must NOT be included in this trial

1. Patients with a PSA value of > 100 ng/mL
2. Any medical condition that, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

Patients with contraindications for either prostatectomy or radiotherapy to the prostate are not eligible for the study. Most contraindications for these treatments are relative, but in general, radiotherapy may be precluded among patients with

- Anorectal disease, such as fistulae, Crohn's disease, and ulcerative colitis,
- Significant obstructive lower urinary tract symptoms,
- Proximal stricture of the urethrae,
- Severe neurogenic bladder dysfunction,
- Enlarged prostate beyond 70-90 ml,
- Previous radiotherapy to the pelvic region.

On the other hand, surgery may be precluded among patients with

- Massive local tumor progression, particularly in the apical region.
- Massive abdominal obesity,
- Contraindications to anesthesia

PARTICIPANTS STOPPING AND WITHDRAWAL CRITERIA

WITHDRAWAL, SUBJECTS DECISION

All patients are free to discontinue their study participation at any time during the study for whatever reason without their decision affecting their future care. If possible, the reasons for withdrawal should be documented in the off-study form.

To allow for intention-to-treat analysis, all randomized patients will be followed up for the primary endpoint, whether or not they complete the scheduled treatment. The patient should be observed for at least 10 years after randomization. However, patients prematurely discontinuing their study participation will have their data deleted upon their request.

WITHDRAWAL, INVESTIGATORS DECISION

Once a subject has been included in the study, the investigator can if he/she thinks it´s necessary, exclude patient from study participation out of e.g. safety reasons (e.g. SAE or another inter-current illness violating the conditions of the study). Other reasons, than safety, for discontinuing patients from study could be the following:

1 Subject not willing to cooperate
2 Subjects lost to follow-up
3 Non compliance of patient

Whenever such decision is made full assessment of the patient should be carried out (if possible) according to this protocol. The discontinuation should be documented in the patient´s medical record and in patient's eCRF. The documentation shall consist of: date and time of the withdrawal and the reasons for withdrawal. If a subject discontinues his participation in the study, the subject number cannot be reused

INTERVENTION

EXPERIMENTAL STUDY ARM

Open retro-pubic or minimally invasive radical prostatectomy. Concurrent extended pelvic lymph-node dissection is strongly recommended in the protocol but may be omitted if local guidelines at participating sites recommend otherwise.

The extended lymph-node dissection shall be done as described by Heidenreich A et al (52) and includes the obturator fossa, the external and internal iliac nodes, and common iliac nodes up to the ureteric crossing. For handling of surgical biopsy specimen, see Appendix A: Standard Operating Procedure (SOP A) Specimen Handling of pathological Specimen.

The experimental study arm includes immediate postoperative radiation to the prostate bed in selected clinical situations depending on the likelihood of remaining local disease after surgery (see flow chart below). Postoperative radiotherapy includes 18 months of treatment with Bicalutamide 150 mg daily.

In general oncology, adjuvant treatment is a treatment given after the primary treatment to lower the risk of tumor recurrence (www.cancer.gov). This inherently implies no signs of remaining disease. Salvage treatment, on the other hand, is defined as treatment given after the cancer has not responded to other treatments. In prostate cancer, the demarcation between adjuvant and salvage has been drawn a certain time after the primary treatment, for example 6 months. To avoid misunderstanding, we will consistently use the words immediate and deferred RT.

The algorithms for immediate and deferred postoperative radiotherapy are depicted separately for pT2 and pT3 tumors in the Figures 1 and 2 below. It should be noted that positive surgical margins range from focal/clinically insignificant to multifocal and/or extensive. Moreover, the prognostic implications of lymph-node-positive disease vary greatly with the number and percentage of affected lymph nodes, and postoperative PSA levels can range from barely measurable to high. Therefore, there can be no firm guidelines for postoperative radiotherapy. **The flow chart therefore suggests what we consider the most likely regimen in each scenario, but the treating clinician should decide whether or not the suggestions are applicable in each case, preferably at multidisciplinary therapy conferences**. Deviance from the suggested regimens, however, shall be recorded in the case report forms.

The postoperative radiotherapy protocol is specified in Appendix B.

REFERENCE STUDY ARM (NON-EXPERIMENTAL)

Regardless of type of radiation treatment, patients will be prescribed 3 months neoadjuvant and 3 months adjuvant maximal androgen blockade (LHRH + antiandrogen 150 mg x 1) followed by 18 months antiandrogen (bicalutamide 150 mg. x 1) treatment (or, alternatively, 18 months of LHRH if single treatment with bicalutamide is not compatible with local treatment standards). Prolonged administration of AA or LHRH is accepted for up to 30 months after the last radiation dose is acceptable if required by local guidelines. Prophylactic radiation to the mammary glands should be done to reduce painful gynecomastia during AA treatment. The RT in the non-experimental arm is specified in the Appendix B

RANDOMIZATION

Patients who meet all inclusion criteria and none of exclusion criteria after screening will be included in the study and randomized to one of the two parallel arms in a 1:1 fashion. Patients will be entered into the study in a strict sequence as their ability for enrolment is confirmed. The subjects are either randomized in to the experimental arm: radical prostatectomy or to the reference arm: radiotherapy. The randomization is stratified by site in order to balance the allocation at each center. The actual randomization is web-based and is performed in the eCRF database after checking inclusion and exclusion criteria.

ETHICAL CONSIDERATIONS AND INSURANCE

This study will be conducted according to ICH-GCP, national law and guidelines and the Helsinki declaration. Before patient inclusion starts, this study protocol will be approved by an ethical review board in each country.

There is no specific insurance for participating subjects, who are covered by the regular health-care insurance plan in their respective country.

STUDY MANAGEMENT

MONITORING

A monitor will check the accuracy of the randomization procedure and check that personnel is familiar with the concept of data recording and reporting according to ICH-GCP in medical records and in eCRF. Monitor will visit the site during the study regularly to conduct source data verification, and also perform a study close out visit after the study has ended to close the site and gather essential documents to sponsor.

Data verification will be performed on 10% of patients after the entry of at least 10 patients. The site file will also be reviewed. We plan to perform regular monitoring visits once a year. The frequency of visits may increase if any specific issues arise. The institution is responsible for ensuring that all relevant materials are available for review including the trial master file, case report forms and patient source documents.

ARCHIVING

The investigator will keep all physical records from the study for 10 years after the final clinical study report under safe conditions.

DATA MANAGEMENT

Data management based on ICH-GCP refers to the activities defined to achieve safe routines to efficiently enter patient information into a database, avoiding errors. The database, data entry screens, and program will be designed in accordance with the clinical trial protocol.

CASE REPORT FORMS

Electronic Case report Forms are produced by Christoffer Lagerros, data engineer. All data capture will be performed using electronic Case Report Forms (eCRF).

ENTERING OF DATA eCRFs

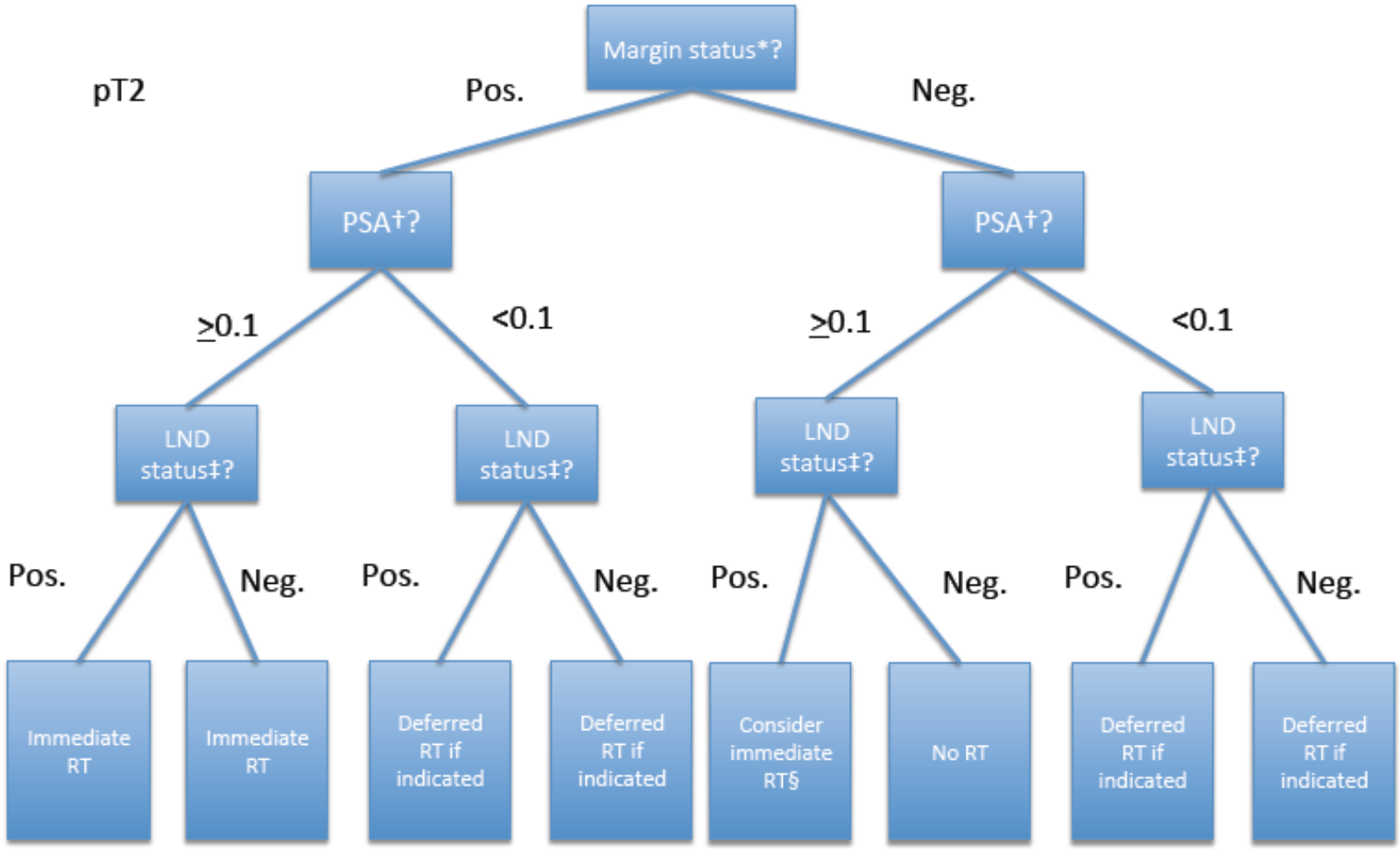
Entering data into the eCRF will be performed by study nurses and investigators at each site. This includes internal quality checks to identify data that are inconsistent, incomplete or inaccurate. Clinical data will be entered directly from the source documents.

DATA ANALYSIS

Data will be analyzed according to the intention-to-treat principle. The exposure groups will be coded to enable blinded statistical analysis.

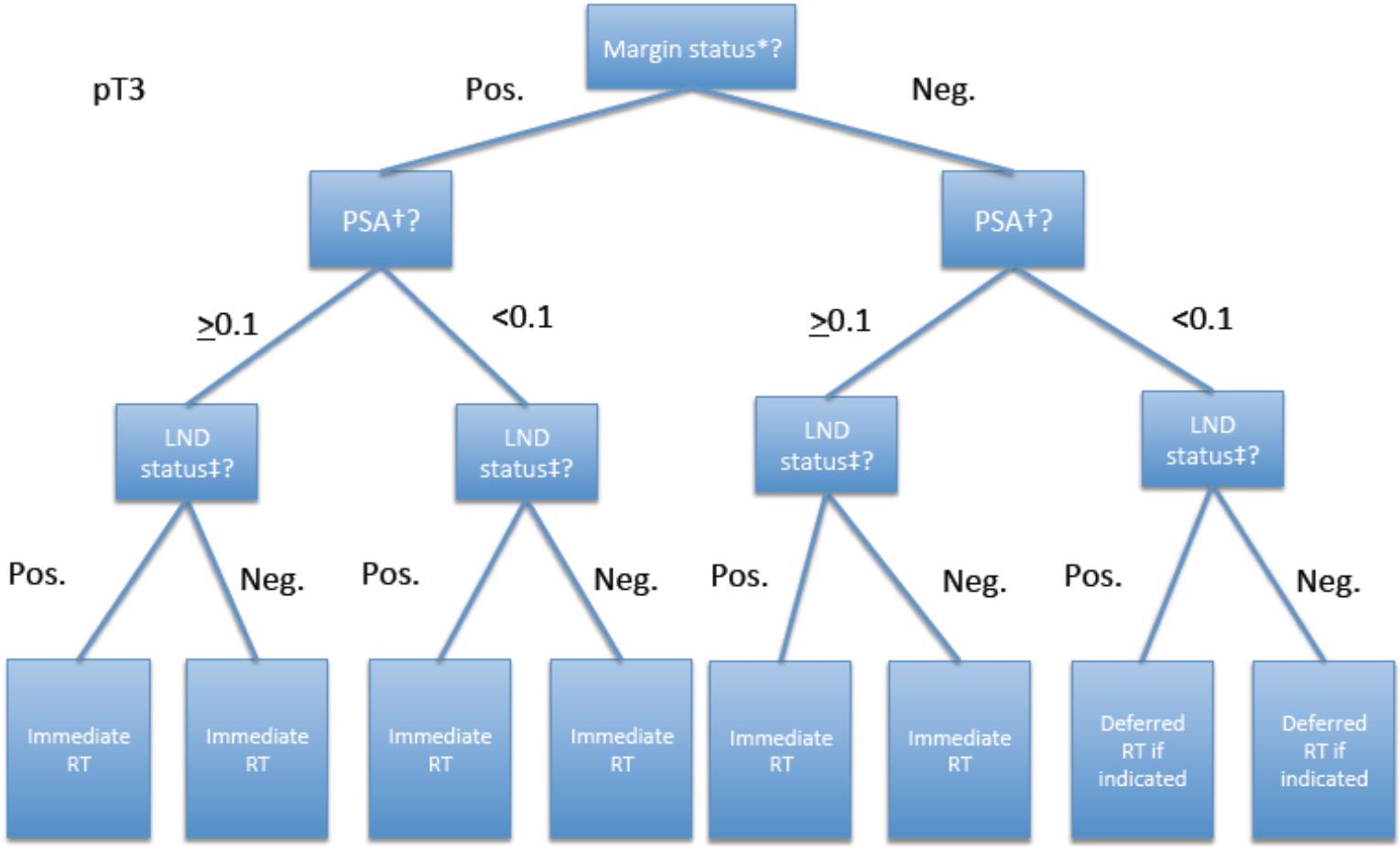
Planned further subgroup analyses: Since low-differentiated tumor progress to metastasized disease at an earlier stage, stratification by Gleason-score category and risk category could reveal heterogeneity between different risk groups. Also, provisional sub-group analysis by type of radiotherapy, type of surgery, PSA-level category and T staging method (MR versus digital rectal examination) is planned.

Figure 1. The algorithm for postoperative RT among patients with pT2 prostate cancer.



*A positive margin is considered clinically significant when the length exceeds 3 mm.(84)
† Postoperative PSA > 2 ng/ml does probably reflect non-localized remaining disease, but we are unaware of any consensus on an upper PSA limit
‡ More than 2-4 cancer-positive lymph nodes does more likely reflect disseminated disease (81).
§If PSA level is low and number of affected lymph nodes is low, RT may be an option in this scenario

Figure 2. The algorithm for postoperative RT among patients with pT3 prostate cancer.



* A positive margin is considered clinically significant when the length exceeds 3 mm.(84)
†Postoperative PSA > 2 ng/ml does probably reflect non-localized remaining disease, but we are unaware of any consensus on an upper PSA limit
‡ More than 2-4 cancer-positive lymph nodes does more likely reflect disseminated disease (81).

STATISTICS

SAMPLE SIZE CALCULATION

Assumptions Outcome: Accrual of study subjects: 3 years. Follow up: 10 years Level of confidence (α): 0.05 With 600+600 and 10 years of follow up, we will have a 90% power to significantly detect (using logrank test) the following absolute risk differences under different scenarios:

Percent risk of outcome in experimental arm	Percent risk of outcome in control arm
10%	12.5%
20%	24%
30%	35%
40%	46%

ALTERNATIVE NON-INFERIORITY TEST

If there is truly no difference between standard and new treatments, then 1120 patients are required to be 90% sure that the upper limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will exclude a difference in favor of the standard treatment of more than 7%.

PUBLICATION POLICIES

The current protocol is registered on www.clinicaltrials.gov prior to commencement of the study in accordance with the guidelines of The International Committee of Medical Journal Editors (ICMJE).
The results from this study will be published irrespective of them being positive or negative. Co-authorship will be granted in accordance with the Uniform Requirements for Manuscript Submitted to Biomedical Journals (URMs; http://www.icmje.org/recommendations/browse/about-the-recommendations/history-of-the-recommendations.html) provided response to manuscript drafts and correspondence in a timely manner. The opportunity to co-author manuscripts will be offered all members of the Trial Management Group (listed above in the Contact Information) and one representative from each participating center contributing with more than 5% of evaluable patients (2 representatives if contributing with more than 30%), and to the statistician who has contributed to collecting/validating and analyzing data, and other persons who have contributed substantially to the implementation and/or evaluation of the trial. Centers contributing with less than 5% of evaluable patients may combine their contribution with another center and share co-authorship alternating. Investigators at participating centers who do not qualify as co-authors will be listed as non-author contributors.

The principal investigator is responsible for carrying out a draft manuscript for discussion among the co-authors. After the results regarding the primary and secondary endpoints of the whole study cohort have been published, investigators are allowed to publish data regarding the primary and secondary endpoints from their own institution if the manuscript has been shown to the Trial Management Group before submission.

The results from different centers will be analyzed together and published as soon as possible. Individual groups/clinicians must not publish data concerning their patients that are directly relevant to questions posed by the study until the Trial Management Group has published its report. The Trial Management Group will form the basis of the Writing Committee and will advise on the nature of all publications. Studies using SPCG-15 data to evaluate endpoints other than those specified in this protocol can be published by the participating institution(s) after approval from the Trial Management Group.

DEFINITION OF CLINICAL EVENTS AND SUGGESTED TREATMENT

In this study, urologists do follow up of operated patients, whereas oncologists do follow up of patients subjected to radiotherapy. Given that modern medical treatment of advanced prostate cancer prolongs survival, the differential follow up is a potential source of bias in the comparison of survival. Therefore, to standardize decision making, **all patients with suspected biochemical progression or CRPC shall be discussed in multidisciplinary therapy conferences involving urologists as well as oncologists.**

BIOCHEMICAL PROGRESSION

Radiotherapy arm: Biochemical progression in the radiotherapy arm will use the *Phoenix definition of progression*.(64)(No biological evidence of disease is defined as the serum PSA level lower than the lowest serum PSA level during follow-up plus 2.0 ng/mL according to ASTRO Phoenix consensus definition. Experimental arm: Biochemical progression in the experimental/intervention arm is defined as a rising PSA level surpassing 0.2 ng/mL.

START OF ANTI-ANDROGEN TREATMENT

Anti-androgen treatment should be initiated among men with a PSA-doubling time of <12months when the PSA level surpasses 10 ng/mL, or upon symptoms or other clinical signs of disease progression. AA treatment includes continuous treatment with Bicalutamide 150 mg daily per os after initial prophylactic breast irradiation.

CASTRATION-RESISTANT PROSTATE CANCER (CRPC)

Definition of castration-resistant prostate cancer is based on EAU guidelines as follows: Castrate levels of serum testosterone (<1.7nM). Three consecutive PSA rises at least 1 week apart, resulting in two 50% increases over the nadir, with a PSA > 2 ng/mL.

SECOND-LINE THERAPY

Second line therapy at the time of progression will be started at the discretion of the treating clinician and will follow the local practice. Decisions should, however, be made at multidisciplinary therapy conferences. Effort should be put into classifying the progression as local or distant before starting second line therapy since one primary endpoint will be metastasis free survival.

DISTANT METASTASES

After each follow-up visit, the patient is categorized as having

a) No suspected distant metastasis
b) Suspected distant metastasis
c) Confirmed distant metastasis

QUALITY OF LIFE

Quality of life will be measured on four different axes (see separate Quality of Life questionnaire):

a) Urinary health
b) Sexual health
c) Bowel health
d) General psychological health

CAUSE OF DEATH

The following classification of deaths shall be attempted:

a) Death from prostate cancer
b) Death from other causes but with recurrent or metastatic prostate cancer
c) Dead from other causes with no evidence of recurrent prostate cancer

SAFETY REPORTING

An adverse event is any untoward medical occurrence in a patient or to whom a medical product or surgical procedure has been administered, including occurrences that are not necessarily caused by or related to that product.
An adverse reaction is any untoward or unintended response to an investigational medical product related to any dose administered.
A serious adverse event (SAE) is an adverse event or adverse reaction that fulfills any of the following criteria:

- Results in death
- Is life-threatening
- Requires hospitalization or prolonging of existing hospitalization
- Results in persistent or significant disability or incapacity

Apart from assessing chronic side effects in the quality-of-life questionnaire, we will report serious adverse events during the treatment phase of the study (0 to 12 months) by **recording any adverse event possibly associated with per-protocol treatment requiring hospitalization on a specific SAE CRF form.** To validate this information, we will also use patient register information from inpatient care to assess frequency, duration, and causes of hospitalizations.

ASSESSMENT OF INTENSITY

Each AE is to be classified by the investigator as mild, moderate or severe.
Mild: Acceptable. The subject is awareness of symptoms or signs, but they are easy tolerated.
Moderate: Disturbing. The AE is discomfort enough to interfere with usual daily activity.
Severe: Unacceptable. The subject is incapacity to work or to do usual daily activities.

ASSESSMENT OF CAUSALITY

Unlikely: The event is most likely related to etiology other than the treatment under study.
Possible: A causal relationship is conceivable and cannot be dismissed.
Probably: Good reason and sufficient documentation to assume a causal relationship.

The investigator responsible for the care of the patient will assess the seriousness, the causality, and the expectedness of the event and report SAEs to the coordinating investigator within seven days. The coordinating investigator will review all SAE reports received and are responsible for reporting to the research ethics committee as appropriate. The coordinating investigator will also keep investigators informed of any safety issues that arise during the course of the trial. Non-serious adverse events will be reported in the final study report.

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APPENDIX A: STANDARD OPERATING PROCEDURE (SOP A) SPECIMEN

HANDLING OF RADICAL PROSTATECTOMY SPECIMEN

RP specimen handling and reporting should be standardized to an extent that would serve the purposes of the study and minimize the need for re-evaluation of the histological glass slides afterwards.

In order to achieve modern standards of collecting biospecimens for further research use, the RP specimen should be transferred immediately to pathology department with shortest possible delay.

MACROSCOPIC INSPECTION PROSTATE

After macroscopic inspection, please

a) Document the weight of the prostate and ink paint of the prostate and base of seminal vesicles. This means that the left and right side should be inked with different colors, (additional ink colors can be used for example in the anterior surface and in the surface facing bladder neck.)
b) As appropriate, retrieve biobanking samples without compromising the diagnostics
c) Dissect apex basis of the prostate using the cone method,(85) containing at least the base of the seminal vesicles, perpendicular to the urethra and section then sagitally parallel to the urethra. The remaining central part should be sectioned transversally, and preferably whole mounted to get the best discretion for positive surgical margins (PSM) and extra-prostatic extension (EPE). For the same reason, the entire prostate should be embedded.

The Gleason-grade evaluation shall be done in accordance with the guidelines published in(86-88). If an ePLND has been done, reporting the number of positive lymph nodes and the number of lymph nodes evaluated is essential. Side-specific report on lymph-node data is recommended but not compulsory.
The anatomy of the prostate capsule is not well defined, and histologically there is no continuous capsule surrounding the glandular structures. The discovery of cancer cells outside the contour of the prostate gland should therefore be reported as EPE instead of extra-capsular extension. The apical border of the prostatectomy specimen is more complex in terms of EPE as the glandular structures are mixed with the skeletal muscles of the urogenital diaphragm, and no identifiable capsule exists. EPE can be assessed as cancer in the inked apical margin. In practice, this is equal to positive surgical margin (PSM). Consensus recommendations state that EPE and its location should always be reported, either focal or non-focal (established, extensive). There are no objective criteria for the designation of the degree of EPE.

PSM is caused either by a true extension of cancer beyond the resection line to the extra-prostatic tissue or by an iatrogenic incision of capsule/intraprostatic tumor (i.e. pT2+ disease). The latter should not be interpreted as EPE. The predictive significance of PSM for disease recurrence is evident,(84,89-92) but there is only limited data available on the significance of PSM in predicting cancer-specific mortality.(91,92) Possible intraoperative violation to prostatic capsule should be recognized while handling the prostatectomy specimen. Consensus recommendations suggest that the extent of PSM should be indicated as focal or multifocal in nature. In addition, the anatomic location should be reported, as well as the length of PSM in millimeters. Finally, the pathology report should note whether PSM is in an area of EPE or if any possible non-repaired intra-prostatic and intra-tumor incision exists.

The pathological TNM stage of the tumor is an independent predictive factor.(16,93,94) Therefore, it should be included in the pathology report of prostatectomy specimens and the most recent version of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) staging system should be used. In the current staging system, all cancers with EPE, regardless of location or extent, are staged as pT3a. There is, however, validated evidence on prognostic significance of EPE subdivision into

focal versus non-focal,(95,96) although the assessment of focal versus non-focal/extensive EPE per se lacks uniform consensus criteria.

Cancer invading the muscle wall of the seminal vesicle is considered as stage pT3b cancer. However, intra-prostatic vesicular structures should not be taken into account while determining seminal vesicle invasion (SVI). Thus, SVI is always by definition EPE.

TABLE 1

Minimum requirements and suggested additional information for radical prostatectomy pathology report

Minimum standard requirements for reporting cancer in a prostatectomy specimen	**Recommended additional information**
1. *Histological type of carcinoma*	
2. *Histological grade* - primary Gleason pattern - secondary Gleason pattern - total Gleason score	 - individual grading of separate significant cancer foci - tertiary pattern and its proportion, modified Gleason score - percentage of Gleason 4-5 cancer
3. *Surgical margin status* - location of PSM	- extent of PSM: focal, multifocal - length of PSM in millimeters - PSM in the area of surgical incision (pT2+) or EPE
4. *EPE* - focal - non-focal (extensive, established)	- site of EPE (basal, apical, lateral)
5. *Tumor quantization* - proportion of prostate involved by cancer	 - prostate size and weight - dimensions (diameter in mm) and location of the dominant cancer nodule
6. *Seminal vesicle invasion*	
7. *Pathological stage, pTNM* - notification of the version of AJCC/UICC staging system - pT = primary tumor -pN = regional lymph nodes, specify the number of positive nodes - pM = distant metastasis	 - number of total lymph nodes examined - diameter of largest lymph node metastasis Other pathologic findings (if present): - perineural invasion - treatment effect on carcinoma - presence of high-grade PIN - inflammation

APPENDIX B: RADIATION TREATMENT

This protocol allows for the following treatment modality options:

- External beam radiotherapy (EBRT) only
- EBRT and high-dose rate (HDR) brachytherapy (BT) combined

RADIOTHERAPY PROTOCOL FOR EXTERNAL BEAM RADIOTHERAPY (EBRT**)**

FACILITY AND EQUIPMENT

- The treatment centre shall have equipment for and previous experience with Intensity Modulated Radiotherapy (IMRT) and/or Volumetric Modulated Arc Therapy (VMAT).
- The make and version of the particular treatment equipment shall be reported to the QA-centre.

PATIENT POSITIONING AND SIMULATION

- Pre-treatment preparation
    - The patient shall be immobilized with at least leg fixation.
    - Among patients treated with EBRT, the patient reference coordinate system shall be defined by using implanted fiducial markers in the prostate.
    - In patients with rectum diameter > 4 cm at the level of the prostate due to faeces or flatus, a new planning CT/MR should be considered after emptying the rectum.
    - The bladder filling protocol should be according to local guidelines with the aim to keep the bladder comfortably filled during the whole RT series with a volume as close as possible to the filling during the treatment planning CT/MR.

- Pre-treatment imaging
    - For structure delineation, CT and (preferably MR imaging) shall be performed with the patient in the treatment position in his fixation device on a flat tabletop.
    - The CT (and MR scanning) shall be performed from L3 to the lower border of trochanter minor.
    - Slice-thickness shall be maximum 3 mm.
    - Treatment planning dose calculations shall be performed based on CT but can also be based on MRI if this technique is implemented and verified at the particular treatment centre. In case MRI based treatment planning and dose calculation is used, any pre-processing of the imaging data (e.g. conversion to appropriate radiation interaction data) shall be reported.
    - Image sets from the different modalities in treatment position shall be co-registered.
    - Reference imaging for IGRT shall be made with well-defined reference system based on the internal fiducials.

VOLUME SELECTION AND DEFINITION

- The recommendations made by ICRU shall be followed.
- The naming of target and organs-at-risk volumes shall follow the Santanam et al IJROBP 83(4): 1344-1349, 2012.
- Target volumes:
    - Clinical Target Volume(s):
        - **Prostate (CTVT1)** shall include the prostate and any potential extra-capsular tumor growth.

        - **Proximal seminal vesicles (CTVT2)** shall include the proximal 2 cm of the seminal vesicles.
        - In case of tumor involvement in the vesicle(s), **the engaged vesicle(s)** shall be outlined separately **(CTVT3)**.
        - **Pelvic nodes (CTVT4)** shall be delineated according to the RTOG guidelines.
    - Planning Target Volume(s):
        - **Prostate (PTVT1)** consists of CTVT1 and a margin of 5-7 mm during the part of the treatment guided by the fiducials. During pelvic + prostate irradiation, where bone matching is used, a 10 mm isotropic margin should be applied to CTV_P.
        - **Proximal seminal vesicles (PTVT2)** consist of CTVT2 and a margin of 5-10 mm.
        - **Tumor engaged vesicle(s) (PTVT3)** consist(s) of CTVT3 and a margin of 5-10 mm.
        - **Pelvic nodes (PTVN)** consist of CTVN and an isotropic margin of 7-10 mm.
- Organs at risk (OARs)
    - The following OARs shall be delineated (structure name within parenthesis):
        - **Rectum (Rectum)**, delineated according to the recommendations by QUANTEC[1]: "*The rectum should be segmented from above the anal verge to the turn into the sigmoid colon, including the rectal contents*."
        - **Anal canal (AnalCanal)** shall be outlined as a separate volume
        - **The urinary bladder (Bladder)** shall be outlined as the outer contour of the bladder, i.e. including the muscle wall.
        - **The penile bulb (PenileBulb)** is defined as the oval-shaped area bounded by the crura, corpora spongiosum and the levator ani muscles (the most proximal portion of the penis) sitting approximately 1-1.5 cm caudal to the prostate. The penile bulb appears as a hyperintense oval-shaped structure on T2-weighted MR images and thus MR-based segmentation is recommended.
        - **BowelBag** is delineated from the level of 2 cm above the PTV-N, then drawing the whole intestinal cavity excluding muscles, vessels and internal organs (other than bowel) down to the most inferior small-or large bowel loop that is not rectum.
        - **The femoral heads (FemoralHead_L and FemoralHead_R)** are delineated circumferentially not including the femur neck.

PLANNING AIMS AND DOSE-VOLUME CONSTRAINTS

- Absorbed dose prescription
    - Fractionation schedules which equals to a biological equivalent of 2 Gy (BED2) to 78 Gy are allowed with dose prescriptions comparable to schedules given in **Table 1.** Hypofractionation schedules with fraction doses >2.5 Gy are not permitted within this protocol. Documented experience of hypofractionated schedules in published reports or quality registration is a requirement.
    - For treatment planning optimization, the physical objectives and constraints shall be prioritized according to the examples given in **Table 2**.
- Fractionation and treatment time
    - Radiotherapy shall be given daily, 5 days per week
    - The overall treatment time shall not exceed 4 days more than an optimal treatment schedule with 7 weekdays whereof 5 treatment days per week. In case of treatment time exceeding this recommendation, corrective compensation shall be made according to local practice.

[1] Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation dose-volume effects in radiation-induced rectal injury. Int J Radiat Oncol Biol Phys. 2010 Mar 1;76(3 Suppl):S123-9. doi: 10.1016/j.ijrobp.2009.03.078.

TREATMENT PLANNING

- The radiation treatment shall be given with 6-18 MV x-rays and with IMRT/VMAT technique.
- Treatment planning technique, e.g. delineation of help structures, and machine dependent constraints, are according to each center's treatment planning manual.

DOSE COMPUTATION

- Maximum allowed voxel size for the dose calculation grid is 3 mm in the transversal plane. A size equal to the CT slice thickness is recommended.
- The make and version of the particular treatment planning system and dose calculation algorithm shall be reported.

TREATMENT VERIFICATION

- Image-guided treatment delivery
    - The position of the fiducials in the prostate shall be estimated based on electronic kV/MV portal imaging or cone beam CT.
    - The verification and correction shall be performed prior to every treatment fraction. The treatment should start as soon as readily possible after the verification/correction.
    - The monitor units (dose) used for verification of position should be considered and compensated for if MV portal imaging is used.

ADDITIONAL CONSIDERATIONS FOR COMBINED MODALITIES

- Drug therapy
    - EBRT should begin after 12 full weeks and preferably before 14 full weeks after the date of the first LHRH agonist injection.

QUALITY ASSURANCE

- Preparatory
    - Reference dosimetry shall be carried out according to IAEA, and verified through external dosimetry audits.
    - A dummy run shall be performed before including patients in the trial. It should include delineation of structures and dose planning.
- Pre-treatment patient specific QA
    - Individual case review shall be performed according to local practice of each centre.

Table 1. Dose prescriptions

Fractionation schedule	Target structure	Number of fractions	Dose per fraction (Gy)	Prescribed total dose (Gy)	($EQD2_3$) (Gy)
A	**PTVT1**	39	2.00	78.0	(78.0)
A	**PTVT3**	35	2.00	70.0	(70.0)
A	**PTVT2**	25	2.00	50.0	(50.0)
A	**PTVN**	25	2.00	50.0	(50.0)
B	**PTVT1**	29	2.50	72.5	(79.8)
B	**PTVT3**	29	2.30	66.7	(70.7)
B	**PTVT2**	29	1.80	52.2	(50.1)
B	**PTVN**	29	1.80	52.2	(50.1)
C	**PTVT1**	39	2	78	(78.0)
C	**PTVT3**	39	1.9	72,8	(70.0)
C	**PTVT2**	39	1.5	58,4	(50.0)
C	**PTVN**	39	1.5	58,4	(50.0)
D_SIB	**PTVT**	35	2.2	77.0	(78.0)
D_SIB	**PTVN**	35	1.6	56.0	(52.0)

In case of simultaneous integrated boost treatment (SIB) the treatment regime will be 2,2 Gy to the prostate (PTVT4) (BED2= 78 Gy, alfa/beta=3) and 1,6 Gy to elective LN (PTVN4) in 35 fractions (BED2= 52 Gy, alfa/beta=3 Gy).

CALCULATION FOR SIMULTANEOUS INTEGRATED BOOST (SIB)

Fraction dose [Gy]
Nominal total dose for 35 f [Gy]
EQD2 [Gy] (α/β = 3 Gy)
Pelvic Lymph nodes: 1,60Gy/35f Nominal dose 56Gy, EQD2 [Gy] (α/β = 3 Gy) 52Gy
Prostate and vesiculae seminales: 2,16Gy-2.2Gy/35f Nominal dose 76-77Gy, EQD2 [Gy] (α/β = 3 Gy) 78-80Gy

ORGANS AT RISK AND DOSE CONSTRAINTS FOR SIB 35F

Rectum: D5% < 72,7 GY, D20% < 68,9 GY, D50% < 59,1 GY, D60% < 49,3 GY.
Not greater or less than 67,0 Gy to half of circumference and not greater or less than 49,3 Gy to entire circumference.

AnalCanal: not more than 67,0 Gy til half of circumference.

Bladder: D20% < 68,9 Gy, D50% < 64,0 Gy. Dmin (D100%) < 49,3 Gy.

FemoralHead: D50% < 49,3 Gy.

IntestinalCavity: D50% < 44,4 Gy.

BladderNeck Dmax < 72,8 Gy.

Table 2A. Dose prescription priorities for fractionation for schedule A

Priority	Structure	Prescribed Dose (Gy)	Dose-volume recommendations
1	**CTVT1 (Prostate)**	78	$D_{98\%} \geq 76$ Gy (97%)
2	**CTVT3 (tumor involved ves)**	72.8	$D_{98\%} \geq 70.7$ Gy (97%)
3	**PTVT1**	78	$D_{95\%} \geq 75$ Gy (96%)
4	**Rectum**		$V_{70Gy} < 20$ %
5	**PTVT1**	78	$D_{98\%} \geq 74$ Gy (95%)
6	**PTVT2**	72.8	$D_{98\%} \geq 68.8$ Gy (94%)
7	**CTVT2 (prox ves, 2cm)**	58.4	$D_{98\%} \geq 55.3.5$Gy (95%)
8	**CTVN (Nodes)**	58.4	$D_{98\%} \geq 55.3$ Gy (95%)
9	**Rectum**		$V_{75Gy} < 15$ %
10	**PTVT3**	58.4	$D_{95\%} \geq 54.1$ Gy (95%)
11	**PTVN**	58.4	$D_{98\%} \geq 54.1$ Gy (93%)
12	**FemoralHeads_L/R**		$D_{2\%} \leq 51$Gy
13	**BowelBag**		$V_{30Gy} < 300$ cm^3 $V_{40Gy} < 150$ cm^3 $V_{45Gy} < 100$ cm^3 $V_{50Gy} < 35$ cm^3
14	**Rectum**		$V_{60Gy} < 35$ %
15	**Body-PTV**		$D_{2\%} \leq 83$ Gy (107%)
16	**Bladder**		$D_{mean} \leq 62$ Gy (80%)

Table 2B. Dose prescription priorities for fractionation for schedule B

Priority	Structure	Prescribed Dose (Gy)	Dose-volume recommendations
1	**CTVT1 (Prostate)**	72.5	$D_{min} \geq 68$ Gy (97%)
2	**CTVT3 (tumor involved ves)**	66.7	$D_{min} \geq 61$ Gy (97%)
3	**PTVT1**	72.5	$D_{95\%} \geq 67$ Gy (96%)
4	**Rectum**		$V_{64Gy} < 20$ %
5	**PTVT1**	72.5	$D_{98\%} \geq 66$ Gy (95%)
6	**PTVT2**	66.7	$D_{98\%} \geq 59$ Gy (94%)
7	**CTVT2 (prox ves, 2cm)**	52.2	$D_{min} \geq 43$Gy (95%)
8	**CTVN (Nodes)**	52.2	$D_{min} \geq 43$Gy (95%)
9	**Rectum**		$V_{69Gy} < 15$ %
10	**PTVT3**	52.2	$D_{95\%} \geq 43$Gy (95%)
11	**PTVN**	52.2	$D_{98\%} \geq 42$ Gy (93%)
12	**FemoralHeads_L/R**		$D_{2\%} \leq 51$Gy
13	**BowelBag**		$V_{28Gy} < 300$ cm^3
14	**Rectum**		$V_{37.5Gy} < 150$ cm^3
15	**Body-PTV**		$V_{42Gy} < 100$ cm^3
16	**Bladder**		$V_{46Gy} < 35$ cm^3

Table 2C. Dose prescription priorities for fractionation for schedule C

Priority	Structure	Dose (Gy)	Dose-volume recommendations
1	**CTVT1 (Prostate)**	78Gy	$D_{98\%} \geq 76$ Gy (97%)
2	**CTVT3 (tumor involved ves)**	70Gy	$D_{98\%} \geq 68$ Gy (97%)
3	**PTVT1**	78Gy	$D_{95\%} \geq 75$ Gy (96%)
4	**Rectum**		$V_{70Gy} < 20$ %
5	**PTVT1**	78Gy	$D_{98\%} \geq 74$ Gy (95%)
6	**PTVT2**	70Gy	$D_{98\%} \geq 66$ Gy (94%)
7	**CTVT2 (prox ves, 2cm)**	50Gy	$D_{98\%} \geq 47.5$Gy (95%)
8	**CTVN (Nodes)**	50Gy	$D_{98\%} \geq 47.5$ Gy (95%)
9	**Rectum**		$V_{75Gy} < 15$ %
10	**PTVT3**	50Gy	$D_{95\%} \geq 47.5$ Gy (95%)
11	**PTVN**	50Gy	$D_{98\%} \geq 46.5$ Gy (93%)
12	**FemoralHeads_L/R**		$D_{2\%} \leq 55$Gy
13	**BowelBag**		$V_{30Gy} < 300$ cm^3 $V_{40Gy} < 150$ cm^3 $V_{45Gy} < 100$ cm^3 $V_{50Gy} < 35$ cm^3
14	**Rectum**		$V_{60Gy} < 35$ %
15	**Body-PTV**		$D_{2\%} \leq 83$ Gy (107%)
16	**Bladder**		$D_{mean} \leq 62$ Gy (80%)

HDR-BOOST

Patients are anesthetized and vital functions are monitored with the patient lying in dorsal lithotomy position. HDR-BT shall be performed by introducing a thread-formed iridium-192 source into hollow steel needles perforating the perineum and placed into the prostatic gland. The needles are inserted by transrectal ultrasound guidance. The treatment plan should encompass the prostatic gland (CTVT1) and 2 mm isotrope margin to the PTVT1.

Table 3

Risk organ	**Brachy regime**	**Constraints**	**Fraction dose/fraction**	**EQD2 HDR (α/β = 3)**	**EQD2 HDR-External RT (α/β = 3)**
Urethra	10 Gy x 2	Max. 11.5 Gy to 0.1 cc	11.5 Gy / 2	66.7 Gy	116.7 Gy
Urethra	15 Gy x 1	Max 16.8 Gy to 0.1 cc	16.8 Gy / 1	66.5 Gy	116.5 Gy
Urethra	10 Gy x 2	Max point dose 12 Gy	12 Gy / 2	72 Gy	122 Gy
Urethra	15 Gy x 1	Max point dose 17.5 Gy	17.5 Gy / 1	71.8 Gy	121.8 Gy
Urethra	10 Gy x 2	Max 7.6 Gy to 2cc	7.6 Gy / 2	32.2 Gy	82.2 Gy
Rectum	15 Gy x 1	Max 11.3 Gy to 2cc*	11.3 Gy / 1	32.3 Gy	82.3 Gy
Rectum	10 Gy x 2	Max 6.6 Gy	6.6 Gy / 2	25.2 Gy	75.3 Gy

*Check visually =< 60% of rectal mucosa to 2cc

EQD2 for rectum and urethra (a/b=3Gy) is 50.8 Gy for 14.5 Gy x 1 and 54.0 Gy for 15.0 Gy x 1.

POST-OPERATIVE RADIOTHERAPY

ENDOCRINE THERAPY

150 mg of bicalutamide is administered for 18 months during and after post-operative radiotherapy, starting up to two weeks before the start of radiation treatment but after profylactic breast irradiation.

PATIENT POSITION AND FIXATION

The patient will be treated in supine position. The position must be the same during planning, simulation and treatment.
The patient should be immobilized according to the standard procedures of each participating centre. The type of fixation device/technique shall be reported in the RTQA-report

PATIENT DATA ACQUISITION

A CT based simulation shall be made in the treatment position for all cases, on a flat table top and with the patient in his fixation device. CT scanning shall be performed with a slice thickness of maximum 3 mm. As an option, MR images that are co-registered with the planning CT images may also be used.

In patients with extremely filled rectum (> 4 cm) due to faeces or gas, new planning CT/MR should be performed prior to treatment planning. The bladder should be comfortably filled.
Images will be obtained from at least the lower end of the sacroiliacal joints to 10 mm below the tuberositas ischii.

Delineation of target volumes and organs at risk (OAR) must be done on CT images, or together with MR images appropriately co-registered with planning CT images. RT will be delivered with megavoltage equipment at energies >= 6 MV, with daily fractions of 2 Gy/5 days per week.

TARGET VOLUMES AND ORGANS-AT-RISK (OAR) VOLUMES

The definition of volumes follows the recommendations made by ICRU in Report 50 and in the supplementary ICRU Report 62 and in ICRU Report 83 for photon beam therapy.

TARGET

Clinical target volume prostate bed CTVT
The CTVT will include the prostate bed in all patients.
Information which may be used to define the prostate bed CTV includes: Histopathologic information of prostate size and tumor extent to specific boundaries of the surgical resection, pre-operative imaging e.g. pelvic CT/MRI studies and post-operative anatomy on planning CT scan.
The definition of the prostate bed CTVT is based on the estimated location of the pre-operative prostate volume plus sites of possible microscopic tumor extension, plus the extent of the surgical bed, and should normally include any surgical clips provided that the normal-tissue dose-constraints are satisfied.
The following areas are at the greatest risk for relapse after prostatectomy and should therefore be included:
Centrally: the urethra-vesical anastomosis
Cranially: the bladder neck
Posteriorly: up to but not including the outer rectal wall, cranially including the most posterior part of the bladder neck

- Caudally: including the apex (15 mm cranially from the penile bulb)
- Laterally: up to the neurovascular bundles (if removed up to the ilio-obturatic muscles)
- Anteriorly: including the anastomosis and the urethral axis.

The original volume of seminal vesicles (including any residual seminal vesicle tissue post-op) will not be considered target if they were not pathologically involved with tumor. If there was pathologic involvement of the seminal vesicles, then the seminal vesicles will be considered target.
We recommend the use one of the following existing published consensus guidelines for construction of CTVT:

- The European Organization for Research and Treatment of Cancer (EORTC) guidelines
- The Faculty of Radiation Oncology Genito-Urinary Group (FROGG)
- The Radiation Therapy Oncology Group (RTOG)

Planning target volume prostate bed PTVT
The planning target volume (PTVT) will add 0.5 - 1.0 cm in all directions, for day-to-day variation in set up and for CTVT motion. Daily image guidance is mandatory. The maximum PTVT is 500 ccm.

ORGANS AT RISK

- The following OARs shall be delineated (structure name within parenthesis):
  - **Rectum (Rectum)**, delineated according to the recommendations by QUANTEC[2]: "*The rectum should be segmented from above the anal verge to the turn into the sigmoid colon, including the rectal contents*." "*The superior limit is where the bowel moves anteriorly, close to the inferior level of the sacroiliac joints, and the inferior limit is commonly at the bottom of the ischial tuberosities.*"
  - **Anal canal (AnalCanal)** shall be outlined as a separate volume with a default extension from the distal end of the anal canal with a caudocranial direction of 4 cm.
  - **The urinary bladder (Bladder)** shall be outlined as the outer contour of the bladder, i.e. including the muscle wall.
  - **The penile bulb (PenileBulb)** is defined as the oval-shaped area bounded by the crura, corpora spongiosum and the levator ani muscles (the most proximal portion of the penis) sitting approximately 1-1.5 cm caudal to the prostate. The penile bulb appears as a hyperintense oval-shaped structure on T2-weighted MR images and thus MR-based segmentation is recommended.
  - **The femoral heads (FemoralHead_L and FemoralHead_R)** are delineated circumferentially not including the femur neck.

Structure names in treatment planning system, Same as for primary radiotherapy treatment, se above.

RADIATION TREATMENT TECHNIQUE

The radiation treatment shall be given with external photon beam therapy with 3D-CRT and/or IMRT (VMAT) techniques. It is left to each centre to decide upon the optimal technique (number of beams, beam weights, beam angles, beam shaping, etc.).
The position shall be verified prior to every fraction with electronic kV or MV portal imaging or x-ray volumetric imaging (cone beam CT). Guidance can either be done using surgical clips or bony structures.

DOSE SPECIFICATIONS

Prescribed average dose to CTV-PB will be 66-70 Gy in 33-35 fractions over 6.5-7.0 weeks. Megavoltage equipment is required with effective photon energies ≥6MV. Minimum source-to-axis distance is 100cm.

[2] Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation dose-volume effects in radiation-induced rectal injury. Int J Radiat Oncol Biol Phys. 2010 Mar 1;76(3 Suppl):S123-9. doi: 10.1016/j.ijrobp.2009.03.078.

The minimal dose to the PTV shall not be less than 95% of the prescribed dose; the maximum, not more than 105% of the prescribed dose.

Table 4. Tolerance doses of risk organs and dose constraints

Priority	Volume	Prescribed dose	
1	CTVT	D_{min} ≥ 95% D_{min} ≥ 66,5 Gy	The minimum dose to CTV-PB shall be greater than or equal to 95% of the prescribed dose, i.e. $D_{mean,PTV-P}$.
2	PTVT	$V_{95\%}$ ≥ 95% $V_{66,5Gy}$ ≥ 95%	The 95% isodose shall cover at least 95% of PTV-PB.
3	Rectum	$V_{90\%}$ ≤ 15% $V63_{Gy}$ ≤ 15%	Less than 15 % of the outlined rectal volume should receive doses greater than 90% of the prescribed dose.
4	PTVT	$D_{98\%}$ ≥ 90% $D_{98\%}$ ≥ 66 Gy	The "near minimum dose" to PTV-PB should be greater than or equal to 90% of the prescribed dose.
5	Rectum	$V_{75\%}$ ≤ 35% $V52{,}5_{Gy}$ ≤ 35%	Less than 35 % of the outlined rectal volume should receive doses greater than 75% of the prescribed dose.
6	Femoral heads_L/R	$D_{2\%}$ ≤ 75% $D_{2\%}$ ≤ 52,5 Gy	The near maximum dose to the femoral heads should be less than or equal to 75% of the prescribed dose.
7	Rectum	$V_{70\%}$ ≤ 50% V_{49Gy} ≤ 50%	Less than 50 % of the outlined rectal volume should receive doses greater than 70% of the prescribed dose.
8	Bladder (Bladder-CTVT)	$V_{90\%}$ ≤ 50% V_{65Gy} ≤ 50%	Less than 50 % of the outlined Bladder-CTV-PB volume should receive doses greater than 90% of the prescribed dose.
9	Bladder (Bladder-CTVT)	$V_{90\%}$ ≤ 70% V_{42Gy} ≤ 70%	Less than 70 % of the outlined Bladder-CTV-PB volume should receive doses greater than 60% of the prescribed dose.
10	Penile Bulb	*Registered*	NA
11	Body	$D_{2\%}$ ≤ 107% $D_{2\%}$ ≤ 75 Gy	The maximum global dose should be less than or equal to 107% of the prescribed dose.

QUALITY ASSURANCE

(Applicable to both primary and postoperative radiotherapy)

A working group will be assigned for collecting treatment and verification data to ensure that the physical quality of the treatments follows the study protocol.
Radiotherapy related treatment information and other relevant documentation for each patient shall be sent to the QA-group at completion of radiotherapy.
Quality audits may be performed by the QA-group during the trial.
The aim of the QA is to ensure uniformity of all radiotherapy data for every patient in order to answer the questions in the trial. Specifically this means:
- To establish a uniform instruction of radiotherapy details,
- To evaluate compliance for all patients with the instructions of the radiotherapy details, and
- To enable a correct evaluation of the endpoints in the trial.

The QA procedure has two parts;
- Dummy run, and
- Individual patient evaluation checks.

DUMMY RUN PROCEDURE

A dummy run will be performed before the start of the patient trial.
The dummy run procedure consists of two separate parts:

1. Delineation of structures (targets and organs at risk)
2. Treatment planning of predefined target volumes

The first part is dedicated to *definition of volumes*. CT images of a prostate cancer patient will be sent from RTQA-office. The target volumes (CTV and PTV) and the organs at risk (rectum, anal canal, urinary bladder, small bowel, penile bulb and femoral heads) shall be delineated on the transversal CT slices according to the study protocol. The CT images and delineated structures shall be sent back to the RTQA-office for evaluation.
The second part is dedicated to *treatment planning*. Each institution shall make a treatment plan for the radiotherapy. The CT images, structures, plan, and dose data together with dose volume histograms (DVH) for all structures shall be sent back to the RTQA-office for evaluation.
The dummy run has to be performed and evaluated by the RTQA team before the centre starts to include patients.
Detailed practical information of the dummy run procedure will be sent out separately to each participating centre.

INDIVIDUAL PATIENT EVALUATION CHECKS OF THE RADIOTHERAPY TREATMENT

A final treatment evaluation of every single patient shall be performed after completion of radiotherapy.
The following parameters will be checked and evaluated at the RTQA-office:
Patient immobilization
CT scanning (number of slices, slice thickness)
Volumes of targets (CTV and PTV) and organs at risk (rectum, anal canal, urinary bladder, small bowel, penile bulb and femoral heads)
3D treatment planning (beam arrangements, beam shaping, beam quality, etc.)
Dose prescription
Dose volume histograms

APPENDIX C: MAGNETIC RESONANCE IMAGING OF THE PROSTATE

For local staging of prostate cancer with MRI, the examination is performed at 1.5 or 3T using an external phased-array coil is sufficient. Imaging sequences consist of high-resolution T2-weighted images of the pelvis in three planes, diffusion-weighted sequences including an ADC-map and a dynamic contrast enhanced sequence during injection of a Gadolinium chelate contrast agent. This examination is sometimes referred to as "multiparametric prostate MRI". MR spectroscopic imaging is sometimes also included in this examination but not part of the minimal clinical standard.
The "Prostate Imaging – Reporting and Data System (PI-RADS) v2 document includes minimal requirements both for hardware, examination protocol and evaluation of MRI-images. For details, please see:

http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/PIRADS/PIRADS%20V2.pdf)

The PI-RADS scoring system facilitates communication of findings on prostate MRI, both for localization of tumors within the prostate as well as grading of suspicion of malignancy. An example of PI-RADS scoring template is enclosed at the end of this section. If dynamic contrast is omitted the guidelines gives alternative PI-RADS scoring.

It is recommended that the MR-examination are evaluated by radiologists specialized in abdominal/prostate radiology and by those having continuous communication with physicians treating these patients.

Postoperative MDT conferences that discuss radiological, surgical and histopathological findings are advantageous in this setting.

MR-imaging protocol (1.5T or 3T)

	Pulse sequence	Orientation	Voxel size 1,5T	Voxel size 3T	Comment
1	Localiser				Buscopan 20mg iv. alt Glucagon 1ml im.
2	T2w_TSE_2D	Axial	4 x 0,5 x 0,5 alt 4 x 0,7 x 0,7	3 x 0,5 x 0,5	
3	T2w_TSE_2D	Coronal	4 x 0,5 x 0,5 alt 4 x 0,7 x 0,7	3 x 0,5 x 0,5	
4	T2w_TSE_2D	Sagital	4 x 0,5 x 0,5 alt 4 x 0,7 x 0,7	3 x 0,5 x 0,5	
5	T2w_TSE_3D	Coronal		0,7 x 0,6 x 0,7	Optional
6	EPI_DWI_2D	Axial	5 x 1,5 x 1,5 alt 4 x 2,0 x 2,0	4 x 1,0 x 1,0 alt 4 x 1,5 x 1,5	Adapted to quality of SNR: 50-100 and 800–1000 s/mm2. For calculation of ADC, the highest b-value that should be used is 1000 s/mm2.
	Localiser				
10	T1w_calibration	Axial	**1,5T** 4 x 1,0 x 1,0 **3T** 4 x 0,7 x 0,7		Variable Flip Angle (VFA)
11	T1w_Spoiled gradient echo_3D	Axial	**1,5T** 4 x 1,0 x 1,0 **3T** 4 x 0,7 x 0,7		Dynamic 3 ml/sek Temporal resolution max 15 s

PI-RADS
PIRADS 1 – Very low (clinically significant cancer is highly unlikely to be present)
PIRADS 2 – Low (clinically significant cancer is unlikely to be present)
PIRADS 3 – Intermediate (the presence of clinically significant cancer is equivocal)
PIRADS 4 – High (clinically significant cancer is likely to be present)
PIRADS 5 – Very high (clinically significant cancer is highly likely to be present)

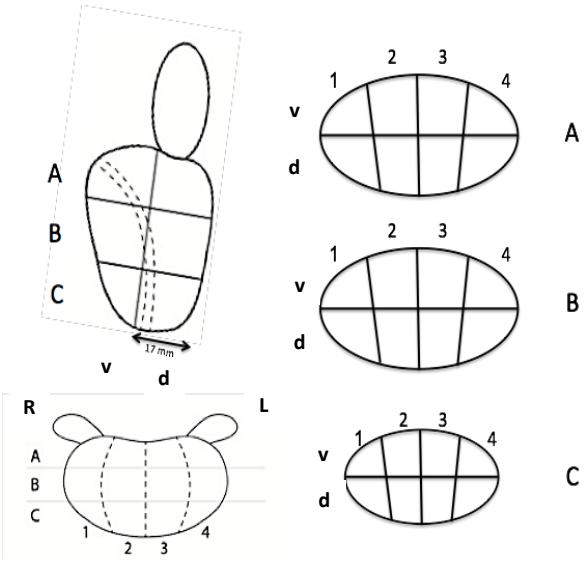
MRI-Reporting template SPCG-15

Name: **PIN:**

Date:

Prostate volume:_____ml

	Tumor 1	Tumor 2	Tumor 3	Tumor 4
Zone				
Largest diam mm				
EPE 1-5				
SVI (R/L) y/n mm				
Lower sphincter inv y/n				
Bladder neck invasion y/n				
PI-RADS T2w(1-5)				
PI-RADS DWI(1-5)				
DCE-MRI (+/-)				
PI-RADS SCORE(1-5)				
Lymph nodes (mm)	R		L	
Bone metastasis y/n				



Reporting template SPCG-15 – Guide

1. Volume; HxLxW x 0.52
2. Largest diam mm; if in the peripheral zone measurement preferably tumor abutment of the capsule
3. EPE; (ExtraProstatic Extension) 1-5. 1=EPE highly unlikely present, 2=EPE unlikely present, 3=EPE equivocal, 4=EPE is likely present, 5=EPE is highly likely present. EPE=4 and 5 can be included in SPCG-15, where (4) has a tumor/capsule interface (abutment) exceeding ≥12 mm together with a bulging capsule, irregular/spiculated capsule and (5) has signs of breach of the capsule with evidence of direct tumor extension.
4. SVI; (Seminal Vesicle Invasion) yes/no with mm growth above the upper part of the prostatic surface.
5. Lower sphincter invasion; Signs of or risk of apical tumor to invade the lower sphincter below the apex.
6. Bladder neck invasion; Signs of or risk of tumors at the base invading the bladder neck.
7. PI-RADS scoring according to the PI-RADS v2 found as pdf. at the reference listed above.
8. Template; v=ventral, d=dorsal, A=Base, B=Mid, C=Apex