Palliative radiotherapy to dominant symptomatic lesion in patients with hormone refractory prostate cancer

PRADO

An international multicenter prospective feasibility study

Sponsor:

Sjællands Universitetshospital Næstved
Klinisk Onkologisk Afdeling og Palliative Enheder

Primary Investigators:

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Confidential: This protocol contains confidential information, which may not be communicated to third parties without permission of the coordinating investigator

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1 General information

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2 Synopsis

Study title	Palliative radiotherapy to dominant symptomatic lesion
Short title	PRADO
Study type	Multicenter feasibility study
Patient cohort	Patients with hormone refractory prostate cancer (HRPC) presenting a dominant symptomatic lesions
Sponsor	Sjællands Universitetshospital Næstved Klinisk Onkologisk Afdeling og Palliative Enheder
Primary Investigator	Jesper Carl, Phd Sjællands Universitetshospital Næstved Klinisk Onkologisk Afdeling og Palliative Enheder
Objective	Feasibility and Safety of local hypo-fractionated radiotherapy of MR outlined lesion for the patient's dominant symptom.
Inclusion criteria (all criteria must be fulfilled)	• Patients with hormone refractory biopsy proven prostate cancer • Presenting with a dominating debilitating symptom • Expected median survival of 3 – 12 months • Focal irradiation of lesion is feasible • Systemic therapy according to guidelines • age ≥18 years • Legal capacity, patient is able to understand the nature, significance and consequences of the trial • Written informed consent
Exclusion criteria (recruitment is not possible if any -at least one- criterion is met)	• Relevant comorbidity (with limitations to administer radiotherapy according to protocol) • Prior radiotherapy which results in limitations to administer radiotherapy according to protocol • No large metal implants in vicinity of lesion • Department dose constraints for normal tissue can't be met • Large bony lesions with extensive osseous destruction • Patients symptoms do not correlate with MR findings
Study therapy	• Image guided radiotherapy (IGRT) with hypo-fractionated simultaneous integrated boost (IMRT) • GTV1 = MR T2w lesion and ADC <= 1200 * 10^{-3} mm^2/s • GTV2 = MR T2w lesion and ADC <= median ADC in GTV1 • Each lesion is a CTV, CTV = GTV • PTV=CTV+ margin according to department standards • Dose-fractionation • CTV1: 4 x 5 Gy • CTV2: 4 x 7 Gy
Primary endpoint	Feasibility: Proportion of study participants that complete radiotherapy with ≥ 90% of prescribed dose
Secondary endpoints	• Dominant symptom (VAS) • Progression-free survival >6 months • Overall survival

	• Acute toxicity • Quality of life • Change in ADC from before to end of treatment • Change in ADC from before to 6 month post treatment
Sample size	34 patients has to be included in the study
Study sites	University Hospital Sjaelland, Naestved UKSH Campus Kiel UKSH Campus Luebeck
Time table	Recruitment period: 12 months Start of study: March 2018 End of study: March 2019 Follow-up: minimum ≥ 6 months
Financing	Interreg (InnoCan)

3 Background and rationale

Prostate cancer is the major cause of cancer death in men living in developed countries. Large autopsy studies found that patients that presented prostate cancer demonstrated metastatic disease in 35% of cases. Prostate cancer metastases were 90% bone metastases, with 90% of the bone metastases involved the spinal cord, followed by lung (46%), liver (25%) and pleura (21%). Another important pathway is the lymphatic system, which is involved in 9 to 16% of cases, especially at the level of obturator, pre-sacral, internal, and common iliac arteries, and sometimes even the extra-regional para-aortic chains (1).
Metastatic or locally advanced prostate cancer (PC) responds well initially to hormonal manipulation by androgen withdrawal and peripheral androgen blockade. However, such patients have high risk of progression to a hormone-refractory prostate cancer (HRPC). Once the tumor has achieved a castration-refractory metastatic stage, treatment options are limited and the average survival of patients ranging from two to three years only (2). Furthermore, HRPC patients will typically be frail old men.
Skeletal metastases account for most of the morbidity in surviving HRPC patients, but patients may also present with dominating disabling symptoms from local pelvic disease progression with an incidence estimated to be about 10%-18% (3, 4), or even higher in node-positive patients treated with anti-androgen therapy alone (5).
In patients with a reasonable expected median survival (6), pelvic radiotherapy (RT) may provide an effective palliation. Studies have demonstrated, radiotherapy contributes to relief of hematuria, pain and other pelvic symptoms, with acceptable toxicity in the majority of patients with HRPC (7-9).
A recent systematic literature search demonstrated good overall symptom response rates despite large variations in radiotherapy dose and fractionation (10), which consequently warrants new prospective studies in this field.
Radiotherapy, dependent on radiation dose-volume, however may lead to increase in radiation-induced toxicities (11). Both GI and GU toxicities do increase with dose and volume of respectively rectum and bladder irradiated (12) (13) (14). Technological advancements in radiotherapy such as image-guided radiotherapy (GRT), intensity modulated radiotherapy (IMRT / VMAT), stereotactic body radiation therapy (SBRT) or stereotactic radiosurgery (SRS) have allowed for significant treatment volume reduction, less normal tissue toxicity and whole-organ dose escalation. A recent review list several retrospective studies showing the effectiveness of SBRT and SRS in prostate cancer metastases (15)
Even further improvement may obtained using more accurate imaging diagnostics for treatment planning, such as advanced MRI (16, 17). Using diffusion weighted imaging (DWI) quantitative measures such as the apparent diffusion coefficient (ADC) has been shown to be the most important imaging modality for predicting tumor location (18) (19) and local tumor recurrence larger than 0.4 ml (20).

The aim of the present study will be to conduct a feasibility study of a new short palliative radiotherapy regime that apply to patients with metastatic HRPC patients presenting with a dominating debilitating symptom and an expected reasonable survival. The dominant symptom can be such as pain, urinary retention, chronic rectal obstruction, bleeding etc., caused by localized progression of the patient's metastatic prostate cancer. This new approach will apply magnetic resonance imaging (MRI) to verify correspondence between the progressing HRPC lesion (DSL =the dominant symptomatic lesion) and the patients corresponding dominant symptom. Diffusion weighted MR imaging (DWI) will apply to identify both the lesion and the most aggressive part of the lesion. The symptomatic lesions will be treated using precision radiotherapy (IGRT+IMRT/VMAT or SBRT/SRS if available) with a dose of 4 x 5 Gy, while for the most aggressive part of the lesion the dose will be escalated to 4 x 7 Gy using a simultaneous integrated boost (SIB) technique.

4 Objective

This prospective study will evaluate the feasibility as the primary endpoint. Secondary endpoints are visual analog score (VAS) of the dominating symptom, symptom progression free survival, evaluation of radiation induced acute toxicity, the influence on quality of life, the progression free survival and change in volume and ADC statistics from baseline as surrogate marker of local response to radiotherapy. The study will analyze patient characteristics, relevant comorbidities and tumor related factors correlation to outcomes. Based on the results of this study, a prospective randomized phase II/III dose escalation study may suggested.

5 Study design and participating centers

This is an international, multi-center single arm prospective feasibility study. Participating sites are:

1. University Hospital Sjaelland, Naestved, Department of Oncology
2. UKSH Campus Kiel, Department of Radiation Oncology
3. UKSH Campus Luebeck, Department of Radiation Oncology

6 Inclusion and exclusion criteria

Patients can be included in the study if they fulfill all of the following inclusion criteria and none of the following exclusion criteria.

Inclusion criteria:

- Patients with hormone refractory biopsy proven prostate cancer (HRPC)
- Presenting with a dominating debilitating symptom
- Expected median survival of 3-12 months (6)
- Focal irradiation of lesion is feasible
- Systemic therapy according to guidelines
- age ≥18 years
- Legal capacity, patient is able to understand the nature, significance and consequences of the trial
- Written informed consent

Exclusion criteria:

- Relevant comorbidity (with limitations to administer radiotherapy according to protocol)
- Prior radiotherapy which results in limitations to administer radiotherapy according to protocol
- No large metal implants in vicinity of lesion
- Department dose constraints for normal tissue can't be met
- Large bony lesions with extensive osseous destruction (e.g. vertebral body)
- Patients symptoms do not correlate with MR findings

7 Risks and toxicities

Patients participating in this study will have standard radiotherapy. Consequently, the participating patients face known risks and toxicities following high dose radiotherapy. Patients participating in this study are offered a higher than normal radiation dose to their dominant lesion, but treatment plans will adhere to department standard dose constraints for all organs at risk in order to avoid excessive risks and toxicities.

8 Registration

The consecutive cohort of HRPC patients will be screened for eligibility according to the inclusion criteria's in this protocol. Estimated median survival for patients to be included should preferably be based on the updated model in (6) (see appendix 1). Before inclusion, patient clinical routine blood lab and radiology results should be reviewed. Available clinical routine diagnostic imaging and lab results may be used to calculate the expected median survival for patients using the model in (6) (see appendix 1). (6)Eligible patients will be informed about the study. After given informed consent, patients may be included in the

study. All patients included in the study receive a patient identification number (PID). The PID is composed of the site number and the running patient number (starting with P01, P02,.. ect.).

Site	SiteID
Naestved, Denmark	C1
Kiel, Germany	C2
Lübeck, Germany	C3

For pseudonymous registration and recording of all protocol data, the department of oncology, Naestved, will be make an electronic web interface (Easytrial) available for participating sites.

9 Systemic therapy

Systemic therapy will be administered according to department standard guidelines. Systemic therapy may be chemotherapy, anti-hormonal therapy, targeted therapies, bisphosphonates or a combination. The type of therapy will be documented. Interruptions of systemic therapy, delays or changes of drugs due to radiotherapy should be avoided.

10 Radiation therapy

10.1 General remarks

The primary endpoint is feasibility. The secondary endpoints are duration of relief from local symptoms, i.e. local symptom progression free survival (LPFS), overall survival, treatment toxicity (RTOG/CTCAE 4.0), Quality of life (EORTC-QLQ-C30 and EPIC26), and change in ADC as surrogate marker of response (21-25). Patients are scheduled for protocol specific follow-up visits at 1, 3, 6 months after end of radiotherapy. Additional MRI (T2w and DWI) will be performed at 1 and 6 months after end of radiotherapy or in case of progression of the dominant symptom.

Preferred technique is hypo-fractionated with high precision radiotherapy (radiosurgery or stereotactic radiotherapy) with few (1 to 5) fractions and ablative total dose. Daily IGRT is mandatory for hypo-fractionated regimens. For the treatment of thoracic lesions and metastases in the upper abdomen, techniques for motion compensation (e.g. breath-hold- or gating techniques) should be used, if available. In specific situations (e.g. spinal metastases with involvement of the spinal canal or cord compression or metastases with infiltration of hollow organs), however, lower doses of radiotherapy may be necessary for adherence of dose constraints or to avoid radiation-induced complications such as perforation. In these cases, moderately hypo-fractionated or even conventionally fractionated regimens should be used. The total dose should exceed at least a dose equivalent to 50Gy in conventional fractionation.

10.2 Treatment planning

3D planning is mandatory. Type of treatment technique (e.g. 3D-IMRT, VMAT or SBRT) is the decision of the radiation oncologist. The reference MR scan (se appendix 2) must be co-registered to the planning CT and the target volumes defined on MR transferred to the planning CT for dose planning.

10.3 Target volumes

Patients included in the study will be subjected to a protocol-specific MRI examination (see MR sequence and example of target delineation in appendix 19-20). A radiologist will read the MRI scan to validate correspondence between MR lesion and the patients dominating symptoms. In case of more than one lesion, decision on priority of target volumes will be made by the radiation oncologist based on clinical expertise. An ADC map will be calculated for the lesion using the DWI sequences. A cutoff ADC value of less than 1200 x 10^{-6} mm2/s in combination with a T2w image will be used to predict the MR lesion (GTV1) (26). The most aggressive part of the lesion (GTV2) will be defined using ADC of less than or equal to a cutoff value calculated as the median ADC value for the GTV1 (25). Notice that GTV2 need not to be one coherent volume, but may consist of several sub-volumes.

For the definition of target volumes, the following aspects should be considered: The clinical target volume (CTV) is the visible macroscopic tumor (GTV). The safety margin for the planning target volume (PTV) should be according to the department standard, and depending on the radiation technique used. The margin for the PTV2 for CTV2 may be chosen to be smaller than for PTV1 as this volume is enclosed in the CTV1, which receives a dose of 4 x 5Gy already.. For the treatment of breathing-dependent lesions (upper abdomen), treatment techniques with motion compensation (e.g. breath-hold or gating) should be used. All four fractions of the treatment should be given within two weeks of starting the radiotherapy.

10.4 Dose specification

The dose will be prescribed as 95%-PTV-coverage. The favorite technique is ablative radiosurgery or hypo-fractionated stereotactic radiotherapy if available, otherwise VMAT or IMRT is allowed. Recommended treatment regime

Technique	***Dose and fractionation regimens***
Hypo-fractionated regime	*PTV1: 4F x 5Gy, total dose 20Gy* *PTV2: 4F x 7Gy, total dose 28Gy*

10.5 Organs at risk

Organs at risk will be contoured if they are (at least partially) visible on transversal CT-slices on which the PTV is contoured or if the distance to PTVs is less 1 cm than cranio-caudal direction. Organs at risk are:

- Spinal cord, brain stem
- Optic nerves and optic chiasm

- eyes
- parotid glands
- lungs
- heart
- esophagus
- liver
- kidneys
- bladder
- rectum

Dose constraints to OARs can be used according to the institutional standard. Doses to OARs (sum plan of all relevant PTVs) will be documented.

Quality assurance procedures will be performed according to the institutional standard. Each participating institution will provide a SOP for quality assurance.

10.6 Start of radiotherapy

Radiotherapy should be started within three weeks after inclusion of the patient in the study.

11 Trial Procedures and Assessment

11.1 Specific diagnostic procedures

A complete staging according to current guidelines with adequate imaging is required. . The available data should give sufficient information about:

- Number of visible metastatic lesions
- location of each lesion (e.g. lung metastasis in left lower lobe, osseous metastases in os sacrum)
- Size of each lesion

Additional specific work-up is not required.

11.2 Baseline examination

A baseline diagnostic MR examination corresponding to dominant symptom must be performed according to trial specifications in appendix 2. The MR images must be co-registered to imaging necessary for radiotherapy planning (CT).

Baseline examination includes:

- Review of medical history inclusive previous anti-cancer treatment
- Review of clinical routine blood and radiology results
- Review of concomitant medication, analgesia, opioids, current systemic anti-cancer treatment
- Tumor staging, grading, classification, localizations, sizes

- Physical examination (incl. height, weight)
- ECOG performance status
- Baseline dominant symptom (VAS score)
- Baseline acute toxicity RTOG/CTCAE v.4.03 scores
- Quality of life (EORTC-QLQ C30)

11.3 End of radiotherapy

At end of radiotherapy, the following must be documented:

- Review of concomitant medication, analgesia, opioids, current systemic anti-cancer treatment
- Review of clinical routine blood results and radiology
- Dominant symptom score (VAS score)
- Acute toxicity (NCI-CTCAE v4.03 score)
- Performance status (ECOG)
- Assessment of AE/SAEs

Details of actually applied treatment are to be documented throughout and to be entered into the CRF at the end of treatment:

- Radiotherapy techniques uses
- Volumes, fractions, doses applied, dose constraint compliance for all organs at risk
- Cumulative doses to target volumes, any boosts

11.4 Follow-up visits

Protocol visits are required at registration for the trial and at end of radiotherapy and at 1,3 and 6 months after end of treatment (see flowchart in appendix 3). At this time, the following examination will be performed:

- Review of concomitant medication, analgesia, opioids, current systemic anti-cancer treatment
- Review of clinical routine blood and radiology results
- Dominant symptom score (VAS)
- Acute toxicities of radiotherapy , RTOG/NCI score
- Quality of life (EORTC-QLQ C30) (only at 6 months)
- ECOG performance status
- Assessment of AE/SAE

All later visits are scheduled according to standard guidelines and institutional procedures.

11.5 Follow-up diagnostics

Protocol specific follow-up MR diagnostic scan is required for patient visit at one and six months after end of radiotherapy or at progression of the dominant symptom. The MR diagnostics should be performed according to the specifications in appendix 2. Remission status evaluated at 6 month based on available clinical data. Follow-up MR Scans will be co-registered to the baseline MR scan. Comparative volume and ADC statistics will be calculated as surrogate markers of response to radiotherapy.

12 Safety management

12.1 Adverse events

An adverse event (AE) is defined as any event experienced by a patient or subject of a clinical trial, which does not necessarily have a causal relationship to the study treatment.

The severity of AEs should be assessed by using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.03). If an AE occurs, which is not described in the CTCAE version 4.03, the following five-point scale should be used for assessment: grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening and grade 5 = fatal.

The investigator must also systematically assess the causal relationship of the AEs to the trial treatment. The AEs should therefore be classified as reasonably related or not reasonably related (unrelated) to trial treatment.

- All AEs experienced will be documented in the appropriate section of the CRF.
- Any clinical AE with severity of grade 4 or 5 must also be reported as an SAE.

Severe adverse events (SAE)

A severe adverse event (SAE) is any untoward medical occurrence that meets the following criteria:

- Results in death.
- Is life-threatening
- Requires hospitalization or prolongs an existing hospitalization.
- Results in persistent or significant disability
- Is a congenital anomaly or birth defect.
- Is otherwise considered medically important.

All SAEs must be documented and reported to the sponsor within 24 hours after awareness of the event using the online web interface for Easytrial.

13 Data and Safety Monitoring Board

Data will be entered pseudonymously into an online web based electronic database, Easytrial, and data stored on servers in Denmark. Access to the web interface is by invitation via email to staff participating in the study only. The Data and Safety Monitoring Board (DSMB) reviews safety after the first ten and after the

last patient have been treated and the respective data validated and tabulated. It may recommend restrictions to treatment regimens and patient eligibility.

14 Endpoint Adjudication Committee

The Endpoint Adjudication Committee (EAC) receives pseudonymized MRI scans and the Radiotherapy treatment plan for all patients up to end of trial. The EAC will assess when progression free survival ended.

15 Quality Assurance

The Monitoring at the German sites according to GCP is performed by ZKS Kiel/Luebeck.

The Danish sites will be monitored according to the Danish regulations in their own responsibility.

16 Statistical aspects

16.1 Case number

The objective of this study is to investigate the feasibility of applying hypo-fractionated radiotherapy to treat a dominant symptomatic lesion in patients with HRPC. The hypothesis is that at least 90% of the recruited patients complete combined systemic and local treatment with at least 90% of scheduled radiation dose administered. We use a two-sided one-sample proportion score test to compare the proportion of feasible cases to a reference value of 90%. We want to detect any difference with statistical significance of 5% and a power of 80% for not overlooking a true proportion non-feasible of 70%. The necessary sample size is estimated to 24 cases. Drop-out may happen either due to exclusion, or because patients withdraw their consent for participation. For patients with poor prognosis a realistic drop-out rate is estimated to be 30%, which implicated that **34 patients** must be included in the study to reach significance.

16.2 Recruitment period and study duration

The recruitment period is scheduled to start in March 2018 and will last 12 months. The primary endpoint (feasibility) will be reached maximum 6 months after inclusion of the last patient. Documentation and data evaluation will take about 3 months. The primary result of the study will probably be available in end 2019.

16.3 Analysis

Patient and tumor characteristics are given as absolute and relative frequencies. Doses, volumes, fractions are listed by technique, by localization of metastasis, and by size. Maximum and median doses applied to organs at risk are described as median, inter-quartile range, and maximum. Summary compliance measures use the worst observation. Further parameter estimation, confidence intervals and tests using data at the metastasis level account for correlation by using GEE methods.

Toxicities are tabulated by grade and time and shown as time profiles of cumulated grades. Adverse events are listed by system organ class (MedDRA), intensity and causality. Progression free survival is estimated using the Kaplan-Meier method.

17 Early termination

17.1 Early termination and close of recruitment

The study has to be terminated immediately, if a SAE with probable association to the study therapy occurs in more the 2 out of the first six patients or more than four out of the first 10 patients or in more than 40% of all recruited patients thereafter. The study may be terminated on the decision of the principal investigator in case of the following events:

- Insufficient recruitment
- new scientific data which either definitively answer the scientific question or require major changes of the protocol which cannot be included in an amendment

17.2 Study termination in individual patients

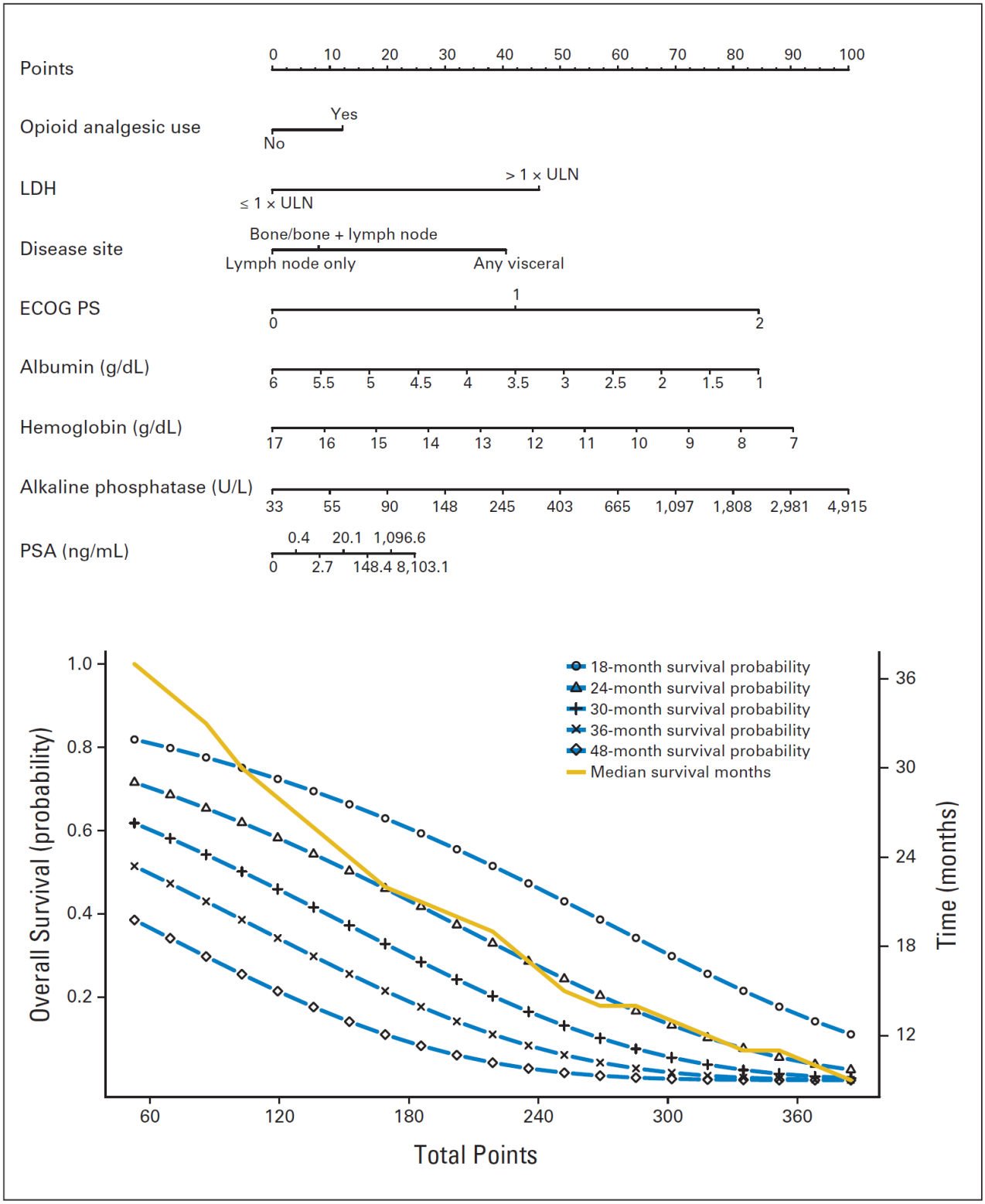
Participation in the study and study specific therapy must be stopped at any time during the study in individual patients for any of the following reasons

- withdrawal of informed consent by the patient
- severe toxicity with limitations or unacceptable risks to administer further study therapy
- inter current disease with limitations to administer protocol therapy
- progression of disease

18 Ethical and legal aspects

The study will be conducted according to the declaration of Helsinki. Approval by the ethical committees of the participating institution is required prior to initiation of the study. Patients must be fully informed about the study and give informed consent prior to inclusion. National rules for data protection must be obeyed.
The study concept has been evaluated by the expert panel of DEGRO (German Association of Radiation Oncology). Approval by the German Radiation Protection Authority (BfS) is not required. A patient insurance will be taken out before the start of the trial for all patients, if necessary according to national rules. The trial will be registered in a primary study register before the start of the study.
This study receive financial support from EU via the Interreg project.

19 Appendix 1 – Calculation of median survival



20 Appendix 2 – Diagnostic MR Protocol sequences

MR protocols are modified/adapted from (24) and (27) to cover the lesion that explains the dominant symptom.

The MR sequence protocol must contain an anatomical (T2w) axial sequence (reference scan see table below), that can be co-registered to the planning CT, ie. the reference scan must include enough rigid anatomical structures for a co-registration with good accuracy. The remaining MR sequences must cover the dominant lesion with adequate margin (typically 50 mm) that will allow for outline of the lesion in 3D. All MR sequences must be acquired with the same dicom origo, ie neither, the patient nor, the dicom origo may be moved between sequence acquisitions. This will allow all MR images to be co-registered to the planning CT.

Sequence	Directions	Slice mm	TR msec	TE msec	Avg
T2-weighted fast SE	Ax* / Cor / Sag	3/ 5/ 5	2850	80	4
T1-weighted GRE SPIR**	Ax	5	1000	3.7	4
Proton density–weighted fast SE	Ax	5	2850	4.7	4
DW imaging*** with free-breathing SE EPI SPIR*	Ax	5	4687	64	8

Avg = number of sample averages

* Reference scan = T2w axial images

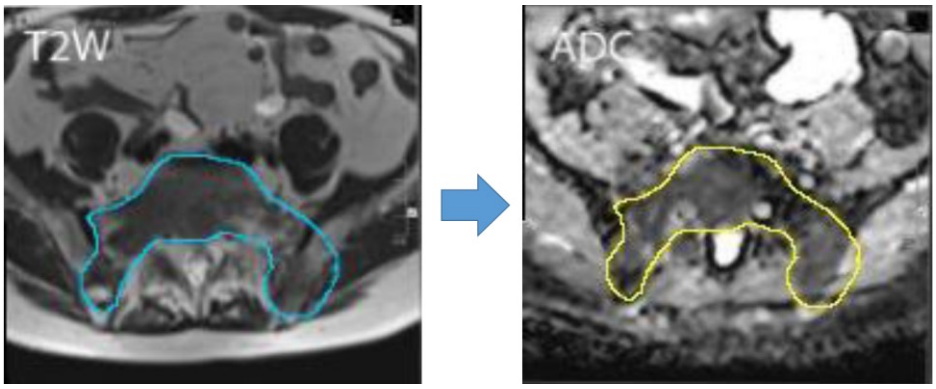
** SPIR = Spectral Presaturation with Inversion Recovery

*** b0 images and three b-values: b=50, 500 og 900 sec^2/mm

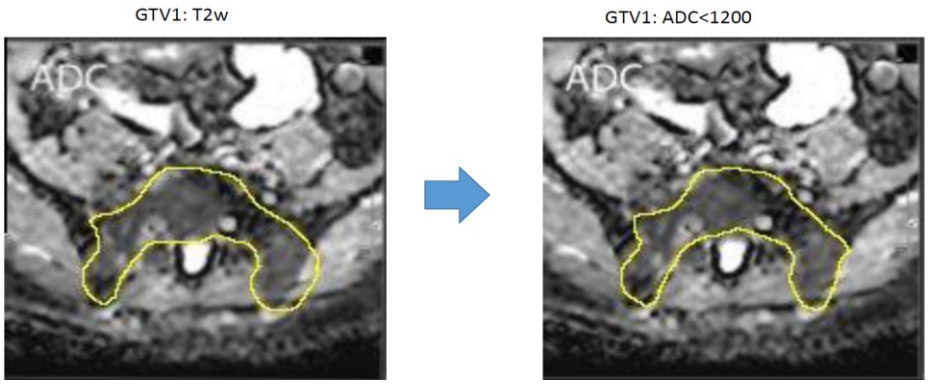
Fat suppression should be preferably be done with a selective method as SPIR if possible. If not the STIR method, less specific, alternative method to use. Some post processing of MR images may be necessary to suppress noise in the images before automatically outlining the GTV. The ADC map should be calculated using all three b-values and mono-exponential fitting.

21 Appendix 3 - Target outline procedure

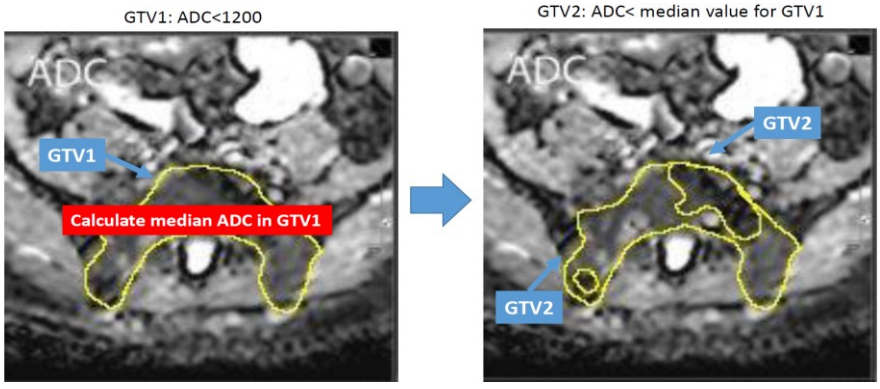
The following example demonstrate the target outline procedure on the MR images. This example is a reconstruction based on images from (28)



The target is outline on the T2W image. This image I co-registered to the ADC map and the outline is transferred to the ADC map.



The outline transferred to the ADC map is subsequently corrected using a threshold for the ADC < 1200 mm^2/s for the target. This target is named GTV1



The median ADC value for the GTV1 target. The median value is used as threshold to obtain the most aggressive part of the target. This subvolume is named GTV2.

22 Appendix 4 – Flowchart for the study

	Inclusion	Visit 1 Baseline before RT	After RT	Visit 2 1 month	Visit 3 3 month	Visit 4 6 month
Screening / Inclusion	X					
Informed Consent	X					
Medical history	X					
MR scanning		X		X		X
Anamnesis		X				
Medical examination		X	X	X	X	X
Local Symptoms		X	X	X	X	X
Quality of Life		X				X
Toxicity		X	X	X	X	X
LPFS			X	X	X	X
ADC Response			X			X
Survival			X	X	X	X
AE/SAE			X	X	X	X
Concomitant medication		X	X	X	X	X
VAS		X	X	X	X	X
ECOG		X	X	X	X	X

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