PROTOCOL

PART: Investigate the Benefit of Elective Para-Aortic Radiotherapy for pN1 Prostate Cancer using Arc Therapy (IMAT/VMAT): study protocol for a non-randomized phase II trial

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ABSTRACT

Introduction: In prostate cancer with histopathological proven pelvic lymph node metastasis (pN1) after extended pelvic lymph node dissection, multimodality treatment consisting of treatment of the primary tumour and whole pelvic radiotherapy combined with androgen deprivation therapy (ADT) offers promising results and results in better cause-specific survival rates compared to ADT alone. However, in case more than one pelvic lymph node is invaded by tumour, approximately 40% of the patients relapse biochemically and clinically. Clinical relapse is present in the para-aortic lymph nodes (M1a disease) in up to 77% of the relapsing cases. We hypothesize that, based on the evidence that positive lymph nodes represent the door to haematogenous dissemination, elective para-aortic irradiation will reduce the development of both retroperitoneal nodal (M1a) and distant metastasis (M1b/M1c disease), postpone the need for palliative androgen deprivation therapy and prolong the time to castration-refractory disease.

Methods: To test this hypothesis, we will conduct a prospective non-randomized phase 2 trial that will study the efficacy of additional elective para-aortic radiation therapy in pN1 patients compared to those who were historically treated with adjuvant whole pelvic radiotherapy alone. We aim to include 137 patients with prostate cancer and presence of pN1 disease after extended pelvic lymph node dissection. With this number of patients, an improvement in clinical relapse free survival (cRFS) at 5 years by 15% can be detected with a power of 80%.

Results: Recruitment of patients for this trial started in 2017. The approximate date when recruitment will be completed is March 2020.

Discussion: This is the first phase II trial to investigate the benefit of an elective para-aortic radiotherapy in prostate cancer patients. The result of this trial can potentially serve as a sound base for a later randomized phase III trial. All participants are given a PART information sheet and required to give written informed consent. Results will be expected to be published in a peer-reviewed journal.

Trial registration: This study is registered at ClinicalTrials.gov, NCT03079323 (March 14, 2017).
**Keywords**: prostate cancer, elective para-aortic radiation therapy, external beam radiotherapy, PART-trial

**INTRODUCTION**

Prostate cancer (PCa) is the most common non-skin malignancy and an important cause of cancer-related mortality in men in industrialized countries worldwide [1,2]. Mortality is highest in high-risk prostate cancer, defined by the guidelines of the European Association of Urology (EAU) as T-stage ≥ cT2c or Gleason score ≥ 8 or Prostate Specific Antigen (PSA) > 20 ng/ml. These patients benefit from aggressive local treatment (surgery and/or radiation therapy). To assess the risk of disease spread to pelvic nodes, predictive nomograms are used [3–5], although the EAU guidelines consider an extended pelvic lymph node dissection (ePLND) as a necessity in high-risk patients [6]. Indeed, ePLND has proven to be the most accurate nodal staging procedure and remains therefore the gold standard [7] with even a positive effect on prostate cancer mortality, certainly in case of limited nodal disease [8] and negative nodes [9].

Historically, patients with positive pelvic lymph nodes (N1) were considered metastatic and treated with lifelong palliative androgen deprivation therapy (ADT) only [10]. However, in the 21st century, an important paradigm shift occurred. At first, local treatment with curative intent is gaining interest in patients with N1 disease [11]. Hereby, also the extent of ePLND plays a crucial role in predicting cause-specific survival (CSS) as has been demonstrated by Abdollah et al. [12]. Secondly, large retrospective series demonstrated an improvement in prostate cancer specific survival (PCSS) when post-operative radiotherapy was added to ADT in pathologically node-positive (pN1) patients [13–15].

In the multidisciplinary approach of pN1 patients, multimodality treatment (MMT) consisting of treatment of the primary tumour, long-term ADT and whole pelvic radiotherapy (WPRT) has become
the standard of care at the Leuven University Hospitals (LUH) (Leuven, Belgium) and at Ghent University Hospital (GUH) (Ghent, Belgium). WPRT is delivered using intensity-modulated or volumetric arc therapy (IMAT / VMAT) [16,17]. Clinical results demonstrated that this MMT is well tolerated and results in 5 years PCSS of >90% with the best results observed in patients having a low number of positive lymph nodes (LN). Indeed, patients presenting with 1 or 2 positive LN had a 5-years PCSS comparable to pN0 patients [18–20].

The number of pathologically metastatic lymph nodes is a determinant for patient outcome. In case >2 LN are pathologically invaded by tumour, 30% to 40% of the patients relapse biochemically and clinically [21,22]. Furthermore some data suggest that extracapsular extension of pelvic nodal metastases is an important negative prognostic factor in pN1 patients [23].

Clinical relapse is present in the para-aortic LN (PALN, M1a disease) in up to 77% of the cases as we observed in references [24,25]. Rischke et al. demonstrated the retroperitoneum to be the most frequent site of relapse after pelvic salvage treatment [26]. In the TNM classification, patients with positive PALN are denominated M1a disease and considered as a separate entity [27]. We hypothesize that these positive PALN will lead to further haematogenous spread (M1b – M1c disease [27]) and that elective para-aortic irradiation will decrease the rate of further metastatic spread, postpone the need for palliative ADT and prolong the time to castration-refractory disease. To test this hypothesis, we designed a prospective non-randomized phase 2 trial that will evaluate the efficacy of elective para-aortic radiotherapy (PART) in pN1 patients compared to those who were historically treated with adjuvant WPRT alone (Figure 1).
Figure 1: Graphic presentation of the study hypothesis
METHODS

Study Design

The PART-trial is a non-randomized phase II trial which was approved by the Medical Ethical Committee of LUH (EC number: B 3222 0163 0604) and is written in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. Patients are recruited during the multidisciplinary consultation Urology-Radiation Oncology and at the Department of Radiation Oncology of LUH, GUH and other participating centres. After giving informed consent, they are included in the trial.

Patient: in- and exclusion criteria

Men, aged >18 years, with histological proven adenocarcinoma of the prostate at biopsy (cT1-4), referred for primary high-dose radiotherapy or at biopsy and after radical prostatectomy (RP) (pT2-4) and presence of pN1 disease after ePLND are eligible for the study. In all participating centres, performing an ePLND is standard of care in high-intermediate and high risk patients, independently whether the primary treatment is RP or high-dose radiotherapy [28,29]. If pN1 disease is present, patients are eligible if one of following criteria is fulfilled:

(1) Two or more positive LN.
(2) Ratio positive LN / removed LN > 7%.
(3) Presence of extracapsular metastatic extension at the level of any LN.

ePLND is defined as the removal of lymph nodes around the external and internal iliac vessels and in the obturator fossa. Removal of additional lymph nodes in the presacral area or around the common iliac vessels is at the discretion of the treating physician (but strongly advised if present on preoperative imaging). The minimum harvest of removed lymph nodes that is considered representative is set at 14. Table 1 summarizes the in- and exclusion criteria.

Table 1: PART-trial: inclusion and exclusion criteria
### Inclusion criteria
- Signed informed consent and willingness to comply with the treatment and follow-up
- Diagnosis of histopathological confirmed prostate cancer
- No former treatment for prostate cancer, except RP and ePLND
- Presence of pN1 disease after ePLND (criteria of pN1 disease defined in the protocol)
- Age > 18
- Karnofsky Performance score > 70
- Ability to understand the informed consent (Helsinki Declaration)

### Exclusion criteria
- Recurrent disease status defined as rising PSA after nadir post-surgery.
- Presence of cM1a, cM1b or cM1c disease [27]. Patients with cN1 disease at RT imaging for planning are excluded.
- Former radiotherapy making WPRT and/or PART impossible
- Prior malignancy, not disease-free > 5 years, except basocellular skin epithelioma
- Severe or active comorbidity likely to impact on the feasibility of WPRT and/or PART (e.g. ulcerative colitis)
- Disorder precluding understanding of trial information
Radiotherapy: structure delineation, planning and delivery.

Structure delineation

Details on delineation of the clinical target volume (CTV) of the pelvic nodal areas can be found in reference [30]. In brief, the elective lymph node areas consisted of the obturator, internal and external iliac, presacral and common iliac nodes [16]. Concerning the prostate bed (postoperative setting) and the prostate (primary setting), both T2-weighted magnetic resonance imaging (MRI) and computed tomography (CT) images are used to optimize delineation. Details can be found in references [31], [32] and [33].

Delineation of the PALN starts caudally at the level where the abdominal aorta splits into both common iliac branches and stops cranially at the level of the renal artery/vein. The CTV of the PALN is created by adding a 7 mm 3-dimensional expansion to the abdominal aorta and inferior caval vein, excluding intestinal loops and vertebral bodies. Unless impaired kidney function, CT-imaging is done using intravenous contrast to optimize visualization of the vessels and improve discrimination with the intestinal loops. The use of oral contrast to better visualize these intestinal loops is left at the discretion of the treating physician. Details concerning protocols on bladder filling and rectal preparation, details can be found in reference [34]. The planning target volume (PTV) of the lymph nodes is created by expanding the CTV with an isotropic margin of 7 mm.

Concerning the organs at risk (OARs), the following structures are delineated: bladder, anal canal, rectum, sigmoid colon, small intestine, large bowel, femoral heads, spinal cord, cauda equine, bone marrow and kidneys. Delineation of the OARs is depicted in figure 2.
Figure 2: Graphic presentation on axial planes (from cranially (renal vessels) to caudally (aortic bifurcation)) and coronal plane of the delineation: CTV-PALN + CTV pelvic LN: purple; CTV prostate bed: red; Bladder: yellow; Sigmoid colon, Small intestine, Large bowel: green; Femoral heads: brown; Bone marrow: light blue; Kidneys: turquoise; Spinal cord, Cauda equina: marine blue

Radiotherapy planning

The applied planning technology is IMAT/VMAT/RapidArc™ (Varian Medical Systems, Palo Alto, CA, USA; Elekta, Stockholm, Sweden) [17] (figure 3). The technology and feasibility to treat the PALN has been published [35].
Figure 3: Dose distribution in PART-trial. Used planning technology is volumetric modulated arc therapy (IMAT/VMAT/RapidArc™). A: Coronal dose distribution; dose range from 0 up to 70 Gray. B: Transverse dose distribution CTV-PALN; dose range from 0 up to 50 Gray

**Dose prescription and treatment delivery**

Dose will be prescribed as $D_{98}$ - i.e. the dose received by 98% of the volume and a surrogate for minimal dose - to the PTV of the pelvic LN and PALN. This $D_{98}$ is 45 Gy, to be delivered in 25 fractions of 1.8 Gy. In case of the postprostatectomy situation, the PTV of the prostate and seminal vesicle bed
will be treated to a median dose of 70 Gy in 35 fractions. In case of primary radiotherapy to the prostate, median PTV dose will be 65 Gy in 25 fractions (moderate hypofractionation). Details on dose prescription and constraints for organs at risk can be found in our previous work [36]. Treatment will be delivered using 6 – 10 Megavoltage Photons from a linear accelerator (both Elekta® and Varian® Systems are used). Image-guided radiotherapy is obligatory and will be performed using daily cone-beam computed tomography (CBCT) [37].

**Hormonal treatment**

Androgen deprivation therapy (ADT) will be started 2 to 4 weeks before the start of radiotherapy in order to overcome the androgen receptor induced radioresistance [38]. The duration of ADT is 24 months (long term) as all patients belong to very high risk population and long term ADT is the standard of care in these patients [39,40]. Both the use of a LHRH-analogue and an antagonist is allowed.

**Primary Endpoint**

The primary endpoint is 5 year-clinical relapse-free survival (cRFS) defined as the absence of any clinical relapse (cR) that would be visible at top of the line imaging (see below). Any detected clinical recurrences (r) will be anatomically mapped and categorized as local (rL), pelvic nodal (rN1), retroperitoneal nodal (rM1a), bone (axial, perpendicular or both, rM1b) or soft-tissue (rM1c). Combinations of different relapse sites are of course possible and will be reported accordingly. Apart from the anatomical site of relapse, the number of relapses, size per relapse and the subsequent treatment will be recorded.

PSA measurements are performed during follow-up according to a fixed schedule (Table 2). If PSA is undetectable, patients are considered free of cR. In case of biochemical relapse (bR), defined as a PSA > 0.2 µg/L in the postprostatectomy setting and a PSA value > nadir +2 µg/L in the primary setting
Positron Emission Tomography - Computed Tomography (PET-CT) imaging using Prostate-Specific Membrane Antigen (PSMA) ligand and/or $^{18}$F/$^{11}$C-choline-based PET-CT imaging is acquired. Additional imaging tools include multiparametric MRI and MRI of the axial and perpendicular bones. The decision to perform additional imaging will be taken after multidisciplinary consensus in all cases.

**Secondary endpoints**

Secondary endpoints are Quality of life (QoL), treatment-related acute and late toxicity, time to palliative ADT, time to castration refractory prostate cancer (CRPC), cause-specific survival (CSS) and in field pelvic and para-aortic disease control.

QoL is measured using the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30) [43]. The EORTC prostate cancer module (QLQ-PR25) [44], the EuroQol 5 dimensions (EQ-5D-5L) questionnaire [45], the International Consultation on Incontinence Short Form (ICIQ-SF) score [46] and the International Index of Erectile Function (IIEF-5) scoring system [47] are used to assess urinary, bowel and sexual functioning and symptoms and to evaluate the side effects of hormonal treatment associated with radiotherapy. QoL questionnaires are handed over to the patient before treatment (baseline score) and at well-defined time points (end of treatment, 1 month, 3 months, 6 months, 9 months after treatment; every 6 months until 5 years after treatment; every 12 months until 10 years after treatment). Treatment-related toxicity is assessed by the Common Toxicity Criteria for adverse events version 4.0 (CTCAE v4.0) [48]. Abdominal pain, diarrhoea, enterocolitis, faecal incontinence, flatulence, haemorrhoids, proctitis, rectal fistula, rectal haemorrhage, rectal pain, non-infectious cystitis, haematuria, urinary frequency, urinary incontinence, urinary retention, urinary tract pain, erectile dysfunction and fatigue are scored as adverse events according to CTCAE v4.0. Symptoms are scored before treatment. PART-induced acute toxicity is scored weekly during radiation treatment and 1
month and 3 months after treatment. Treatment-induced late toxicity is scored at 6, 9 and 12 months after treatment, every 6 months until 5 years after treatment and every 12 months until 10 years after treatment.

Time to palliative ADT is defined as secondary endpoint of this trial. Indications to initiate palliative ADT are based on the EAU guidelines [41,42] and include: PSA > 50μg/l and/or PSA doubling time <6 months and/or symptoms due to progressive disease. In case of oligometastatic recurrence (1-3 synchronous metastases), metastasis-directed therapy is the preferential treatment option [49]. Time to CRPC is defined according to the criteria defined in the EAU guidelines [41,42]. Cause-specific survival (CSS) is defined as the interval from the date of diagnosis to the date of death from prostate cancer or to the last follow-up date for censoring purposes, if the patient is alive and is still being followed at the time of data cut-off.

**Laboratory analysis**

All laboratory tests are considered standard and include: PSA measurement, peripheral blood cell count with formula, kidney function tests, liver function tests and testosterone measurement. This laboratory tests are done during every follow-up visit.

**Time Schedule**

The aim is to recruit the necessary number of patients within a timeframe of 48 months. Follow-up of these patients will be life-long in order to correctly estimate the primary and secondary endpoints. Reports on acute PART-induced toxicity and quality-of-life will be expected within 6 months after closure of the trial. The primary endpoint will be calculated after a median follow-up of 60 months.
Table 2: SPIRIT 2013 diagram: PART-trial

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Imaging (after MOC decision)  

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* Standard examinations; Laboratory analysis is described in the protocol.

Safety

This project has been granted by “Kom op tegen Kanker” (study number: S59533). The investigators shall report all serious adverse events (grade 3 or more) immediately to the sponsor. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by code numbers. For reported deaths of a subject, the investigator shall supply the sponsor and the accredited ethics committee with any additional information requested. Patients will be withdrawn from PART if they develop grade 4 toxicity. Based on former experience in cervical cancer, the chance that grade 4 toxicity occurs when para-aortic radiotherapy is delivered, is negligible [50].

The investigator shall ensure that all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the minister, and to the competent ethics committee, and in any case no later than seven days after knowledge by the investigator of such a case.

All other suspected unexpected serious adverse reactions shall be reported to the minister and to the ethics committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the investigator. Furthermore the principal investigator shall also inform the other investigators.

Sample size and statistics
We aim to improve cRFS at 5 years by 15% (primary end point). This would result in a cRFS of 75% at 5 years compared to the control group with WPRT only who reaches a 5-years cRFS of 60% [18,20]. For a log-rank test comparing two survival curves with a one-sided significance level of 0.1, assuming uniform accrual with an accrual time of 48 months and a follow-up time of 12 months, a sample size of 137 is required to obtain a power of at least 80%. Taken into account a drop-out of 10%, we aim including 151 patients. The control group consists of pN1 patients treated with adjuvant ADT and WPRT alone from whom the data have been published before [20]. Statistics will be performed using the latest version of SPSS.

RESULTS

Ethical approval to conduct this study (version 2.0 from 1 December 2016) was granted by the Medical Ethics Committee UZ/KU Leuven (14/12/2016). Written informed consent of patients is mandatory before recruitment. Recruitment of patients started in 2017. The approximate date when recruitment will be completed is March 2020.
DISCUSSION

Currently, management of pN1 PCa is shifting towards a multimodal approach aiming at cure. Several recent studies showed an improved CSS when adjuvant radiation therapy was added to ADT [13,20,50–52]. Unfortunately, recurrences are still observed. Data suggest relapse at the site of the PALN due to ascending PCa lymphatic spread from the pelvis up to the retroperitoneum in about 75% in case of lymph node only recurrence [24,25]. New strategies to further enhance locoregional control while maintaining an acceptable level of toxicity are a possible tool to improve cure rates as locoregional relapse is linked to metastatic progression [53,54]. The use of extended-field IMRT to the PALN plus concurrent cisplatin in cervical cancer improved the outcome for patients with LN-positive stage IB2-IIIB cervical cancer [55]. Based on the evidence that positive LN are observed before haematogenous spread occurs, we hypothesize that elective PA irradiation will reduce the development of distant metastasis, postpone the need for palliative ADT and prolong the time to castration-refractory disease.

This protocol describes the design of a non-randomized phase II trial to evaluate the clinical effectiveness of elective para-aortic radiotherapy using arc therapy for reducing disease recurrence in pN1 prostate cancer patients. To the best of our knowledge, this is the first phase II trial investigating the benefit of an elective para-aortic radiotherapy in prostate cancer patients. Its results will hopefully provide a sound basis for a prospective randomised Phase III study randomising patients between WPRT only and WPRT with PALN irradiation.
List of abbreviations

PART: Para-Aortic Radiotherapy
IMAT: Intensity Modulated Arc Therapy
VMAT: Volume Modulated Arc Therapy
ADT: Androgen Deprivation Therapy
cRFS: Clinical Relapse Free Survival
PCa: Prostate Cancer
EAU: European Association of Urology
PSA: Prostate Specific Antigen
ePLND: Extended Pelvic Lymph Node Dissection
CSS: Cause-specific Survival
PCSS: Prostate Cancer Specific Survival
MMT: Multimodality Treatment
WPRT: Whole Pelvic Radiotherapy
LUH: Leuven University Hospitals
GUH: Ghent University Hospital
LN: Lymph Nodes
PALN: Para-Aortic Lymph Nodes
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
RP: Radical Prostatectomy
CTV: Clinical Target Volume
MRI: Magnetic Resonance Imaging
CT: Computed Tomography
PTV: Planned Target Volume
OARs: Organs at Risk
CBCT: Cone-Beam Computed Tomography
cR: Clinical Relapse
R: Recurrences
bR: Biochemical Relapse
PET-CT: Positron Emission Tomography – Computed Tomography
PSMA: Prostate-Specific Membrane Antigen
QoL: Quality of Life
CRPC: Castration Refractory Prostate Cancer
EORTC: European Organization for Research and Treatment of Cancer
CTCAE: Common Toxicity Criteria for Adverse Events
Consent for publication
Not applicable.

Availability of data and material
The data set used and/or analysed during the current study is available from the corresponding author on reasonable request. Not all data are obtained yet since the study is still ongoing.

Conflicts of Interest
The authors declare that they have no competing interests.

Author contributions
CD participated in the data collection. GDM is the principle investigator. GDM and CD completed the ethics application and revisions. GDM, SJ and VF have been involved in all stages of study design, together with LD, NL, WE, PD, LVDB, WC, HVD, LVW, KD, PO, PB, KH, and CB. All authors read and approved the final manuscript.

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REFERENCES


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FIGURE LEGENDS

Figure 1: Graphic presentation of the study hypothesis

Figure 2: Graphic presentation on axial planes (from cranially (renal vessels) to caudally (aortic bifurcation)) and coronal plane of the delineation: CTV-PALN + CTV pelvic LN: purple; CTV prostate bed: red; Bladder: yellow; Sigmoid colon, Small intestine, Large bowel: green; Femoral heads: brown; Bone marrow: light blue; Kidneys: turquoise; Spinal cord, Cauda equina: marine blue

Figure 3: Dose distribution in PART-trial. Used planning technology is volumetric modulated arc therapy (IMAT/VMAT/RapidArc™). A: Coronal dose distribution; dose range from 0 up to 70 Gray. B: Transverse dose distribution CTV-PALN; dose range from 0 up to 50 Gray