

Protocol

Benefits of Elective Para-Aortic Radiotherapy for pN1 Prostate Cancer Using Arc Therapy (Intensity-Modulated or Volumetric Modulated Arc Therapy): Protocol for a Nonrandomized Phase II Trial

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Abstract

Background: In patients with prostate cancer (PCa) with histopathologically proven pelvic lymph node (LN) metastasis (pN1) after extended pelvic lymph node dissection (ePLND), multimodality treatment consisting of treatment of the primary tumor and whole pelvic radiotherapy (WPRT) combined with androgen deprivation therapy (ADT) offers promising results, leading to better cause-specific survival rates compared with ADT alone. However, in case more than one pelvic LN is invaded by the tumor, approximately 40% of the patients relapse biochemically and clinically. Clinical relapse is present in the para-aortic LNs (M1a disease) in up to 77% of the relapsing cases.

Objective: We hypothesize that, based on the evidence that positive LNs represent the door to hematogenous dissemination, elective para-aortic irradiation will reduce the development of both retroperitoneal nodal (M1a) and distant metastasis (M1b or M1c disease), postpone the need for palliative ADT, and prolong the time to castration-refractory disease.

Methods: To test this hypothesis, we will conduct a prospective, nonrandomized phase II trial to study the efficacy of additional elective para-aortic radiotherapy (PART) in pN1 patients compared with those who were historically treated with adjuvant WPRT alone. We aim to include 137 patients with PCa and presence of pN1 disease after ePLND. With this number of patients, an improvement of 15% in the 5-year clinical relapse-free survival can be detected with a power of 80%.

Results: Recruitment of patients for this trial started in 2017 and will be completed approximately by March 2020.

Conclusions: This is the first phase II trial to investigate the benefits of an elective PART in patients with PCa. The results of this trial will 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 are expected to be published in a peer-reviewed journal.

Trial Registration: ClinicalTrials.gov NCT03079323; <https://clinicaltrials.gov/ct2/show/NCT03079323> (Archived by WebCite at <http://www.webcitation.org/73ELimv1d>)

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KEYWORDS

elective para-aortic radiotherapy; external beam radiotherapy; PART trial; prostate cancer

Introduction

Prostate cancer (PCa) is the most common nonskin malignancy and an important cause of cancer-related mortality in men in industrialized countries worldwide [1,2]. Mortality is highest in patients with high-risk PCa, defined by the guidelines of the European Association of Urology (EAU) as T-stage \geq cT2c or Gleason score \geq 8 or prostate-specific antigen (PSA) $>$ 20 ng/mL. These patients benefit from aggressive local treatment (surgery with or without adjuvant radiotherapy or primary radiotherapy). 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, therefore, remains the gold standard [7] with even a positive effect on PCa mortality, certainly in case of limited nodal disease [8] and negative nodes [9].

Historically, patients with positive pelvic lymph nodes (LNs; 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. 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 demonstrated by Abdollah et al [12]. Second, large retrospective series demonstrated an improvement in prostate cancer-specific survival (PCSS) when postoperative radiotherapy was added to ADT in pathologically node-positive (pN1) patients [13-15].

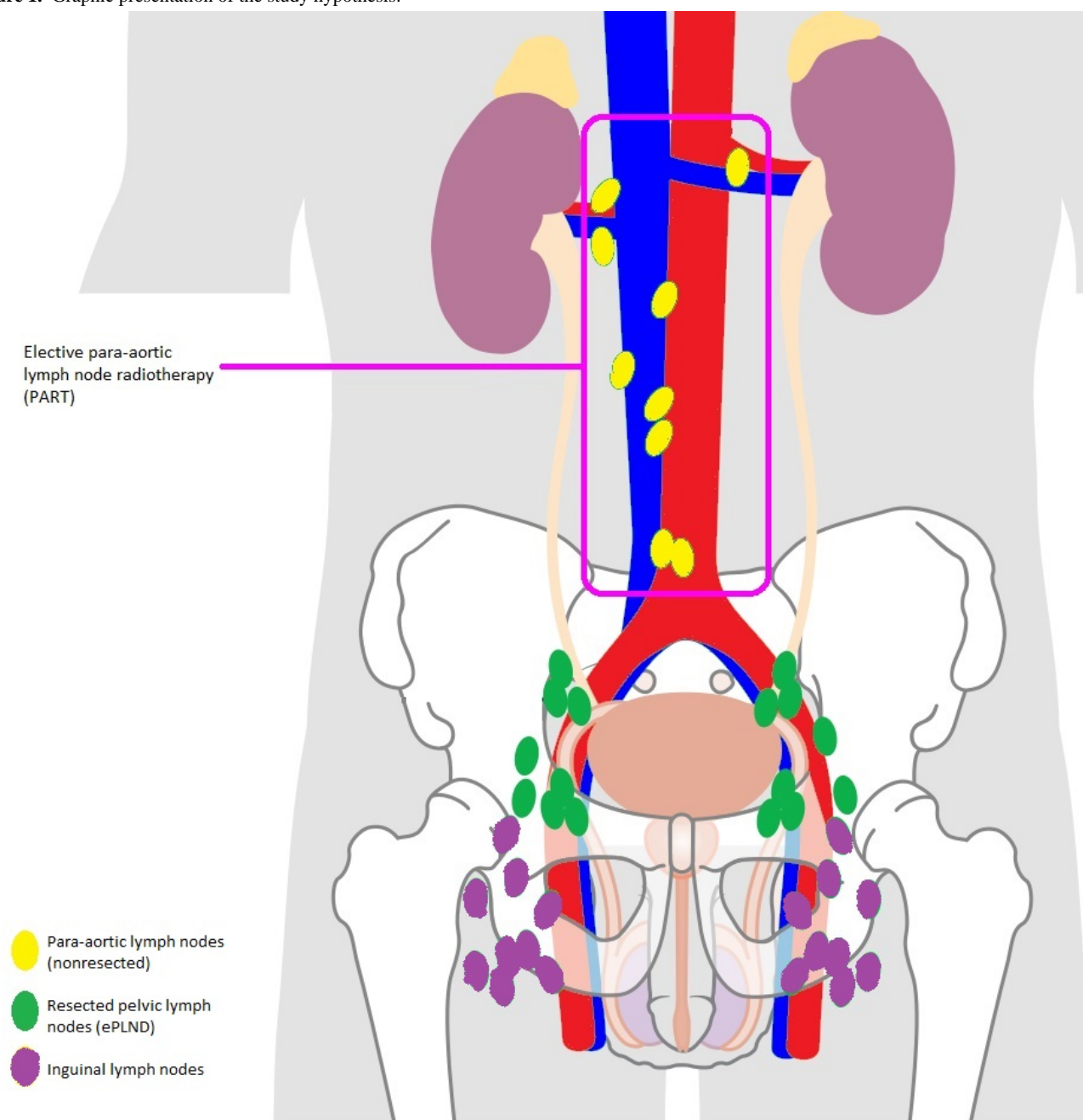
In the multidisciplinary approach for pN1 patients, multimodality treatment consisting of treatment of the primary tumor, long-term ADT, and whole pelvic radiotherapy (WPRT) has become the standard of care at the Leuven University Hospitals (LUH; Leuven, Belgium) and at the Ghent University

Hospital (GUH; Ghent, Belgium). WPRT is delivered using intensity-modulated or volumetric modulated arc therapy (IMAT/VMAT) [16,17]. Clinical results demonstrated that this multimodality treatment is well tolerated and results in 5-year PCSS of $>$ 90%, with the best results observed in patients having a low number of positive LNs. Indeed, patients presenting with 1 or 2 positive LNs had a 5-year PCSS comparable to that of pN0 patients [18-20].

The number of pathologically metastatic LNs is a determinant for patient outcome. In case $>$ 2 LNs are pathologically invaded by the tumor, 30%-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].

Reportedly, clinical relapse (cR) is present in the para-aortic LNs (PALN, M1a disease) in up to 77% of the cases [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 PALNs will lead to further hematogenous 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, nonrandomized phase II trial to evaluate the efficacy of elective para-aortic radiotherapy (PART) in pN1 patients compared with those who were historically treated with adjuvant WPRT alone (Figure 1).

This trial is novel and unique as it is the first to investigate the irradiation of the PALN region in pN1 patients with PCa to prevent further metastasis. This strategy has already been evaluated in advanced cervical cancer, but to the best of our knowledge, never in patients with PCa.

Figure 1. Graphic presentation of the study hypothesis.

Methods

Study Design

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

Inclusion and Exclusion Criteria

Men aged >18 years with histologically proven adenocarcinoma of the prostate at biopsy (cT1-4) who are referred for primary high-dose radiotherapy or patients after radical prostatectomy (RP; pT2-4) with presence of pN1 disease after ePLND are eligible for the study. pN1 disease is defined as the presence of regional LN metastasis in the true pelvis. These regions include the common iliac nodes, presacral nodes, external and internal iliac nodes, and obturator nodes [27]. In all participating centers, performing an ePLND is the standard of care in high-intermediate and high-risk patients, independent of whether the primary treatment is RP or high-dose radiotherapy [7,28]. If pN1 disease is present, patients are eligible if one of the following criteria is fulfilled:

1. Two or more positive LNs

2. Positive LNs/removed LNs >7%
3. Presence of extracapsular metastatic extension at the level of any LN

ePLND is defined as the removal of LNs around the external and internal iliac vessels and in the obturator fossa. Removal of additional LNs 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 LNs that is considered representative is set at 14. [Textbox 1](#) summarizes the inclusion and exclusion criteria.

After amending, patients with pN1 disease in the salvage setting will be allowed in the PART trial and will be prospectively followed with the same treatment protocol and study design to obtain data about acute and late toxicity. These data will be analyzed separately and will not interfere with the initial set-up of statistics.

Radiotherapy: Structure Delineation, Planning and Delivery

Structure Delineation

Details on delineation of the clinical target volume (CTV) of the pelvic nodal areas are provided elsewhere [29]. Briefly, the elective LN 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, as detailed elsewhere [30-32].

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 and 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 kidney function is impaired, CT imaging is done using intravenous contrast to optimize the 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 are provided elsewhere [33]. The planned target volume (PTV) of the LNs 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. [Figure 2](#) depicts the delineation of the OARs.

Radiotherapy Planning

The applied planning technology is IMAT/VMAT/RapidArc (Varian Medical Systems, Palo Alto, CA, USA; Elekta, Stockholm, Sweden; [Figure 3](#)) [17]. The technology and feasibility to treat the PALN have been published [34].

Textbox 1. Para-aortic radiotherapy (PART) trial: inclusion and exclusion criteria.

Inclusion criteria

- Signed informed consent and willingness to comply with the treatment and follow-up
- Diagnosis of histopathologically confirmed prostate cancer
- No former treatment for prostate cancer, except radical prostatectomy and extended pelvic lymph node dissection (ePLND)
- Presence of pathologically node-positive (pN1) disease after ePLND (criteria of pN1 disease defined in the protocol)
- Age >18 years
- Karnofsky Performance score >70
- Ability to understand the informed consent (Helsinki Declaration)

Exclusion criteria

- Recurrent disease status defined as rising prostate-specific antigen after nadir postoperatively
- Presence of cM1a, cM1b, or cM1c disease [27]; patients with cN1 disease at radiotherapy imaging for planning are excluded
- Former radiotherapy, making whole pelvic radiotherapy (WPRT) or PART impossible
- Prior malignancy, not disease-free >5 years, except basocellular skin epithelioma
- Severe or active comorbidity likely to impact the feasibility of WPRT or PART (eg, ulcerative colitis)
- Disorder precluding the understanding of trial information

Figure 2. Graphic presentation of the delineation: clinical target volume (CTV)-para-aortic lymph node (LN)+CTV pelvic LN: purple; CTV prostate bed: red; bladder: yellow; sigmoid colon, small intestine, and large bowel: green; femoral heads: brown; bone marrow: light blue; kidneys: turquoise; spinal cord and cauda equina: marine blue.

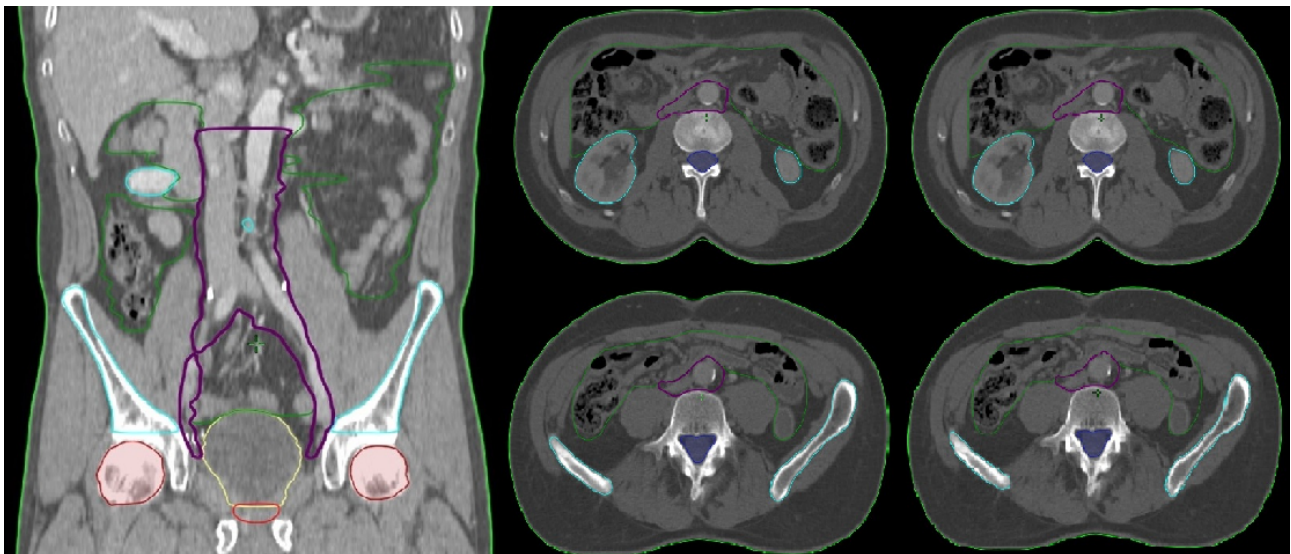
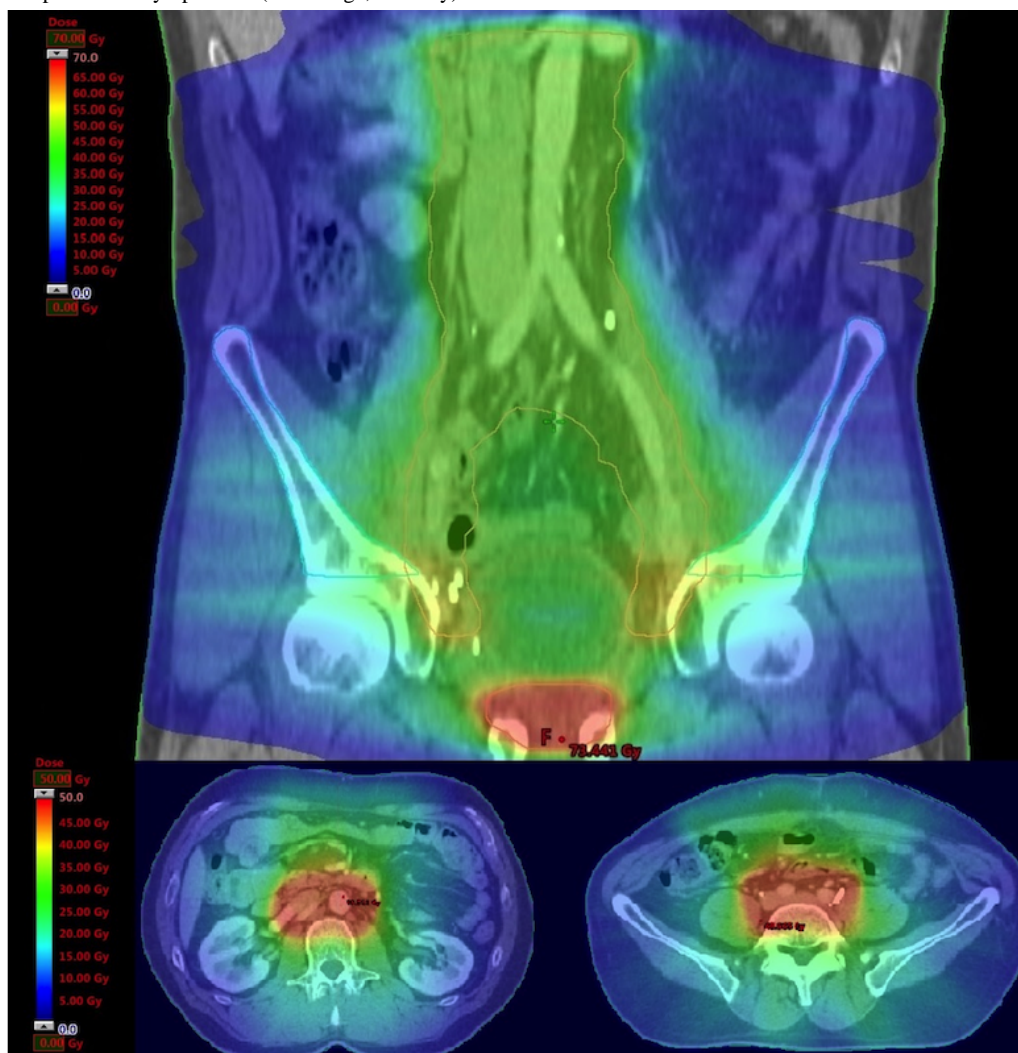


Figure 3. Dose distribution in para-aortic radiotherapy trial. Top: coronal dose distribution (dose range: 0-70 Gy); bottom: transverse dose distribution clinical target volume-para-aortic lymph node (dose range, 0-50 Gy).



Dose Prescription and Treatment Delivery

Dose will be prescribed as D_{98} (ie, 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 with a median dose of 70 Gy in 35 fractions. In case of primary radiotherapy to the prostate, the median PTV dose will be 65 Gy in 25 fractions (moderate hypofractionation). Details on dose prescription and constraints for OARs are provided elsewhere [16]. Treatment will be delivered using 6 to 10-MV 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 CT [35].

Hormonal Treatment

ADT will be started 2-4 weeks before the start of radiotherapy to overcome the androgen receptor-induced radioresistance [36]. The duration of ADT is 24 months (long term) as all patients belong to a very high-risk population and long-term ADT is the standard of care in these patients [37,38]. Of note, both the use of an luteinizing hormone-releasing hormone-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 cR that would be visible at top of the line imaging (see below). Any detected clinical recurrences (r) would 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 1). If PSA is undetectable, patients are considered free of cR. In case of biochemical relapse, defined as PSA >0.2 $\mu\text{g/L}$ in the postprostatectomy setting and PSA $>\text{nadir}+2$ $\mu\text{g/L}$ in the primary setting [39,40]. In addition, positron emission tomography-CT (PET-CT) imaging using prostate-specific membrane antigen ligand or $^{18}\text{F}/^{11}\text{C}$ -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.

Table 1. Standard Protocol Items: Recommendations for Interventional Trials 2013 diagram: Para-Aortic Radiotherapy (PART)-trial.

Timepoint	Study period	Postallocation				
		Enrollment: Screen visit & pre-PART (-t ₁)		During PART		Follow-up
				Weekly	Last day	Month 1, 3, 6, 9, 12
Enrollment						
Eligibility screen	X					
Informed consent	X					
Interventions: Elective PART				— ^a		
Assessments						
Clinical examination	X		X	X	X	X
Laboratory analysis ^b	X		X	X	X	X
Registration of pretreatment gastrointestinal and genitourinary morbidities ^b	X					
Registration quality of life using validated questionnaires	X		X	X	X	X
Registration of PART-induced toxicity (Common Toxicity Criteria for adverse events) ^b		X	X	X	X	X
Imaging (after discussion at an interdisciplinary tumor board)	X			X ^c	X ^c	X ^c

^aElective PART occurs during the whole period—daily instead of weekly, including the last day.

^bStandard examinations; laboratory analysis is described in the protocol.

^cIn case of prostate-specific antigen relapse or symptoms.

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), CSS, and in-field pelvic and para-aortic disease control.

The QoL is measured using the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire [41]. In addition, the EORTC prostate cancer module [42], the EuroQol 5 dimensions questionnaire [43], the International Consultation on Incontinence Short Form score [44], and the International Index of Erectile Function scoring system [45] are used to assess urinary, bowel, and sexual functioning and symptoms and evaluate the side effects of hormonal treatment associated with radiotherapy. QoL questionnaires are handed over to patients before treatment (baseline score) and at well-defined time points (end of treatment; 1 month, 3 months, 6 months, and 9 months after treatment; every 6 months until 5 years after treatment; and every 12 months until 10 years after treatment). QoL results will be presented in accordance with guidelines for reporting health-related QoL outcomes in cancer clinical trials published by the EORTC [46].

Treatment-related toxicity is assessed using the Common Toxicity Criteria for adverse events version 4.0 (CTCAE v4.0) [47]. Abdominal pain, diarrhea, enterocolitis, fecal incontinence, flatulence, hemorrhoids, proctitis, rectal fistula, rectal hemorrhage, rectal pain, noninfectious cystitis, hematuria, 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. In addition, PART-induced acute toxicity (CTCAE v4.0) is scored weekly during radiation treatment and 1 month and 3 months after treatment. Furthermore, treatment-induced late toxicity (CTCAE v4.0) 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 the secondary endpoint of this trial. Indications to initiate palliative ADT are based on the EAU guidelines [39,40] and include the following: PSA >50 µg/L or PSA doubling time <6 months or symptoms due to progressive disease. In case of oligometastatic recurrence (1-3 synchronous metastases), metastasis-directed therapy is the preferential treatment option [48]. Time to CRPC is defined according to the criteria defined in the EAU guidelines [39,40]. CSS is defined as the interval from the date of diagnosis to the date of death from PCa 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. These 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 lifelong to correctly estimate the primary and secondary endpoints. Reports on acute PART-induced toxicity and QoL will be expected within 6 months of the closure of the trial. Furthermore, the primary endpoint will be calculated after a median follow-up of 60 months.

Safety

This project has been funded by “Kom op tegen Kanker” (study number: S59533). The investigators shall report all serious adverse events (grade 3 or higher) 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, there is negligible chance for occurrence of grade 4 toxicity when PART is delivered [49].

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 7 days after knowledge by the investigator of such a case.

All other suspected unexpected serious adverse reactions shall be reported to the minister and the ethics committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the investigator. Furthermore, the principal investigator shall inform other investigators.

Sample Size and Statistics

We aim to improve 5-year cRFS by 15% (primary endpoint). This would result in a 5-year cRFS of 75% compared with the control group with WPRT only that reaches a 5-year cRFS of 60% [18,20]. For a log-rank test comparing two survival curves with a one-sided significance level of .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%. Taking into account a dropout of 10%, we aim to include 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]. The incidence of acute and late toxicity will be recorded. In addition, actuarial risk estimates for developing acute and late toxicity will be calculated using Kaplan-Meier analysis. Time to palliative ADT, time to CRPC, CSS, and in-field pelvic and para-aortic disease control will be calculated using Kaplan-Meier actuarial analysis. cRFS, time to CRPC, CSS, and in-field pelvic and para-aortic disease control times are defined from the date of LN dissection until an event or last follow-up. Statistical analysis will be performed using the latest version of SPSS (IBM Corp, Armonk, NY, USA).

Results

Ethical approval to conduct this study (version 2.0 from December 1, 2016) was granted by the Medical Ethics Committee University Hospitals/Catholic University Leuven (14/12/2016). Written informed consent of patients is mandatory before recruitment. Recruitment of patients started in 2017 and is expected to be completed by March 2020.

As a result of the PART trial, we will publish the 5-year cRFS, defined as the absence of any cR that would be visible at top of the line imaging, our primary endpoint. Furthermore, we will compare these results with the 5-year cRFS of a historical control group of patients who underwent WPRT; the results of this historical control group have already been published by Poelaert et al [20]. This control group includes patients with PCa who underwent PLND and pelvic radiotherapy between January 2000 and January 2016 at a tertiary center (GUH). Those patients were rigorously treated by several authors of this manuscript (GDM, VF, KDC, and NL). A total of 154 pN1 patients with PCa who received WPRT were included. As described in the “Sample size and Statistics” section, survival curves of both groups will be compared using log-rank test. Besides, acute toxicity and QoL results will be published after short-term follow-up, whereas treatment-related late toxicity and QoL results, time to palliative ADT, time to CRPC, CSS, and in-field pelvic and para-aortic disease control will be published after a longer follow-up period.

Discussion

Currently, management of pN1 PCa is shifting toward a multimodal approach aiming at cure. Several recent studies have shown an improved CSS when adjuvant radiotherapy was added to ADT [13,20,49-51]. 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% cases of LN-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 [52,53]. 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 [54]. Based on the evidence that positive LNs are observed before hematogenous spread occurs, we hypothesize that elective para-aortic 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 nonrandomized phase II trial to evaluate the clinical effectiveness of elective PART using arc therapy for reducing disease recurrence in pN1 patients with PCa. To the best of our knowledge, this is the first phase II trial investigating the benefit of an elective PART in patients with PCa. The results of this study will hopefully provide a sound basis for a prospective randomized phase III study randomizing patients between WPRT only and WPRT with PALN irradiation.

Acknowledgments

The project is funded by “Kom Op Tegen Kanker” (ref #0010048). The granting bodies are not involved in data collection or analysis.

Authors' 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, HV, LVW, KD, PO, PB, KH, and CB.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Funding approval (Kom Op Tegen Kanker / Foundation Against Cancer) based on peer review process (Dutch).

[\[PDF File \(Adobe PDF File\), 2MB-Multimedia Appendix 1\]](#)

Multimedia Appendix 2

Funding approval (Kom Op Tegen Kanker / Foundation against Cancer) based on peer review process (English translation).

[\[PDF File \(Adobe PDF File\), 33KB-Multimedia Appendix 2\]](#)

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Abbreviations

- ADT:** androgen deprivation therapy
- cR:** clinical relapse
- cRFS:** clinical relapse-free survival
- CRPC:** castration-refractory prostate cancer
- CSS:** cause-specific survival
- CT:** computed tomography
- CTCAE:** Common Toxicity Criteria for Adverse Events
- CTV:** clinical target volume
- EAU:** European Association of Urology
- EORTC:** European Organization for Research and Treatment of Cancer

ePLND: extended pelvic lymph node dissection
GUH: Ghent University Hospital
IMAT: intensity-modulated arc therapy
LN: lymph node
LUH: Leuven University Hospitals
MRI: magnetic resonance imaging
OARs: organs at risk
PALN: para-aortic lymph node
PART: para-aortic radiotherapy
PCa: prostate cancer
PCSS: prostate cancer-specific survival
PSA: prostate-specific antigen
PTV: planned target volume
QoL: quality of life
RP: radical prostatectomy
VMAT: volume-modulated arc therapy
WPRT: whole pelvic radiotherapy

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