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Prostate Cancer

Evaluating the Impact of Prostate Only Versus Pelvic Radiotherapy for Pathological Node-positive Prostate Cancer: First Results from the Multicenter Phase 3 PROPER Trial

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Abstract

Background: The optimal treatment for patients with pathological node-positive (pN1) prostate cancer (PCa) is unclear.
Objective: To evaluate whether whole-pelvis radiotherapy (WPRT) improves clinical relapse-free survival (cRFS) in comparison to prostate-only radiotherapy (PORT) in pN1 PCa.
Design, setting, and participants: PROPER was a phase 3 trial randomizing patients to WPRT or PORT. All patients had pN1cM0 PCa with fewer than five lymph nodes involved.
Intervention: All patients underwent pelvic lymph node dissection followed by radical prostatectomy/primary radiotherapy + 2 yr of androgen deprivation therapy (ADT). Patients were randomized to PORT (arm A) or WPRT (arm B).
Outcome measurements and statistical analysis: The primary outcome was cRFS. The secondary endpoints were overall survival (OS), biochemical relapse–free survival (bRFS), and toxicity. The study was stopped because of poor accrual in June 2021 after the inclusion of 69 patients. We report on OS, bRFS, cRFS, and acute and late toxicity.
Results and limitations: The median follow-up was 30 mo in arm A (n = 33) and 36 mo in arm B (n = 31). The 3-yr OS rate was 92% ± 5% in arm A and 93% ± 5% in arm B (p = 0.61). None of the patients died of PCa. The 3-yr bRFS was 79% ± 9% in arm A and 92% ± 5% in arm B (p = 0.08). The 3-yr cRFS rate was 88% ± 6% in arm A and 92% ± 5% in arm B (p = 0.31). No pelvic recurrence was observed in arm B. Acute grade 2 gastrointestinal toxicity was higher with WPRT (15% in arm A vs 45% in arm B; p = 0.03). Limitations are the early closure because of poor accrual and the limited follow-up.

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Conclusions: The results of our trial are hypothesis-generating but add evidence supporting the recommendation to offer WPRT to patients with pN1 PCa. However, WPRT is associated with more acute gastrointestinal toxicity.

Patient summary: We looked at the impact of radiotherapy to the whole pelvis (WPRT) for patients with prostate cancer that had spread to the lymph nodes. Although the trial was closed early because of poor enrolment, we found that WPRT improves survival free from relapse, and no recurrences were observed in the pelvis. WPRT is associated with more acute side effects on the gastrointestinal system in comparison to radiotherapy to just the prostate.

1. Introduction

The optimal treatment for patients with node-positive (N1) prostate cancer (PCa) remains unclear. Within the umbrella term N1 PCa, we must distinguish between clinical (c)N1 and pathological (p)N1 disease, as they represent different disease states with different outcomes.

For patients with cN1 PCa, there is a shift towards combination therapies, including external beam radiotherapy (EBRT) with androgen deprivation therapy (ADT), which reduces overall mortality by 50% in comparison to ADT alone [1]. This is in line with the STAMPEDE trial, confirming the positive impact on outcomes of local therapy in low-volume metastatic PCa [2].

Weak recommendations in international guidelines on adjuvant therapies for pN1 PCa reflect a lack of evidence in this specific setting [3]. Moreover, not all patients with pN1 PCa have similar outcomes. A recent meta-analysis on elective pelvic irradiation advocated the use of adjuvant EBRT for all patients with two to four positive lymph nodes (LNs) [4]. This was based on a retrospective analysis that showed that adjuvant EBRT and ADT after radical prostatectomy (RP) significantly improved the cancer-specific survival of patients with pN1 PCa with one to four positive LNs [5]. For patients with one or two positive LNs, adjuvant EBRT was only beneficial for those with a Gleason score >6 and pT3b/4 stage or positive surgical margins [5]. In that trial, >15% of patients received prostate bed–only EBRT (PORT) [5].

The risk of LN involvement increases with adverse tumor characteristics. For patients with two out of three high-risk features (pT3, International Society of Urological Pathology grade group 4–5, and positive surgical margins), adjuvant PORT is recommended [3]. The same guidelines advise to observe patients with two or fewer positive LNs and undetectable prostate-specific antigen (PSA) [3].

On the basis of these guidelines, one could hypothesize that PORT can be offered to patients with adverse pathological characteristics but two or fewer involved LNs and low PSA. Because WPRT increases toxicity [6], omission of the pelvic LN regions from the radiation field whenever possible is desirable.

The aim of this trial was to evaluate whether WPRT + 2 yr of ADT improves clinical relapse-free survival (cRFS) in comparison to PORT + 2 yr of ADT in patients with pN1 PCa with fewer than five LNs involved.

2. Patients and methods

This was a phase 3 stratified randomized trial to test the efficacy of WPRT for pN1 PCa. Randomization was based on the number of involved LNs since patients with a higher number of positive LNs experience poorer prognosis (Supplementary Fig. 1). The trial was approved by the Ethics Committee of Ghent University Hospital and registered at ClinicalTrials.gov (NCT02745587).

The hypothesis was that WPRT + 2 yr of ADT (arm B) would result in significantly better cRFS of 15% in comparison to PORT + 2 yr of ADT (arm A).

Patients were eligible if they had adenocarcinoma of the prostate without distant metastases (M0) on conventional imaging and were willing to be treated with local therapy to the prostate using either RP or EBRT. All patients underwent diagnostic pelvic LN dissection (PLND) as a staging modality. The time of patient referral after RP was at the discretion of the treating physician; therefore, both adjuvant and salvage EBRT were allowed. All patients started ADT (a luteinizing hormone–releasing hormone antagonist or agonist, or an antiandrogen) for a period of 18–24 mo.

Exclusion criteria were more than four positive LNs, prior pelvic EBRT, another primary tumor (except for nonmelanoma skin tumors) diagnosed <5 yr before enrollment, and the presence of any condition hampering compliance.

The primary endpoint was cRFS, defined as the absence of clinical relapse on imaging (computed tomography [CT] of the thorax, abdomen, and pelvis; bone scan or prostate-specific membrane antigen [PSMA] positron emission tomography [PET]-CT) performed at the time of biochemical relapse (according to the Phoenix definition for primary EBRT, or PSA >0.2 ng/ml for RP) and calculated from the last day of RT until clinical relapse.

Secondary endpoints reported here are acute toxicity (during and $\leq$3 mo after RT), late toxicity (>3 mo after RT), biochemical RFS (bRFS), and overall survival (OS).

Gastrointestinal (GI) and genitourinary (GU) toxicity was scored using the Common Terminology Criteria for Adverse Events v4.0 [7].

Pretreatment imaging consisted of CT and magnetic resonance imaging (MRI). The clinical target volume (CTV) in arm A consisted of the prostate in the primary setting, and the prostate bed in the adjuvant/salvage setting. For patients randomized to arm B, the pelvic LNs along the common, internal, and external iliac arteries, obturator fossa, and presacral nodes were delineated and expanded with a 2-mm margin to create the CTV_LN.

The planning target volume (PTV) was created by expanding the CTV by 5 mm. Similarly, the PTV_LN was created by applying an isotropic expansion of 5 mm around the CTV_LN.

If an intraprostatic lesion was detected on MRI, it was delineated separately and used for a simultaneous integrated boost in the primary setting. Details of the planning and dose objectives are summarized in Supplementary Table 1.

All patients were treated with intensity-modulated arc RT. Patient preparation and positioning were performed according to the institutional protocol.

2.1. Statistical considerations

The study was initially designed to include 330 patients in an 8-yr study period comprising a 5-yr accrual period and 3-yr follow-up. The relevant population includes patients with LN involvement receiving ADT. A survival curve reflecting the type of difference anticipated is shown in Fig. 1 of the study by Briganti et al. [8]. Sample size calculations were performed using SAS v9.4. Assuming a hazard rate of 0.0782 in both groups (hazard ratio [HR] = 1) during the first 3 yr, and hazard rates of 0.1826 and 0.0621 in the control and experimental groups, respectively (HR = 0.34) in the following 5 yr, a sample size of 165 patients per group would be sufficient to obtain 80% power (at an α level of 5%) to detect a difference in survival time using the log-rank test for an accrual time of 5 yr and a total study period of 8 yr.

The trial was stopped prematurely owing to poor accrual in June 2021. Poor accrual was due to the patient's refusal for randomization, fewer surgical procedures due to the COVID pandemic and increased resistance to performing PLND due to lack of evidence of its benefit.

The Kaplan-Meier product limit method was used to estimate OS, bRFS, and cRFS, calculated from the end of EBRT until the event. We compared the incidence of acute and late GI and GU toxicities between the groups. Statistically significant differences between the groups were calculated using Fisher's exact test. SPSS v28 for Windows (IBM, Armonk, NY, USA) was used for all analyses. Statistical significance was set at $p < 0.05$.

3. Results

From May 2016 to June 2021, 69 patients were randomized. After excluding five patients, 33 patients were treated in arm A and 31 in arm B (Supplementary Fig. 1). The median number of resected LNs was 17 (range 6–41) and 64% of patients had only one positive LN (Supplementary Fig. 2).

The median follow-up was 30 mo in arm A and 36 mo in arm B. The patient and tumor characteristics are presented in Table 1. Eighteen patients received salvage RT. Median PSA at the time of salvage RT was 0.14 ng/dl (range 0.011–0.72).

At the time of analysis, 50 patients (78%) had stopped ADT (26 in arm A and 24 in arm B).

3.1. Clinical outcome

During the study period, five patients died (2 in arm A and 3 in arm B) with 3-yr OS of 92% ± 5% in arm A and 93% ± 5% in arm B ($p = 0.61$). None of the patients died of PCa.

The 3-yr bRFS rate was 79% ± 9% for arm A and 92% ± 5% for arm B ($p = 0.08$; Fig. 1). An overview of the tumor characteristics of the patients with biochemical relapse is presented in Supplementary Table 2.

Seven patients (11%) experienced clinical relapse (5 in arm A and 2 in arm B). Three patients had bone metastases only (2 in arm A, 1 in arm B), one patient had bone and retroperitoneal metastases (arm B), one patient had pelvic and retroperitoneal LN recurrence (arm A), and one patient

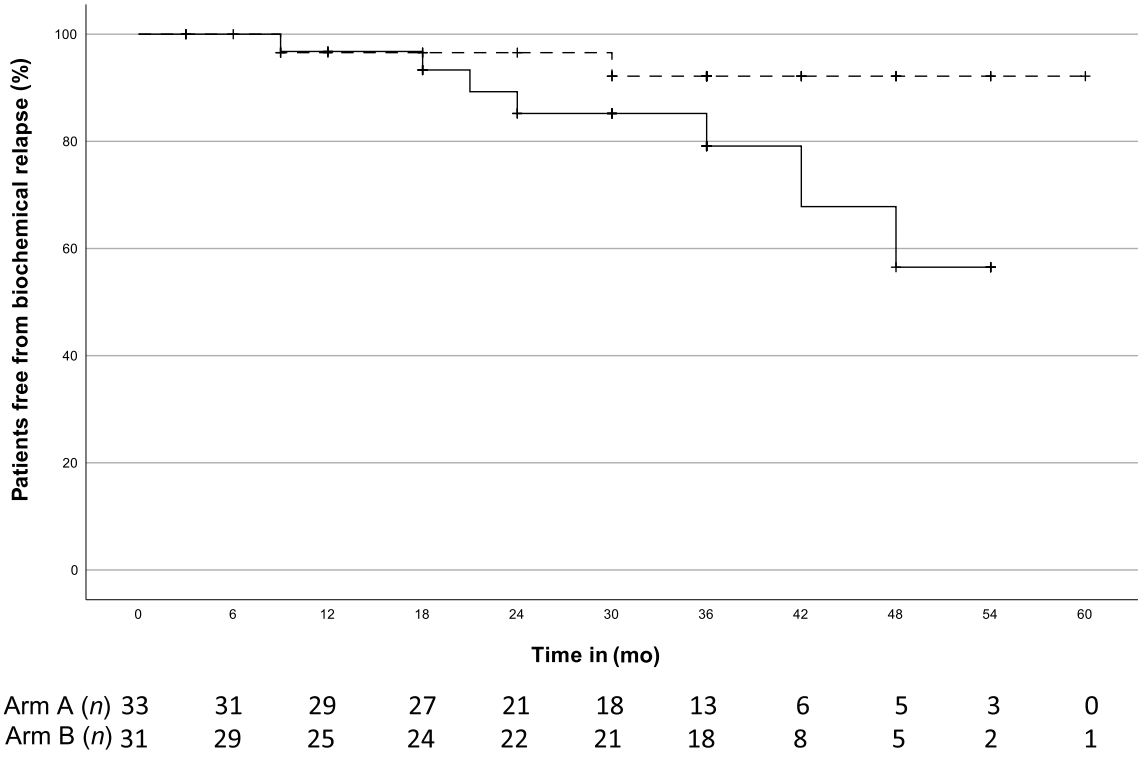

Fig. 1 – Biochemical relapse–free survival.

Table 1 – Tumor and patient characteristics

	All patients (*n* = 64)	Arm A (*n* = 33)	Arm B (*n* = 31)
Median follow-up, mo (range)	36 (3–60)	30 (3–60)	36 (3–60)
Median prostate-specific antigen, ng/ml (range)	11 (3–119)	13 (5–119)	11 (3–38)
Median age, yr (range)	69 (57–81)	69 (57–81)	70 (57–81)
Median hormonal therapy duration, mo (range)	24 (5–24)	24 (5–24)	24 (6–24)
Diabetes, *n* (%)	10 (15)	6 (18)	4 (13)
Hypertension, *n* (%)	28 (41)	13 (39)	15 (48)
Hemorrhoids, *n* (%)	6 (9)	4 (12)	2 (6)
Transurethral resection of the prostate, *n* (%)	6 (9)	3 (9)	3 (10)
Anticoagulants, *n* (%)	21 (31)	9 (27)	12 (39)
Anticholesterolemia drugs, *n* (%)	28 (41)	15 (45)	13 (42)
Gleason score, *n* (%)			
Gleason 7	20 (29)	10 (30)	10 (32)
Gleason 8	17 (25)	10 (30)	7 (23)
Gleason 9	26 (38)	12 (36)	14 (45)
Gleason 10	1 (2)	1 (3)	0
Clinical tumor stage, *n* (%)			
T1	5	1 (3)	4 (13)
T2	26	14 (42)	12 (39)
T3	29	15 (45)	14 (45)
T4	4	3 (9)	1 (3)
Clinically node-positive, *n* (%)	9	6 (18)	3 (10)
Surgery, *n* (%)	51 (75)	26 (79)	25 (81)
Number of involved lymph nodes, *n* (%)			
1 node	41 (64)	20 (61)	21 (67)
2 nodes	17 (27)	9 (27)	8 (26)
3 or 4 nodes	6 (9)	4 (12)	2 (6)
Positive surgical margins, *n* (%)	32 (63)	18 (55)	14 (45)

had both pelvic LN recurrence and bone metastases (arm A) at the time of relapse. One patient randomized to arm A had local relapse with pelvic LN recurrence. No pelvic recurrence was observed in arm B (Fig. 2).

The 3-yr cRFS rate was 88% ± 6% for arm A and 92% ± 5% for arm B (p = 0.31).

3.2. GI toxicity

In arm A, 15% of the patients experienced acute grade 2 GI toxicity. Significantly more patients experienced acute GI toxicity in arm B, with grade 2 toxicity reported by 45% (p = 0.03).

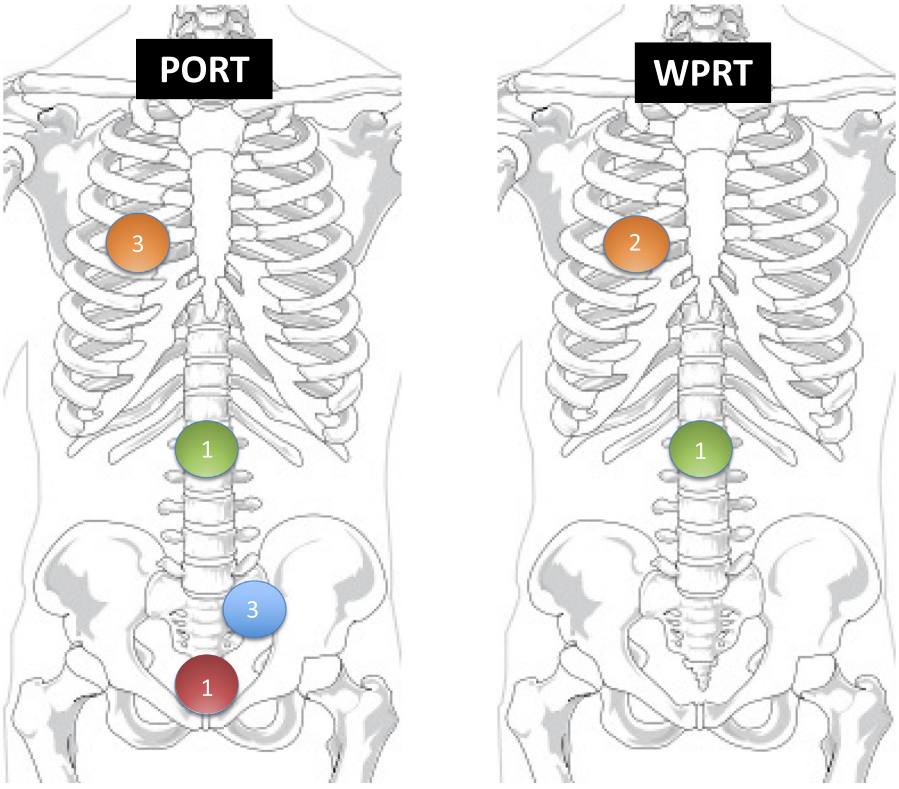

Fig. 2 – Overview of sites of relapse by treatment arm. PORT = prostate-only radiotherapy; WPRT = whole-pelvis radiotherapy.

There was no significant difference in late overall GI toxicity between the groups. In arm A, 3% of patients experienced late grade 2 or 3 GI toxicities. In arm B, one patient developed a grade 4 anal fistula 2 yr after adjuvant EBRT. No late grade 3 GI toxicities were reported in arm B. Late grade 2 GI toxicity was observed in 21% of the patients in arm B.

3.3. *GU toxicity*

Acute grade 2 and 3 GU toxicities were experienced by 27% and 21% of the patients in arm A, and in 39% and 13% of the patients in arm B, respectively (p = 0.68).

At 18 mo after EBRT, one patient in arm A underwent surgery because of grade 4 frequency, retention, dysuria, and nocturia requiring cystectomy with Bricker derivation. In arm A, 28% and 16% of patients experienced late grade 2 and grade 3 GU toxicities, respectively. In arm B, late grade 2 and 3 GU toxicities were reported by 38% and 3% of patients, respectively. There was no significant difference in late GU toxicity between the groups.

Figures 3 and 4 provide an overview of the incidence of GI and GU toxicities by time point up to 36-mo follow-up. The incidence of GI toxicity decreased rapidly with time, in contrast to GU toxicity, which remained stable and even increased with longer follow-up.

4. Discussion

Most patients with pN1 PCa do not receive additional therapy or are treated with ADT alone [9]. Retrospective analyses support the use of adjuvant EBRT for pN1 PCa [5,10] and adjuvant instead of salvage EBRT for pN1 PCa has recently been recommended as it decreases all-cause mortality [11]. There are conflicting data regarding selection of patients who truly benefit from adjuvant EBRT according to LN burden, so prospective trials in pN1 PCa are warranted.

Owing to early closure of our study, the results are hypothesis-generating; however, several findings are worth highlighting.

At median follow-up of 3 yr, we observed a 13% increase (from 79% to 92%) in bRFS, a well-recognized precursor of clinical relapse, with WPRT in comparison to PORT, with no pelvic recurrences observed in the WPRT group.

Some 64% of our patients had only one positive LN, suggesting that even for patients with a low positive LN burden, WPRT might be advantageous. This is in line with the study by Abdollah et al [5,12], in which patients with up to two positive LNs benefited from adjuvant EBRT when they presented with a Gleason score >6 and high-risk features, which was the case for all our patients.

By contrast, Tilki et al. [11] suggested that the reduction in all-cause mortality for patients with more than 11 LNs removed and one to three positive LNs was limited, and therefore recommended opting for a personalized approach balancing life expectancy against the toxicity of WPRT in this group. We confirmed a significantly higher rate of acute GI toxicity in the WPRT group. GI toxicity decreases with time, but it is generally accepted that acute GI toxicity predicts late toxicity [13].

In our study, two patients experienced grade 4 toxicity. The dose delivered to the prostate bed was higher (70 Gy) than currently recommended [14]. It has been shown that

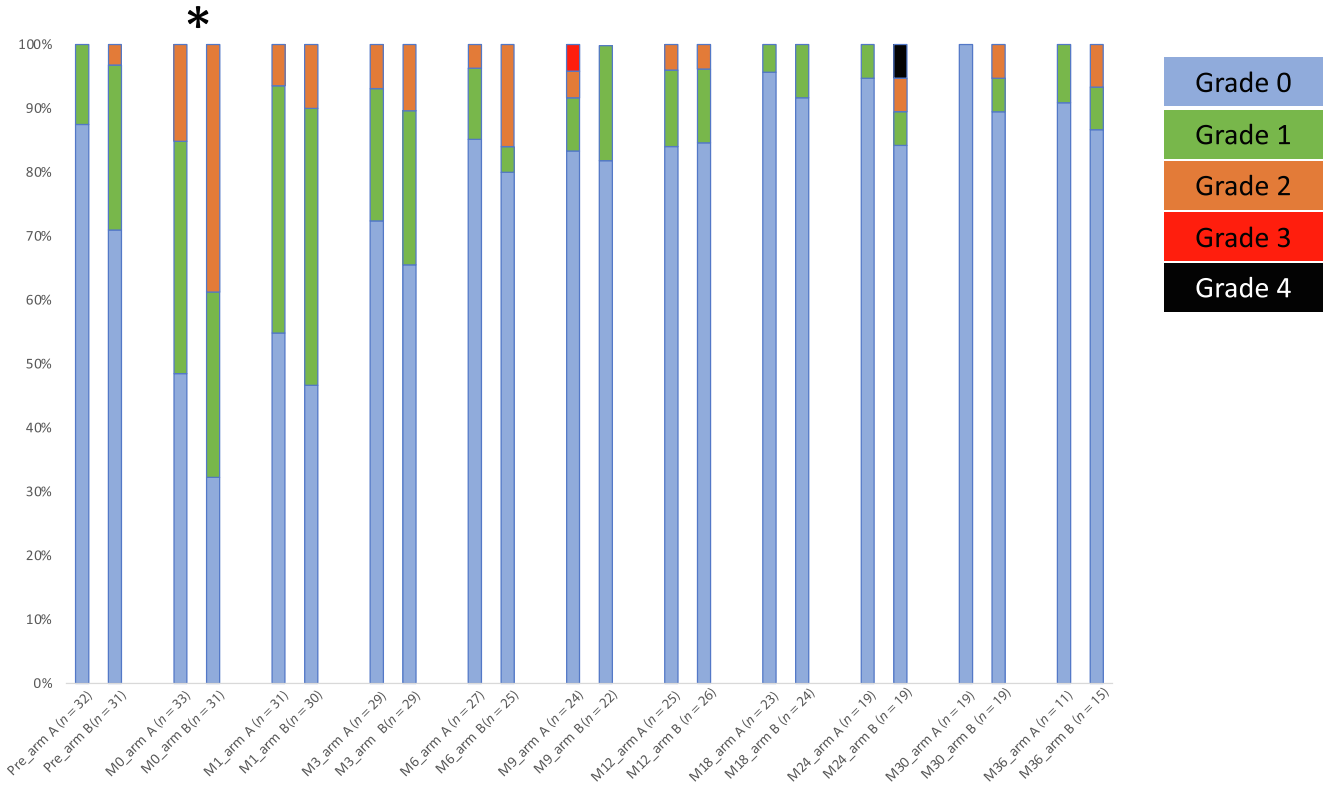

Fig. 3 – Overview of the incidence of gastrointestinal toxicity by time point up to 36-mo follow-up for the two groups. *Statistically significant difference between the groups (p = 0.032).

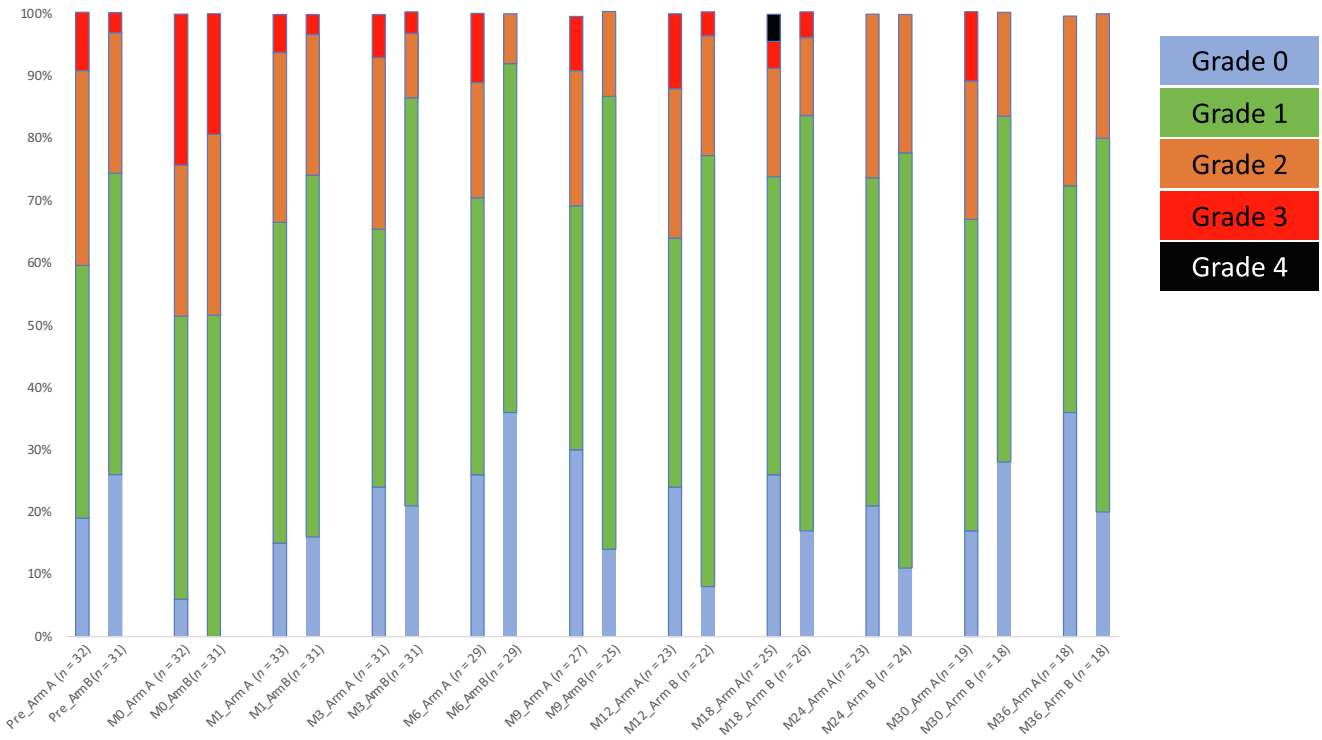

Fig. 4 – Overview of the incidence of genitourinary toxicity by time point up to 36-mo follow-up for the two groups.

increasing the dose from 64 to 70 Gy is associated with significantly more toxicity without providing a patient benefit [14].

A potential benefit of WPRT has been shown for patients with N0 PCa [15,16]. In the SPPORT trial, WPRT and ADT resulted in significantly better progression-free survival in comparison to PORT ± ADT in patients with N0 PCa with persistent or rising PSA levels after RP [15]. For patients with high-risk N0 PCa treated with primary EBRT, WPRT resulted in better bRFS in comparison to PORT [16], with a Kaplan-Meier bRFS curve that resembles the one in our study.

PSMA PET-CT is more accurate than conventional imaging in detecting metastases [17]. Especially in the pN1 PCa setting, PSMA PET-CT could be useful in differentiating patients who truly benefit from WPRT (in terms of prevention of locoregional relapses) from patients who already harbor distant metastases at diagnosis. However, the place of PSMA PET-CT in the primary setting is widely debated, as there are no data on outcomes to guide subsequent management. The place of PSMA PET-CT in the recurrent setting is better defined. A systematic review found that locoregional LN recurrence occurs in 38% of patients diagnosed with biochemical recurrence after local treatment [18]. WPRT in the nodal recurrent setting is being evaluated in the STORM trial, with patients randomized to metastasis-directed therapy (including PLND) with or without WPRT (NCT03569241). Whether prophylactic WPRT is superior to WPRT at the time of diagnosis of nodal recurrence in PCa is unknown.

For PCa, treatment intensification is beneficial at different disease stages. According to one study, lifelong ADT has been adopted as the standard of care for pN1 PCa [19]. Retrospective trials have evaluated the added value of ADT with EBRT, with conflicting results [13,20,21]. ADT is often lifelong for patients with pN1 PCa. As ADT has numerous side effects, one could argue that when adding adjuvant EBRT, the duration of ADT can be limited to 2–3 yr, analogous to primary EBRT for high-risk PCa [22]. The role of ADT + EBRT in the postoperative setting is currently further being investigated in the RADICALS-HD trial (NCT00541047).

For cN1 PCa, intensification of treatment with androgen receptor–targeted agents leads to better metastasis-free survival [23]. The INNOVATE trial is evaluating whether a similar effect can be expected in the pN1 setting and is randomizing patients with pN1 PCa to salvage WPRT + ADT for 2 yr or WPRT + 2 yr of ADT + apalutamide (NCT04134260). The ANZUP1801 trial is investigating the added value of darolutamide in combination with ADT + EBRT in patients with pN1 PCa (NCT04136353).

There is no evidence supporting the use of adjuvant chemotherapy according to the randomized SPCG-12 trial, which failed to show an improvement in bRFS for six cycles of docetaxel after RP, including pN1 disease [24]. Whether inclusion of the para-aortic LN areas improves outcomes without excessive toxicity is the subject of research in the PART trial [25].

Early closure due to poor accrual and limited follow-up are limitations of our trial. Performing PLND without RP is not a standard of care as it does not impact outcomes, but it allows for better risk stratification, as the number of positive LNs is linked to outcomes [26–28]. To date, no imaging modality has surpassed PLND as a staging tool.

We hypothesized that PLND is the best staging tool and could guide the selection of patients who would benefit

from WPRT. Patients with an involved LN risk of >15% according to the Roach formula were referred for PLND staging [29]. At the time of designing the trial, the results of the POP-RT trial were unknown and there was much controversy regarding the performance of WPRT in all patients with high-risk PCa.

Our results support the hypothesis that PLND is a staging tool rather than a treatment itself [30].

5. Conclusions

Owing to early closure of our prospective trial in a pN1 PCa population, the results are hypothesis-generating. Our study provides evidence that supports the international recommendation to offer WPRT to patients with pN1 PCa and suggests that the benefit of WPRT can be expanded to patients with a low burden of pN1 disease and high-risk features. However, WPRT is associated with more acute GI toxicity.

Author contributions: Valérie Fonteyne had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Fonteyne.
Acquisition of data: Fonteyne, Van Praet, Ost, Van Bruwaene, Liefhooghe, Berghen, De Meerleer, Verbaeys, Lumen.
Analysis and interpretation of data: Fonteyne.
Drafting of the manuscript: Fonteyne.
Critical revision of the manuscript for important intellectual content: Ost, Van Praet, Van Bruwaene, Liefhooghe, Berghen, De Meerleer Ben Vanneste, Verbaeys, Verbeke, Lumen.
Statistical analysis: Fonteyne.
Obtaining funding: Fonteyne.
Administrative, technical, or material support: Fonteyne.
Supervision: Fonteyne.
Other: None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euf.2022.09.005.

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