



Palliative RT in prostate cancer

Palliative pelvic radiotherapy for symptomatic incurable prostate cancer – A prospective multicenter study



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ABSTRACT

Background and purpose: Radiotherapy is used to palliate pelvic symptoms of castration resistant prostate cancer (CRPC). However, magnitude and time course of effects and toxicities are poorly documented. Study aims were to evaluate changes in patient-reported target symptoms (TS), health-related quality of life (HRQOL) and toxicity following palliative pelvic radiotherapy (PPRT) of CRPC.

Material and methods: 47 patients with CRPC and a symptomatic pelvic mass prescribed PPRT with 30–39 Gy were prospectively included. Primary endpoint was patient-reported improvement or complete resolution of the TS twelve weeks after PPRT. HRQOL changes were explored. Toxicity was physician-evaluated.

Results: Lower urinary tract symptoms (LUTS) (45%), hematuria (26%) and pain (19%) were the most common TS. In the 40 evaluable patients, overall TS response twelve weeks after PPRT was 70%. TS responses were 8/18 for LUTS, 11/12 for hematuria, and 7/9 for pain. Global HRQOL improved transiently. The most common toxicity was grade 1 or 2 diarrhea (50%). There was no grade 4 toxicity.

Conclusions: In the majority of patients with CRPC and a symptomatic pelvic tumor, PPRT with 30–39 Gy contributes to relief of hematuria, pain and other pelvic symptoms, with acceptable toxicity. Future studies should investigate whether PPRT regimens can be simplified.

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In approximately 15–20% of patients with castration-resistant prostate cancer (CRPC), growth of a pelvic tumor dominates the clinical picture which is typified by micturition problems, pain, hemorrhage, and obstruction of viscera and lymphatics [1]. In these patients, palliative pelvic external beam radiotherapy (PPRT) is often used although evidence regarding timing, duration and magnitude of symptom relief and toxicity is deficient. A recent literature review indicates a trend toward positive effects yet there is a need to prospectively document efficacy for palliation of various symptoms [2].

The lack of prospective studies in these patients, coupled with heterogeneity and multiplicity of pelvic symptoms, meant that a phase two study was the natural first step in establishing an evidence base for PPRT of CRPC. Research in palliative radiotherapy presents several challenges including a high rate of attrition and difficulty in measuring validated, well-defined end-points in a

population with rapidly declining health. Dedicated studies, addressing the symptomatic effects of palliative radiotherapy are therefore needed [3], and a pilot study has demonstrated feasibility in this elderly population with prostate cancer, using patient-reported outcomes [4]. The most appropriate fractionation regimen for palliation of symptoms is uncertain and clinical practices therefore vary [2]. According to an informal survey of Norwegian radiation oncologists, 30–39 Gray (Gy) in 3 Gy fractions was most widely used at the start of the study.

The primary aim of the current study was to prospectively evaluate the palliative effect of PPRT in patients with CRPC and a symptomatic pelvic tumor 12 weeks after the completion of PPRT. Secondly, we explored HRQOL, symptom status and toxicity at the end of and six and 12 weeks after radiotherapy.

Methods

Study design and patients

Between November, 2009 and June, 2014, seven of nine radiotherapy centers in Norway conducted this phase 2 study.

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Eligible patients with CRPC presented with a symptomatic soft-tissue pelvic mass (primary tumor, recurrence or metastasis due to adenocarcinoma of the prostate), independent of the simultaneous presence of metastases. They had to be ≥ 18 years, with a life expectancy greater than three months. Radiotherapy had to have been prescribed in the range of 30–39 Gy in 3 Gy fractions by referring physicians. Patients were ineligible if they were unable to comply with study questionnaires, had started systemic anti-neoplastic treatment within four weeks of baseline, or if this was planned within six weeks after radiotherapy. Patients who had previously been treated with pelvic radiotherapy, had a synchronous pelvic cancer or other cancer requiring treatment were ineligible, as were those receiving treatment with an investigational drug.

Treatment

In order to limit heterogeneity, external beam radiotherapy was delivered in 10–13 fractions of 3 Gy. Treatment planning was preferably done by computerized tomography. Gross tumor volume (GTV) encompassed the prostate tumor, pathologically enlarged lymph nodes, or a combination of these. Planning target volume included the GTV and a margin of 1.0–2.0 cm. Field set-up was at the discretion of the treating physician. There were no limitations on the supportive interventions that could be given during the study.

Data collection

Four study visits were scheduled; at baseline (14–0 days prior to radiotherapy), at the completion of radiotherapy (± 3 days), and six and twelve weeks (± 7 days) after completion of treatment. Background data pertaining to prostate cancer history were collected from patient records. Ancillary palliative procedures and medication use were documented. Survival data were obtained from the Norwegian Cause of Death Registry.

Symptom and toxicity assessment

Patients were asked at baseline to identify a “target symptom”, the chief pelvic complaint that they hoped the radiotherapy would relieve. At each of the three follow-up visits they were asked to describe the target symptom severity compared to baseline as either “worse”, “unchanged”, “better” or “resolved”. The two latter alternatives, better or resolved, were regarded as “response”.

To assess HRQOL and characterize pain the validated Norwegian versions of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30, version 3.0) [5,6] and Brief Pain Inventory short form, with body map (BPI) [7,8] were used at each study visit. Questionnaires were administered and collected at the radiotherapy centers. Radiotherapists were responsible for ensuring that forms were completed and they were available to assist the study participants, as needed. In instances where patients were prevented from attending study follow-up visits, an attempt was made to contact them by telephone and administer the questionnaires via post.

Physicians prospectively graded pre-specified pelvic symptoms and potential toxicities according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v.3.0) [9] criteria at each study visit.

Statistical considerations

The primary endpoint was the proportion of patients reporting improved or resolved target symptom severity compared to baseline at the 12-week follow-up visit. Secondary endpoints were

changes in target symptom severity at the end of treatment and at the 6-week follow up visit, as well as HRQOL and degree of toxicity at all of the follow-up study visits.

A target symptom response rate of at least 30–40% was deemed clinically meaningful. If the true response rate is 40%, a total of 47 patients would be needed to obtain 90% power to exclude a response rate of $< 20\%$, with significance level of 5%. Correspondingly, the power would be 80% with a total of 35 patients. With 40 evaluable patients the maximum length of a 95% confidence interval for the proportion of responders is $\pm 15\%$.

With regard to the secondary endpoint, a change of ≥ 10 points in the EORTC QLQ-C30 global QOL score is considered clinically significant [10]. Assuming a standard deviation in the range of 20–25 [11], 32–51 patients would give a power of 80%. Thus, a total of 40 evaluable patients were deemed sufficient to detect relevant effects on both primary and secondary outcomes.

Descriptive statistics were generated to describe the population, treatment given, and the primary endpoint. 95% confidence intervals were also estimated. Results for the main target symptom subgroups (lower urinary tract symptoms [12] (LUTS), macroscopic hematuria, pain) are presented separately due to clinical relevance.

Differences in median HRQOL score from baseline to each follow-up visit are assessed by the 2-tailed Wilcoxon signed rank test (significance level of $p < 0.05$) for paired data. Toxicity is presented in percent of patients with each grade of symptoms at the four study visits. In order to describe the study population, Kaplan–Meier survival analysis was performed with the observation time spanning from the start of radiotherapy to death or through 2013.

Ethical considerations

Study participants gave written informed consent. The study was approved by the Regional Ethical Committee (ref. S-09080c 2009/1695) and the Privacy Protection Council in Norway (ref. 20940) and by hospital institutional boards. The study was registered on ClinicalTrials.gov (ref. NCT01023529).

Results

Patient and treatment characteristics

Forty-seven patients were included and all completed the prescribed radiotherapy (Fig. 1). Five patients died during the study (three of prostate cancer, two of unrelated causes) and deteriorating general health of an additional two precluded their

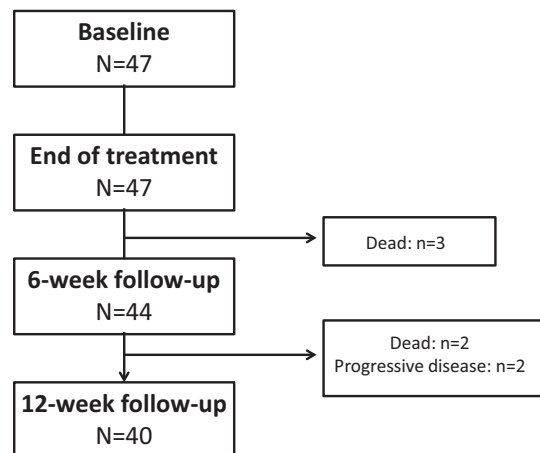


Fig. 1. Inclusion and follow-up of patients.

participation to completion of the study. Forty patients were evaluable 12 weeks after PPRT.

The 47 included patients had a median age of 79 years and 34 had documented metastatic disease (Table 1). All patients had undergone androgen deprivation therapy and eight had been given prior chemotherapy. The median time since diagnosis was 68.5 months. The most frequent patient-reported target symptoms were LUTS, macroscopic hematuria, and pain.

PPRT was delivered in 3 Gy fractions, to a mean total dose of 34.5 Gy (range 27–39 Gy) (Table 2). The irradiated volume varied from 252 to 5500 cm³ (median 737 cm³). In the majority of patients, radiotherapy was planned with three-dimensional computed tomography and delivered conformally, with multiple fields.

Symptom palliation

Of the 40 patients evaluable for target symptom severity 12 weeks after PPRT, 18 reported complete resolution, 10 improvement, 10 unchanged severity and two reported worsening target symptoms. Improvement or complete resolution of the target symptom was achieved in 62% of the evaluable patients at the end of radiotherapy, 80% after six weeks, and 70% after 12 weeks (Table 3).

Table 1
Patient characteristics at baseline (N = 47).

Parameter	Value
Age (years)	
Median (range)	79 (60–93)
ECOG performance status (n)	
0	8
1	25
2	13
3	1
Patients with documented metastatic disease (n)	
Total	34
Skeletal	24
Lymphnode	24
Time since diagnosis (months)	
Median (range)	68.5 (9–214)
Laboratory values, median (range)	
PSA (µg/L)	59 (1–2266)
Albumin (g/L)	40 (27–47)
Hemoglobin (g/dL)	12.1 (7.9–16.5)
Previous cancer treatment (n)	
Prostatectomy	0
Orchiectomy	1
TURP	19
Chemotherapy	8
Androgen deprivation therapy	47
Patients' target symptom (n)	
LUTS	21
Hematuria	12
Pain	9
Rectal obstruction	3
Lower extremity/scrotal edema	2
Opiate analgesic use (n)	10
Anticholinergic use for bladder spasm (n)	5
Urinary tract intervention (n)	
Nephrostomy	7
Ureteric stent	1
Suprapubic catheter	5
Permanent urethral catheter	6
Intermittent catheterization	2

LUTS = lower urinary tract symptoms (symptoms relating to storage and/or voiding disturbance);

ECOG = Eastern Cooperative Oncology Group; TURP = transurethral resection of the prostate;

PSA = prostate-specific antigen.

Table 2
Palliative pelvic radiotherapy.

Radiotherapy delivered (n) ^a	
27 Gy in 9 f	1
30 Gy in 10 f	19
36 Gy in 12 f	10
39 Gy in 13 f	17
Radiotherapy target (n)	
Primary tumor	46
Pathological lymph nodes only	1
Primary tumor and pathological lymph nodes	10
Volume treated (90% target dose, in cm ³)	
Median (range)	737 (252–5500)
Treatment planning (n)	
Conformal 3-dimensional CT plans	45
Conventional	2
Number of treatment fields	
Median (range)	4 (2–9)

Gy = Gray; f = fractions; CT = computed tomography.

^a Two patients did not complete the prescribed radiotherapy course (one due to an infection and the other due to a fall resulting in a fracture).

According to intention to treat analysis, overall response rate for all included patients (n = 47) after 12 weeks was 60% (28/47). For the subgroups of patients with LUTS, macroscopic hematuria and pain, response rates were 38%, 92% and 78%, respectively. Eighty-seven percent (41/47) of all included patients reported complete resolution or improvement of target symptom at at least one of their follow-up visits.

The most consistent results were reported for palliation of macroscopic hematuria (100% response after 12 weeks among the 40 evaluable patients) while outcomes for patients with LUTS were more variable. Variation of symptom severity over time for individual patients in the main target symptom groups is schematically displayed in Fig. 2.

Compared to baseline, median global QOL score for patients that remained in the study increased by 12.5 points (p = 0.032) at the six-week follow-up. Clinically meaningful improvement was reported by 16/41 (39%) of patients at the six-week follow-up and 15/40 (38%) of patients at the 12-week follow-up (Table 3).

Ancillary palliative interventions

Of the 21 patients that required bladder catheters, ureteric stents, nephrostomies, or a combination of these at baseline (Table 1), five had discontinued the intervention by the 12-week follow-up. Six patients underwent urinary tract intervention (six bladder catheter placements, one transurethral resection of the prostate (TURP)) during the study period.

Although only nine patients identified pain as their target symptom, 29 patients reported pain on the BPI at at least one study visit. Of these, 20 (69%) referred to pelvic pain. Opioids were used by 11/47 (23%) patients at baseline, 13/47 (28%) at the end of radiotherapy, 7/44 (16%) at the six-week follow-up and 10/40 (25%) at the 12-week follow-up.

Two patients were given palliative radiotherapy of skeletal metastases (hip, spine) during the study period. One patient was given docetaxel five days prior to the 12-week follow-up visit.

Toxicity

Transient mild to moderate diarrhea at the end of radiotherapy was the most frequent toxicity seen (50%) (Fig. 3). Pelvic symptoms in general improved during the study. There were no interruptions or premature terminations of radiotherapy due to toxicity. There were no grade 4 toxicities.

Table 3
Target symptom response and HRQOL compared to baseline.

Proportion of evaluable patients reporting target symptom severity improved or resolved (95% CI)					
Number of patients with target symptom at baseline		End of radiotherapy	6 week follow-up	12 week follow-up	
LUTS	<i>n</i> = 21	6/21 29% (0.10–0.48)	10/18 56% (0.33–0.79)	8/18 44% (0.21–0.67)	
Macroscopic hematuria	<i>n</i> = 12	11/12 92% (0.77–1.0)	11/11 100%	11/11 100%	
Pelvic pain	<i>n</i> = 9	8/9 89% (0.69–1.0)	9/9 100%	7/9 78% (0.51–1.0)	
Other [#]	<i>n</i> = 5	4/5 80% (0.45–1.0)	3/3 100%	2/2 100%	
Total	<i>n</i> = 47	29/47 62% (0.48–0.76)	33/41 80% (0.68–0.92)	28/40 70% (0.56–0.84)	
Global QOL compared to baseline		Proportion of evaluable patients (95% CI)			
		End of radiotherapy	6 week follow-up	12 week follow-up	
Clinically significant improvement [†]		12/47 26% (0.13–0.39)	16/41 39% (0.24–0.51)	15/40 38% (0.23–0.53)	
Stable ^{**}		26/47 55% (0.40–0.70)	20/41 49% (0.33–0.65)	14/40 35% (0.20–0.50)	
Clinically significant deterioration ^{***}		9/47 19% (0.08–0.30)	5/41 12% (0.02–0.22)	11/40 28% (0.14–0.42)	
		HRQOL: global health status score median (IQR); <i>p</i> -value [□]			
		Baseline	End of radiotherapy	6 week follow-up	12 week follow-up
Global QOL score	50.0 (33–67) <i>n</i> = 47	58.3 (42–75) <i>n</i> = 47 <i>p</i> = 0.229	66.7 (50–83) <i>n</i> = 41 <i>p</i> = 0.032	62.5 (50–83) <i>n</i> = 40 <i>p</i> = 0.340	

CI = confidence interval; LUTS = lower urinary tract symptoms (symptoms relating to storage and/or voiding disturbance); HRQOL = health-related quality of life; IQR = inter-quartile range.

[#] Edema, rectal obstruction.

[†] Increase \geq 10 points.

^{**} Values within nine points of baseline score.

^{***} Decrease \geq 10 points.

[□] Score compared to baseline.

Survival

At the time of analysis, median duration of study follow-up was 40 months (range 11–60). Median overall survival among the included patients was 20 months (range 1–55) from the time of radiotherapy start.

Discussion

This study demonstrates that in patients with CRPC, symptoms resulting from an advanced pelvic tumor are well-palliated with PPRT. However, response rate, degree of response, onset and durability of effect varied for the three major target symptom groups. Macroscopic hematuria and pain responded rapidly and consistently, with the majority of patients experiencing improvement or complete resolution of their target symptom during the treatment period. The palliative effect in the LUTS subgroup was less frequent, of slower onset, and more variable than for the other target symptom subgroups.

The frequency, degree, and duration of side-effects in this study appear acceptable. In fact, pelvic symptom burden decreased over

the course of the study (see Fig. 3), likely reflecting the fact that the positive effect on the constellation of pelvic symptoms beyond those defined as the target symptom, outweighed toxicities of treatment. This is also exhibited in the stability and transient improvement in HRQOL in the three months after PPRT, despite the patients having progressive prostate cancer and limited survival at treatment start.

Various systemic treatments of CRPC have been shown to improve survival and health-related quality of life (HRQOL) in patients with metastatic disease, although their effect on symptoms resulting from the pelvic primary tumor is largely unknown [13–15], and no studies are available which document the effects of PPRT on HRQOL [2]. The results of this study support findings of the retrospective studies of PPRT of PC to date [2] and are consistent with symptomatic effects reported for PPRT of other pelvic malignancies such as bladder [16], cervical [17], and rectal [18] cancers.

Prolonged local pelvic control and improved survival have been shown in patients with non-metastatic CRPC selected for treatment with higher doses of PPRT (40–55 Gy) [19]. The majority of incurable patients selected for such treatment aiming to delay

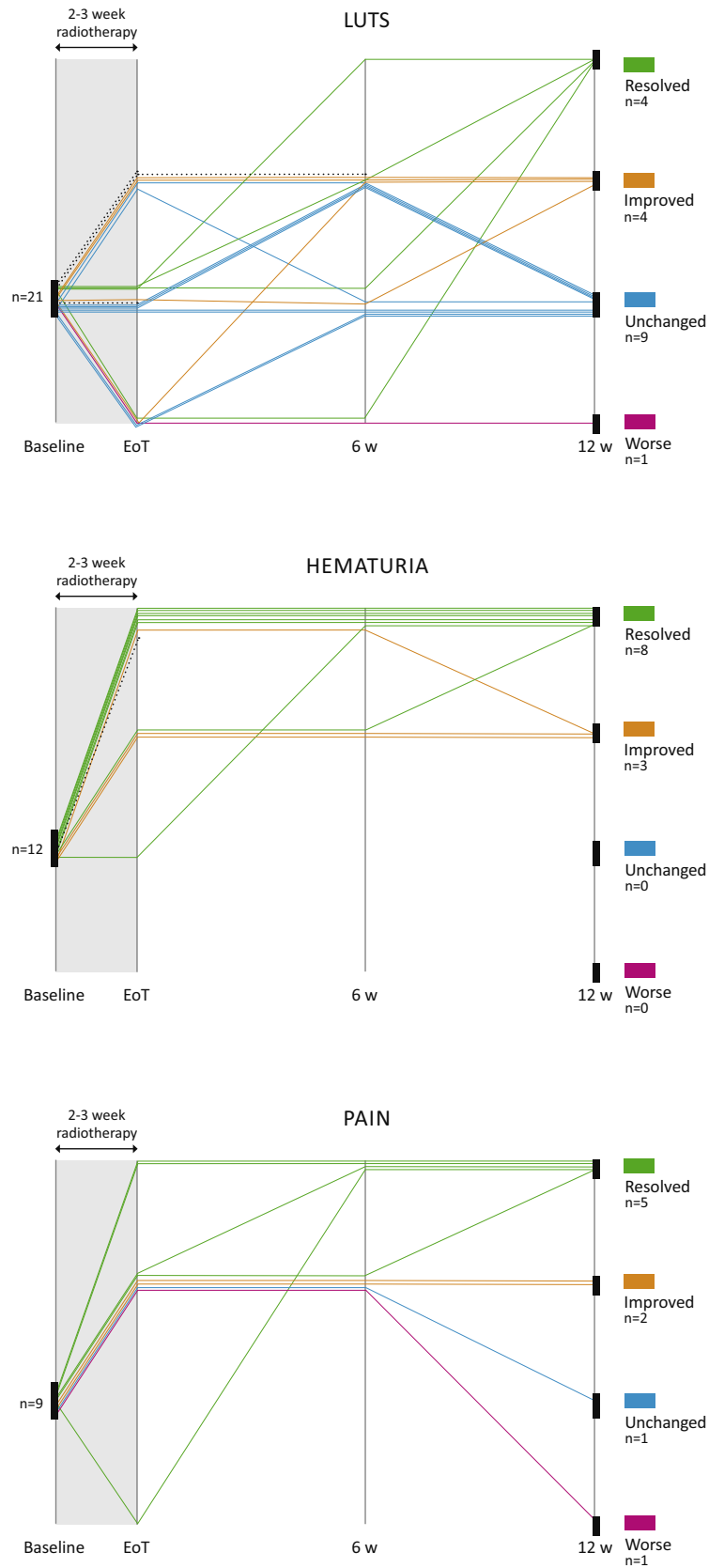


Fig. 2. Patient-reported target symptom severity over time compared with baseline for the three major target symptoms. EOT = end of treatment; w = week follow-up; ... = patients who did not complete the study.

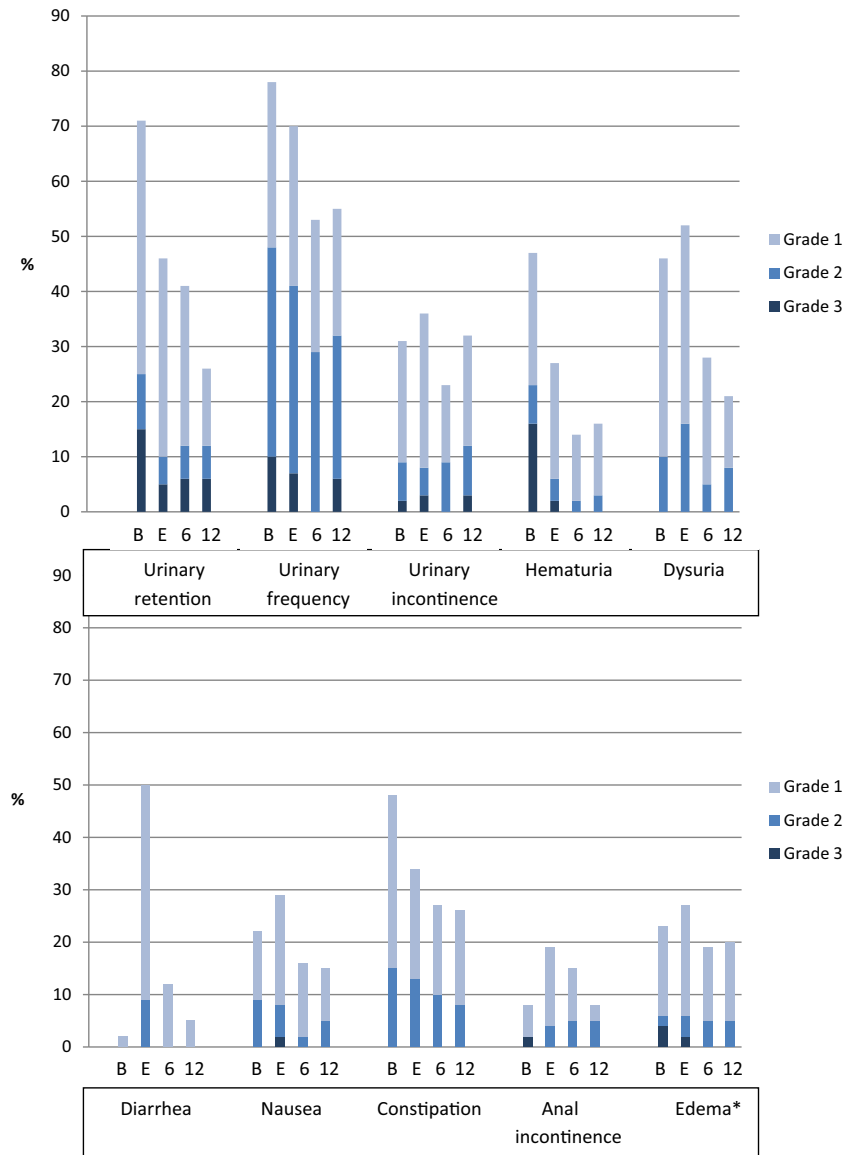


Fig. 3. Toxicity. Percent of patients reporting various symptoms at each of the four study visits. Symptoms graded according to NCI-CTCAE v. 3.0. There were no grade 4 symptoms reported. * = lower extremity or scrotal edema. B = baseline; E = end of treatment; 6 = 6-week follow-up; 12 = 12-week follow-up.

negative outcomes, are asymptomatic [4,19]. Patients in the current study were prescribed doses less than 40 Gy prior to study entry, primarily due to their more advanced stages of disease in need of palliation coupled with a more limited life-expectancy.

To our knowledge, this is the first prospective study exploring symptomatic effects of PPRT of CRPC, yielding information not only about the magnitude, but also the onset and duration of effects and toxicities. It is the first study to make use of patient-reported outcomes and prospective, active capture of the specific toxicities associated with PPRT, in order to explore the risk-benefit balance. It was a multi-center study of relatively unselected and elderly patients, and findings are therefore presumed generalizable. Despite the modest number of included patients, it was sufficient to meet statistical goals. The study made use of modern conformal radiotherapy techniques, a relatively limited range of doses, and was standardized in terms of target volume definitions. However there was a degree of heterogeneity both in total radiotherapy dose and, due to variable tumor volumes, the volumes treated.

Palliative care of cancer patients consists of a multidimensional, interdisciplinary approach to patients with terminal disease, often making use of several simultaneous interventions. As such, effects of the interventions overlap and are difficult to reliably separate. This presents a challenge when attempting to study singular standardized interventions within the greater framework of palliative care, as was done in the present study. Results therefore apply to “palliation which includes PPRT”, rather than to the isolated effect of PPRT.

Several patients underwent interventions during the study period that may have impacted on symptom severity. However, for ethical reasons, no restrictions were placed on these ancillary treatments. Randomization of participants to continued palliative care, with or without PPRT could have reduced the influence of these confounding factors. However, despite the scant research base [2], there is some evidence and a strong clinical tradition for the use of PPRT in this clinical context. We therefore deemed it unethical to withhold PPRT from a control group.

Included patients had progressive CRPC, and in addition to the pelvic tumor the majority had skeletal metastases. Metastases were largely left untreated during the approximately four-month study period, and were therefore likely to progress, leading to worsening symptoms and HRQOL. Although attempts were made to limit confounding by non-pelvic symptoms, the study data could not, for example, determine what specific location of pain caused patients to alter their analgesic use. The anchor-based responses to the question of target symptom severity are therefore better indicators of the degree of pelvic pain than pain scores and amount of analgesic used. By the same token, separation of toxicity resulting from the PPRT from symptoms of tumor progression was not feasible and although low, treatment-related toxicity may therefore be overestimated.

So as not to overburden participants, the study did not require longer duration of follow-up or more frequent symptom evaluation or procedures. Symptom reassessment at only three fixed time points may have led to missing peaks of toxicity or transient changes in symptoms, thereby misrepresenting the true course of symptoms and side-effects. In addition, 12 weeks of follow-up after PPRT is insufficient to evaluate delayed or longer-term symptom palliation, the need for repeated intervention and to explore possible long-term side-effects. This is particularly important given that the median survival from the time of PPRT was 20 months.

Palliative TURP is a treatment option for LUTS, although nearly 40% of patients with CRPC do not benefit [20]. Symptomatic outcomes of TURP in prostate cancer patients improve when preoperative urodynamic testing selects for intervention only those patients with manifest obstruction [21]. Due to the poorer response rate among the subgroup of patients with LUTS in this study, it may be worthwhile to examine the use of urodynamics prior to PPRT, and to optimize medical treatment of bladder dysfunction in these patients.

Several patients with hematuria reported complete resolution after a single fraction of 3 Gy (results not shown), while those with LUTS tended to respond later. This raises the question of the appropriateness of different radiotherapy approaches for different target symptoms and should be investigated in fractionation studies. Lower total doses, hypofractionated or delivered as single fractions of for example 8 Gy, and repeated as needed may be appropriate for palliation of hematuria while higher doses requiring fractionation may be necessary to affect bladder outlet or lymphatic obstruction, where tumor-shrinkage is thought to be necessary. If the effects of and tolerance for lower doses or shorter courses of radiotherapy can be demonstrated to be equivalent to those seen with higher doses and longer regimens, as has been shown in skeletal metastases from prostate cancer [22], then simplified radiotherapy could improve patient convenience, conserve resources and reduce treatment costs.

Conclusion

In patients with CRPC and a symptomatic pelvic mass, PPRT with doses in the range of 30–39 Gy contributes to effective palliation of macroscopic hematuria, pain and other pelvic symptoms. The applied radiotherapy does not impart significant toxicity.

To our knowledge, this is the only prospective study of PPRT of patients with CRPC which reports symptom outcomes. It provides data against which future studies can be compared and that may serve as a basis for planning studies. The question of optimal radiotherapy dose and fractionation scheme in this context remains unanswered and the possibility of lower doses and simpler, shorter treatments warrants investigation.

Conflict of interest statement

There are no potential conflicts of interest.

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