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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.

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. Secondarily, 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 antineoplastic 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 ±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

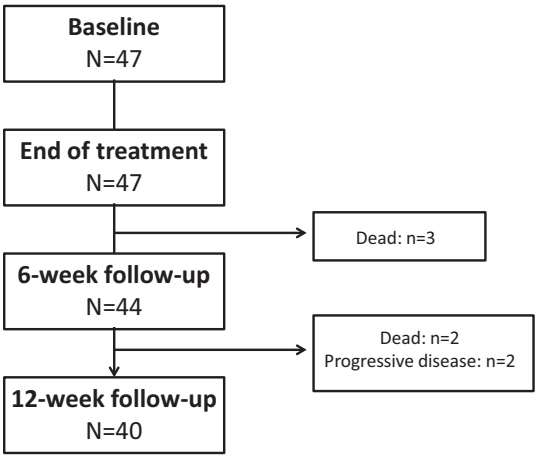

Fig. 1. Inclusion and follow-up of patients.