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Systematic review

Palliative pelvic radiotherapy of symptomatic incurable prostate cancer – A systematic review ☆

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ABSTRACT

Background and purpose: Patients with prostate cancer (PC) and a symptomatic pelvic tumor may be treated with palliative pelvic radiotherapy for symptom relief or to delay symptom progression. Radiotherapy dose and fractionation regimens vary. We aimed to provide an overview of the literature and to evaluate palliative pelvic radiotherapy of PC focusing on symptomatic effect, quality of life (QOL), and toxicity, and to determine the optimal radiotherapy schedule. *Material and methods:* Systematic literature searches of Medline, Embase and Cochrane databases were performed through 2011. Studies reporting symptom and QOL responses were eligible. *Results:* Nine studies were included, all retrospective chart reviews. There were large variations in radiotherapy dose and fractionation. Overall symptom response rate was 75% and positive responses were reported for hemorrhage (73%), pain (80%), bladder outlet obstruction (63%), rectal symptoms (78%) and ureteric obstruction (62%). Toxicity results were not evaluable. *Conclusions:* Despite limitations in the review process and the included studies, we conclude that pelvic radiotherapy for symptomatic PC appears to provide effective palliation of a variety of symptoms. There is currently no valid documentation regarding onset or duration of palliation. No recommendations can be provided regarding target dose or fractionation schedule in this context.
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Incurable prostate cancer represents a spectrum of clinical scenarios where the cancer has spread beyond the prostate gland, although there is controversy regarding the extraprostatic extension that rules out a curative treatment approach [1]. Advanced prostate cancer commonly disseminates to the skeleton and lymph nodes. Androgen deprivation is the most common initial therapeutic approach in this situation although resistance to castrate levels of testosterone typically develops after approximately 3 years of treatment [2]. Among 15–20% of these cases of castration-resistant prostate cancer (CRPC), the clinical picture is dominated by local extension of the primary tumor [3] resulting in pelvic symptoms such as pain, obstruction and hemorrhage. Palliative pelvic radiotherapy may, in such cases, relieve existing symptoms, prevent symptom progression and delay local extension.

There is a movement toward hypofractionated, simplified palliative radiotherapy regimens in several clinical scenarios that have demonstrated equivalent symptomatic responses to those achieved with traditional, longer courses of treatment [4,5]. No standard regimen exists for the delivery of palliative pelvic radiotherapy of prostate cancer. Approximately 50% of all radiotherapy courses are given with palliative intent and this figure is predicted to increase [6]. Palliative pelvic radiotherapy of prostate cancer remains underutilized, likely as a consequence of the lack of good evidence of its effect and fear of toxicity [7]. To the best of our knowledge, there are no published reviews that summarize the evidence of its palliative treatment effects.

The aim of this systematic review was to identify and evaluate published studies describing the effects of palliative pelvic external beam radiotherapy (EBRT) of symptomatic, incurable prostate cancer in order to determine its effect on pelvic symptoms and quality of life (QOL). We also reviewed the toxicity reported in order to gain a better understanding of the risk–benefit balance. Furthermore, we attempted to evaluate treatment schedules in order to determine whether there exists an optimal dose or fractionation scheme. Implications of the findings for clinical practice and future research are discussed.

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Methods

Within limitations imposed by the nature of the existing publications on palliative pelvic radiotherapy of prostate cancer, we have followed the guidelines for a qualitative synthesis laid out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement [8]. In addition, the review process followed a scientific research protocol.

Search strategy

Searches of the Medline, Embase and Cochrane library databases were performed through December, 2011. The following MESH terms illustrate the search strategy used in Medline: (*radiotherapy OR radiation OR radiation oncology*) *AND* (*palliative care or terminal care*) *AND prostatic neoplasms*. Resultant titles/abstracts were screened by four authors (MC, MG, CK, IV). Further studies were identified manually from the reference lists of articles reviewed in full-text (MC). Studies were identified by their English title (used in database indexing and in reference lists). All studies published in European languages were considered for inclusion. Native speakers were used to assess eligibility and translations were performed as necessary.

Eligibility criteria

Published full-text studies that evaluated pelvic EBRT of prostate cancer given with palliative intent were considered eligible for inclusion. Studies that evaluated these patients as a subgroup were also included, as long as results within this subgroup were clearly reported. Reports evaluating curative radiotherapy doses given in "palliative situations" were included if the incurable patients could be identified as a subgroup. Only studies that reported symptom or QOL outcomes were included. All study designs (other than case-reports and reviews) were eligible. Published reports using weak scientific methodology (including retrospective reviews of patient charts) were included in order to ensure as complete an overview of the existing evidence as possible. Studies that combined palliative pelvic radiotherapy with other tumor-directed interventions (except ongoing hormonal manipulation) and those that evaluated re-irradiation were excluded.

Evaluation of studies

There is no standard reliable and validated tool for assessing the "quality" of observational and other nonrandomized studies [9]. Articles were therefore evaluated using an assessment form based partly on recommendations from the Cochrane group [10] and modified for our use after pilot-testing. Our evaluation criteria qualitatively focused on the internal validity of the individual studies and included an assessment of the risk of bias at the study and outcome levels. Potential articles were evaluated at the full-text level by four of the authors (MC, MG, CK, IV) and final selection was based on consensus.

Data extraction and management

Data regarding the study characteristics and outcomes of interest (symptom response, QOL, and toxicity) were extracted from the included studies, into tables. Data extraction was performed independently by two reviewers (MC, IV) and a third reviewer was consulted to resolve discrepancies. The data extraction procedure was first pilot tested on five randomly selected studies and then modified before implementation. A meta-analysis was not feasible due to the heterogeneity of studies being reviewed. Data are instead presented in table form, using explanatory headings. An attempt has been made to link the quality of the included studies to the interpretation of their results.

Results

Study selection

After removal of duplicates, the database searches yielded 927 records. These titles/abstracts were screened, leaving 184 records (both original research and review), which were then reviewed in full text. The reference lists of the selected full-text records yielded an additional 43 articles for full-text review. The list of full-length articles was refined, according to the inclusion/exclusion criteria, to a short-list of 34 eligible studies which were evaluated according to the preset assessment form. Of these, nine studies met the inclusion criteria and were included in the final analysis (Fig. 1).

Study characteristics

The median number of relevant patients in the included studies was 26 (range 11–119) with a pooled total of 315 patients. The studies described treatments spanning a 46-year period, from 1961 to 2007. None of the studies were prospective. Where methods of data collection were reported, symptom-data had been extracted retrospectively from physicians' clinical notes. There were no reports of QOL or other patient-reported outcomes (PROs). No studies used standardized scales for symptom evaluation. An overview of the characteristics of the nine included studies can be found in Table 1.

Patient characteristics and symptoms

The study populations were heterogeneous (Table 1). Four studies included patients with both CRPC and castration-sensitive disease [11–14]. The six studies that reported the metastatic status of their population, reported a combination of patients with and without distant metastases [11–13,15–17]. There was a range of target symptoms among the studies (Table 2) and not uncommonly, there were constellations of symptoms in the same patients. The most commonly reported symptoms were related to bladder outlet obstruction (BOO), hemorrhage and pain. In addition, rectal symptoms and ureteral obstruction were indications for treatment. Some patients were treated primarily to obtain local tumor control and prevent tumor progression and thus, symptomatic response was a secondary finding [14,16].

Radiotherapy dose and fractionation

Radiotherapy method, dose, schedule, and target definitions were heterogeneous and varied greatly not only between studies, but also within studies. Reported fraction sizes varied across studies from <2 to 8 Gy and total doses ranged from 8 to 76 Gy (Table 1). The most commonly used fraction sizes were in the range of 2–3 Gy daily. Calculation of biologically effective doses was not possible due to inadequate description of the radiotherapy delivered in several of the studies.

Treatment response

The definition of response criteria varied between the studies and responses were reported at variable time points after radiotherapy. In most studies response was defined as symptomatic relief, graded retrospectively by a physician or researcher on a 2–4 point scale (Table 1). Response in ureteric obstruction was determined radiographically. Reported overall response, without