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. © 2013 The Authors. Published by Elsevier Ireland Ltd. All rights reserved. Radiotherapy and Oncology 110 (2014) 55–60

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.
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
specifying symptom-types, ranged from 60% to 100% in the re-
viewed studies [12,13,15–18], with a pooled response rate of
75%. Details are presented in Table 2 and where individual symp-
tom response data could be extracted from the studies, these have
been pooled into symptom categories (Table 3).

**Durability of response**

Median duration of symptomatic relief could not be determined
due to heterogeneous reporting. See Table 2 for details. Among the
range of symptoms reported, hematuria tended to be an early
responding symptom and in some cases it resolved during the
course of radiotherapy [14] or after delivery of a single large frac-
tion [19].

**Dose–response**

The studies could not reliably demonstrate a dose–response ef-
fect. Furuya claimed that higher radiotherapy doses may produce

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**Table 1**

Characteristics of studies of palliative pelvic radiotherapy of prostate cancer.

<table>
<thead>
<tr>
<th>Author/ year</th>
<th>Study design and treatment period</th>
<th>Patients</th>
<th>Radiotherapy (dose range/fraction size/treatment period)</th>
<th>Relevant outcome</th>
<th>Patient follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hindson 2007 [16]</td>
<td>Retrospective 2002–2006</td>
<td>N = 35 locally advanced, with pelvic symptoms</td>
<td>CRPC</td>
<td>30–70 Gy/2–3 Gy (9 days per 2 wk)</td>
<td>Symptom relief at 6 mo, 4 point scale</td>
</tr>
<tr>
<td>Perez 1993 [19]</td>
<td>Retrospective NR</td>
<td>N = 26 locally advanced, with pelvic symptoms</td>
<td>CRPC</td>
<td>50–60 Gy</td>
<td>Symptom relief</td>
</tr>
</tbody>
</table>

N, number of subjects in the study; RSN, number of subjects in the relevant subgroup; NR, not reported; mo, month; wk, week; CRPC, castration-resistant prostate cancer.
prolonged local control [16] while Hindson did not find a dose–response among his population [17].

**Toxicity**

Six of the nine studies addressed the toxicity of the radiotherapy [11–14,16,19]. The toxicities reported were mostly mild/moderate. The findings are summarized in Table 4. The specific toxicities reported included proctitis, diarrhea, tenesmus, pollakisuria, dysuria, hematuria, dermatitis, emesis, lethargy and worsening ureteral obstruction. None of the procedures for documenting toxicity in the included studies were systematic. One study used a validated grading scale to describe the degree of toxicity [19].

**Discussion**

This systematic review of the literature demonstrates the lack of documentation regarding relevant outcomes of palliative pelvic EBRT of prostate cancer. Despite a broad and comprehensive literature search, we found no prospective studies that complied with our eligibility criteria. The included studies indicated a positive effect of palliative pelvic radiotherapy on hemorrhage, pain, BOO, rectal symptoms and ureteric obstruction as well as an overall symptomatic response among patients. We found no conclusive evidence for a relationship between dose or fractionation and the palliative effects.

PROs are the preferred measures with which to assess the effects of palliative interventions among cancer patients. There was a complete absence of PROs, including QOL, in the reviewed studies.

Prospective studies of palliative pelvic radiotherapy of prostate cancer are difficult to conduct. Important obstacles include multiplicity and progression of symptoms and confounding treatments, particularly increasing doses of analgesia, during study follow-up. In addition, many patients have short life expectancies, making adherence to study protocols difficult.

The above factors may in part explain why the identified publications are characterized by mostly small retrospective studies. Patient characteristics and radiotherapy prescriptions vary substantially, even within studies, and the source documentation from which the retrospective data have been extracted often lacks important information about study subjects and evaluated treatments. In addition, many studies evaluate radiotherapy without reporting likely confounders such as previous treatment, hormonal manipulation and concomitant analgesic medication use. As such, their relative contributions cannot accurately be determined. This limits the reliability and generalizability of the results concerning the effectiveness of palliative pelvic radiotherapy.

The pooled overall response rate of 75% appears promising despite shortcomings in the methods used to evaluate symptoms. It is noteworthy that the favorable response rates reflect highly variable radiotherapy practices. A proportion of those treated for hemorrhage achieved partial or complete relief at relatively low radiotherapy doses (most often single fractions of 8 Gy), although some patients did eventually require retreatment [12]. The durability of this response appeared to be substantial and there was response to retreatment in cases of symptom recurrence during...
Toxicity reported in studies of palliative pelvic radiotherapy of prostate cancer.

<table>
<thead>
<tr>
<th>Study</th>
<th>Acute toxicity</th>
<th>Genitourinary</th>
<th>Skin/connective tissue</th>
<th>Late toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green [13] 1974</td>
<td>NR</td>
<td>1/11 severe (72 Gy)</td>
<td>NR</td>
<td>1/11 rectal sloughing at 6 mo (76 Gy)</td>
</tr>
<tr>
<td>Hindson [17] 2007</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kraus [14] 1972</td>
<td>Mild 18/33</td>
<td>Mild 8/33</td>
<td>Mild</td>
<td>None</td>
</tr>
<tr>
<td>Kynaston [19] 1990</td>
<td>WHO grade 1–2</td>
<td>None</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Perez [18] 1993</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR, not reported; mo, months; WHO, World Health Organization.

a Mild indicates that the author has described the toxicity as "mild" or as not requiring more than symptomatic measures.
b Moderate indicates that the author has described the toxicity as "moderate" or that the treatment was interrupted due to toxicity.
c Severe indicates that the author has described the toxicity as "severe" or that the treatment was discontinued due to toxicity.

The follow-up period [19]. These findings are consistent with studies of hypofractionated radiotherapy of bone metastases [5]. Both patients with pain and with obstructive symptoms, including BfO and rectal disturbance appear to have been palliated and whereas it is unclear to what degree analgesics were used, the duration of responses approached one year in several of the re-reviewed studies [13,14,19].

The frequency of complications and degree of toxicity are most likely underestimated in the included studies due to the non-systematic manner in which the patients were followed up. In addition, late toxicity and local disease progression may be difficult to differentiate, as exemplified by fistula-formation eight months after radiotherapy in the study by Kraus et al. [14]. In studies of palliative interventions, carefully weighing the burden of treatment against the benefit provided is of utmost importance. In this context, patient reported toxicity should be assessed in a prospective and systematic manner using validated instruments.

Several studies reported highly variable radiotherapy prescriptions, with total doses that varied up to nearly fivefold [13]. Although all nine studies reported symptomatic improvement in the majority of patients, they did not allow for conclusions regarding dose–response or the most effective fractionation regimens. While Furuya described a relationship between dose and survival among his sample, this trend should be interpreted with caution as it may be the result of selection of patients with longer life-expectancies for more intensive treatments rather than demonstration of a life-prolonging effect of the palliative radiotherapy itself. The studies do not document that palliative radiotherapy of the pelvic tumor improves survival time among patients with metastatic disease. However, patients with incurable prostate cancer confined to the pelvis seem to have better prognoses compared to those with systemic disease [16,20]. This is an important consideration when selecting patients for higher target doses of palliative pelvic radiotherapy where there is hope for prolonged survival and subsequent need for prolonged pelvic tumor control. However, if symptomatic effect can be shown with hypofractionated radiotherapy or at low total doses, more patients are likely to be referred for this treatment in the future.

There are risks of bias intrinsic to the review process that should be taken into consideration when interpreting these results. In particular, negative studies and those without significant findings systematically remain unpublished which may lead to overestimation of the effect of a specific intervention. Retrospective extraction of physician reported symptom response presents a risk of bias, potentially leading to an overly optimistic result of the treatment effect [21]. Attrition may also introduce bias as the included patients have relatively short life expectancies and many were lost to follow-up [12]. In addition, it may be inappropriate to extrapolate some aspects of the older studies to today’s clinical scenarios as staging procedures and radiotherapy techniques have changed considerably during the last 20 years.

Conclusion

Palliative pelvic radiotherapy of prostate cancer appears effective for a range of symptoms, with a favorable benefit to toxicity ratio. However, based on the current literature, it is impossible to draw reliable conclusions regarding the magnitude, onset or duration of the beneficial and detrimental effects. In addition, optimal dose and fractionation regimen still need to be defined. A better understanding of these unresolved issues must come from prospective studies of patient-reported symptom response and QOL [22].

Authors’ contributions

All authors contributed to the development of the idea for this review. MC wrote the research protocol, which was approved by all co-authors. The primary database searches and selection of articles were carried out by MC, MG, CK and IV. MC wrote the first draft of the manuscript, on which the remaining authors provided feedback. The five authors all approved the final version of the manuscript.

Conflicts of interest

There are no potential conflicts of interest.

Acknowledgements

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