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Original Article

Efficacy of High-dose Palliative Radiotherapy for Localised, Castration-resistant Prostate Cancer

R. White [*], R. Khor [*†], M. Bressel [‡], G. Duchesne [*†§¶], S. Williams [*†], P. Bowden [||], K. Tai [*], F. Foroudi [*†]

[*] Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia
[†] Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, VIC, Australia
[‡] Centre for Biostatistics and Clinical Trials, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia
[§] Department of Biochemistry, Monash University, Melbourne, VIC, Australia
[¶] Department of Medical Radiations, Monash Univeristy, Melbourne, VIC, Australia
[||] Radiation Oncology, Epworth Healthcare, Melbourne, VIC, Australia

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Abstract

Aims: There are limited outcome data after radiotherapy treatment for clinically localised, castration-resistant prostate cancer. We report our single institution experience on patient outcomes in this group using high-dose palliative radiotherapy (HDPRT).
Materials and methods: A retrospective review of patient hospital records was conducted in prostate cancer patients treated with palliative intent radiotherapy and restricted to those who had castration-resistant disease, no evidence of regional or distant disease and who received a local radiotherapy dose equivalent to 40 Gy or greater.
Results: Fifty-one patients met the study criteria, 88% of these had high-risk disease at initial diagnosis. The median time to delivery of HDPRT was 66 months and the median follow-up from HDPRT was 54 months. Grade 3 or worse toxicity was experienced in 8%. The estimated freedom from local failure, cause-specific survival and overall survival at 5 years were 81, 65 and 35%, respectively. Local procedures were a significant contributor to local morbidity, with the most common procedure a transurethral resection of the prostate (27% patients). Only two patients died from complications of local failure.
Conclusion: HDPRT was well tolerated and provided a high rate of local control in a clinically localised castration-resistant prostate cancer population. Although prostate cancer remained the most frequent cause of death, some patients had extended survival without evidence of disease progression.

Key words: Castration-resistant prostate cancer; palliative; radiotherapy

Introduction

In men with prostate cancer, the development of castration resistance heralds the emergence of clonogens that have circumvented primary means of androgen deprivation [1]. This phase of the disease is considered end stage in patients with established metastatic disease, with a median survival of about 15 months treated with newer chemotherapy or androgen pathway modulators [1,2]. A proportion of men, typically those treated with primary androgen deprivation therapy (ADT), develop evidence of castration-resistant prostate cancer (CRPC) without evidence of regional or distant metastatic disease. If no definitive local treatment has previously been delivered, these men represent a management conundrum. The only medical body that currently provides recommendations specifically for asymptomatic or minimally symptomatic non-metastatic CRPC is the American Urological Association. They currently suggest observation with continuation of ADT based on level C evidence [3].

External beam radiotherapy (EBRT) is the obvious modality to control local disease in this highly selected group if symptoms arise, but outcomes of this approach are not well

Author for correspondence: R. White, Department of Radiation Oncology, Locked Bag 1, A'Beckett St, Melbourne, VIC 8006 Australia. Tel: +61-3-9656-1111; Fax: +61-3-9656-1424.
E-mail address: rohenwhite@hotmail.com (R. White).

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documented. A recent systematic review highlighted the inadequacy of the existing literature in both non-metastatic and metastatic CRPC after pelvic radiotherapy and was unable to make any formal recommendations regarding the optimal dose and fractionation [4].

A high-dose palliative radiotherapy (HDPRT) regimen has been used at our institution for localised CRPC, either when local symptoms become evident or when a patient is considered at imminent risk of their development. The latter is based on clinical evidence of local progression, for example, new palpable tumour progression and/or surrounding tissue invasion. The HDPRT regimens aim to give a total dose of $\geq$40 Gy with the most common schedule being 50 Gy in 20 daily fractions over 4 weeks. The rationale for HDPRT is that a curative intent dose will probably introduce unnecessary cost, toxicity and time commitment in a group with likely micrometastases and, hence, ultimately, incurable disease, whereas low-dose palliative regimens risk inadequate durability of local control in a cohort that may exhibit extended survival.

The primary aim of this study was to report on clinical local failure in patients who have received HDPRT for localised CRPC. The secondary aims were to report on morbidity inclusive of invasive procedures, tolerability of HDPRT, patterns of disease failure, cause-specific and overall survival. Predictive factors for local failure and overall survival were also explored.

Materials and Methods

Approval for this study was granted from our institutional Human Ethics Committee.

Data Collection

All patients who received palliative dose radiotherapy to the prostate between the years of 2002 and 2010 inclusive were retrospectively identified from the hospital administrative database. The electronic medical record of each patient was reviewed by a specialty registrar and patients were eligible if they had evidence of both CRPC and N0M0 disease before HDPRT. The latter was based on a normal bone scan and/or computed tomography imaging within 3 months of radiotherapy or the absence of clinical suspicion on history and examination. Castration resistance was defined as a rising prostate-specific antigen (PSA) and/or clinical evidence of progressive disease despite being on ADT. Patients were not required to exhibit local symptoms to be eligible for the study. Patients were excluded if they had received previous pelvic radiotherapy and if the course of prostate radiotherapy was considered to be of curative intent or if the total prescribed dose was $<$40 Gy.

Patient and tumour characteristics, mortality dates and cause of death were gathered from the computerised clinical record and supplemented by information from hospitals, general practitioners and urology practices. Grade 3 or worse radiotherapy-related toxicity was retrospectively scored from the computerised clinical record using the common terminology criteria for adverse events version 3.0 (CTCAEv3) [5]. Survival data were reconciled with the state registry, which aggregates national-level mortality data.

Radiotherapy

All radiotherapy was delivered with megavoltage EBRT using computed tomography-based three-dimensional conformal planning. The clinical target volume was defined as the prostate and any visible tumour extension on computed tomography. A 1 cm uniform expansion was used to create the planning target volume. An acceptable plan covered the planning target volume by the 95% isodose and was typically comprised of between three and five beams of $>$10 MV energy with rectum, bladder and small bowel appropriately shielded by multileaf collimators. An organ at risk constraint (V40Gy $<$ 40%) was applied to the rectum when using the 55 Gy in 20 daily fractions regimen. All HDPRT regimens involved once daily treatment, 5 days per week. Pelvic nodes were not included in the irradiated volume. Implanted fiducial markers were not used.

End Points

Clinical local failure was the primary end point and defined as new and/or progressive symptoms attributable to local disease. Local, regional and distant failure events were collected, as was the nature and timing of required local procedures. Local morbidity was defined as local failure or the requirement of a local procedure. This was considered a useful end point to identify the true incidence of pelvic morbidity beyond uncontrolled local disease, recognising that uncontrolled regional disease and late radiotherapy toxicity can also contribute.

The failure location was determined through documentation of physical examination and/or imaging. Regional failure was defined as recurrence in pelvic lymph nodes below the sacral ala and distant failure was defined as the appearance of metastases at a site representing haematogenous dissemination or nodal sites beyond the pelvis. Clinical criteria only (not PSA) were used to identify failure. Freedom from local failure at 3 and 5 years after treatment was estimated, as was prostate cancer-specific survival and overall survival.

Statistical Considerations

Descriptive statistics to summarise clinical data were reported in the form of medians, standard deviations and ranges for quantitative variables. Categorical variables were reported in the form of count and percentage. Three and 5 year event rates were estimated with 95% confidence intervals using Kaplan–Meier methods. Log-rank tests and Cox regression methods were used to evaluate the effect of possible predictive factors for local failure and overall survival. The median follow-up time was estimated using the reverse Kaplan–Meier method. All statistical analyses were conducted using R 3.0 [6].