Radiotherapy and Oncology 107 (2013) 274–281

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

Boosting imaging defined dominant prostatic tumors: A systematic review

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ARTICLE INFO

Article history:
Received 2 December 2012
Received in revised form 8 April 2013
Accepted 21 April 2013
Available online 20 June 2013

Keywords:
Prostate
DIL
Boost
GTV
MRI
PET
SPECT

ABSTRACT

Introduction: Dominant cancer foci within the prostate are associated with sites of local recurrence post radiotherapy. In this systematic review we sought to address the question: "what is the clinical evidence to support differential boosting to an imaging defined GTV volume within the prostate when delivered by external beam or brachytherapy".

Materials and methods: A systematic review was conducted to identify clinical series reporting the use of radiation boosts to imaging defined GTVs.

Results: Thirteen papers describing 11 unique patient series and 833 patients in total were identified. Methods and details of GTV definition and treatment varied substantially between series. GTV boosts were on average 8 Gy (range 3–35 Gy) for external beam, or 150% for brachytherapy (range 130–155%) and GTV volumes were small (<10 ml). Reported toxicity rates were low and may reflect the modest boost doses, small volumes and conservative DVH constraints employed in most studies. Variability in patient populations, study methodologies and outcomes reporting precluded conclusions regarding efficacy.

Conclusions: Despite a large cohort of patients treated differential boosts to imaging defined intra-prostatic targets, conclusions regarding optimal techniques and/or efficacy of this approach are elusive, and this approach cannot be considered standard of care. There is a need to build consensus and evidence. Ongoing prospective randomized trials are underway and will help to better define the role of differential prostate boosts based on imaging defined GTVs.

Prostate cancer is a multi-focal disease and conventional therapies address this by treating the whole gland. In the case of radiation, such an approach however, may be limiting to the efficacy of radiotherapy as escalation of dose to improve tumor control may be limited by adjacent organ at risk tolerance [1].

Whole mount prostate pathology studies suggest in many cases a dominant cancer focus exists within the gland and may be a driver of the aggressiveness of the cancer and the epicenter of recurrence post treatment [2,3]. Thus strategies to identify and intensify treatment to dominant prostate foci (Gross Tumor Volume/GTV) are under active investigation. Advances in Positron Emission Tomography (PET), Single Positron Emission Tomography (SPECT) and magnetic resonance imaging (MRI) show promise in identifying prostate GTVs and advances in precision radiotherapy enable dose intensification [4–8]. In this systematic review we sought to address the question: "is there clinical evidence to support differential boosting to an imaging defined GTV boost within the prostate when delivered by external beam or brachytherapy (low dose or high dose rate)". In particular we were interested in techniques used for GTV definition on imaging for boosting and clinical endpoints of toxicity (both acute and late) and efficacy (biochemical and clinical control) among men so treated.

Materials and methods

Formulation of the research question, search strategy and data extraction elements were agreed upon by the lead authors (GB,CM) in advance of the literature review. A search of the PubMed database for the years January 1, 2000–June 30, 2012 was conducted using the following search strategy "(intraprostatic[tw] OR intraprostatic[tw] OR DIL[tw] OR ipl[tw]) AND (radiation[tw] OR radiotherapy[tw] OR brachytherapy[tw]) AND prostate[tw]". Papers describing focal salvage treatment (e.g. Nguyen [9] image guidance for whole gland therapy (e.g. Menard [10]) or partial gland therapy based on anatomically defined (not lesion defined) targets (e.g. Nguyen [11]) or where a focal boost was based exclusively on biopsy results (e.g. Gaudet [12]) rather than lesion imaging were excluded. Papers included needed to available as full published manuscripts, available in English and reporting at least one clinical

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0167-8140/$ - see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.radonc.2013.04.027

outcome (toxicity or efficacy) among treated patients (papers reporting planning studies without actual patient treatment and single case reports were not included), Full text versions of the eligible papers were retrieved and reviewed including manual searching of the bibliographies for other applicable papers. In the case of one paper [13] the corresponding author was contacted for additional information regarding clinical outcomes and this lead to the identification of a companion paper [14] with this information. For the review, data extracted for each series included year of report, number of patients treated, proportion of low, intermediate and high risk patients (NCCN criteria) included in the series, median PSA among the patient population, methods used for GTV imaging and GTV delineation criteria, PTV1 delineation criteria, boost technique used and dose of the boost, use of supplementary pelvic nodal or androgen deprivation therapy, acute and late toxicity observed (along with toxicity scale used) clinical outcomes (clinical and/or biochemical control) and series specific observations were extracted. Nomenclature regarding intra-prostatic lesion definition differed significantly between patient series; for the purposes of this systematic review, GTV refers to imaging defined intra-prostatic lesions; PTV1 refers to the volumetric expansion on the GTV for the boost and PTV2 refers to the volumetric expansion of the whole prostate volume to account for setup and delivery uncertainty. Initial data extraction was undertaken by one author (GB) with review by a second author (CM). The remaining authors (MH, UVH) contributed to the analysis and interpretation of the extracted results and the manuscript. Given the heterogeneous nature of the patient series reported, no formal attempt at a quantitation of bias or analysis of pooled results was attempted however qualitative appraisal of the relative strengths and weaknesses of the individual series was made and qualitative statements are included in the results and discussion of the papers. The primary outcomes of interest were safety (toxicity reported), efficacy (clinical and biochemical control) as well as method of lesion delineation.

Results

In total, thirteen papers describing eleven unique patient series with a total of 833 patients were identified for data extraction. A flow diagram of the search results is available in Fig. 1. As outlined in Table 1, the analyzed literature [13–25] included patients treated with external beam (EBXRT) focal boost ($n = 5$ with simultaneous boost; $n = 1$ with sequential boost) as well as low dose rate brachytherapy (LDR, $n = 4$) and high dose rate brachytherapy (HDR, $n = 1$). Heterogeneity between the series restricted analyses to qualitative descriptions and pooling of results of data was not possible. The majority of series were prospective series examining relatively small numbers of patients. The largest external beam series (Fontenye et al. [24–26]) was limited by its retrospective nature and lack of an MRI panel confirming to current standards [4]. The largest brachytherapy series (Ellis et al. [27]) utilized an imaging modality with recognized technical challenges in interpretation and limited histopathologic validation. Approximately one quarter of the patients described met the NCCN criteria [28] for low risk. Androgen deprivation therapy varied among series as did the use of nodal radiation. Techniques for GTV definition used Standard Uptake Value (SUV) thresholds on ^{111}In-Capromab SPECT ($n = 2$) or ^{18}F-Fluorocholine PET imaging ($n = 1$). MRI based series (8) generally used a 1.5T magnet with endorectal (ERC) and pelvic coils. The T2W sequence was most commonly used (GTV = decreased intensity with a mass like appearance) with Dynamic Contrast Enhanced (DCE, GTV = increased enhancement); Diffusion Weighted derived apparent diffusion coefficient

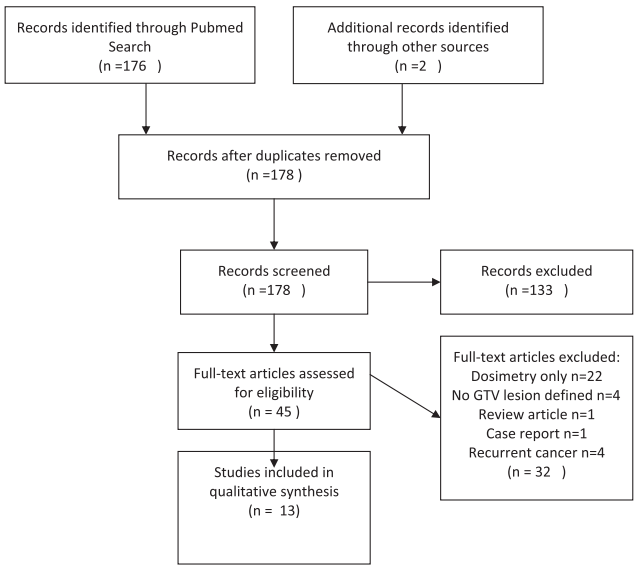

Fig. 1. PRISMA diagram of systematic review results.

maps (DWI/ADC, GTV = regions of decreased ADC values) or magnetic resonance spectroscopy (MRSI, GTV = increased choline + creatinine:citrate ratio) used less often. Only one series [25] utilized T2W + DWI + DCE which reflects the current consensus guidelines for prostate imaging [26,29]. Imaging defined GTVs were transferred to planning images (Computed Tomography/CT or Ultrasound/US) through image registration ($n = 6$) or manual transfer/"cognitive fusion" ($n = 5$). Where reported, GTV volumes ranged from 3.5–6.8 ml; multiple GTVs were defined in 10% of patients and close GTV proximity (<3–5 mm) to Organs at Risk (OAR) was noted. Most series defined a PTV1 (most commonly 3–4 mm, excluding OAR) for the GTV. For EBXRT series, PTV2 doses ranged from 64–78 Gy; PTV1 doses from 80–94.5 Gy. The average differential dose (PTV2–PTV1) was 8 Gy (BED2, $a/b = 3$ Gy, range 3–35 Gy). The most common EBXRT rectal dose constraints was V70 <15–30% with rectal Dmax of 76–80 Gy; bladder constraints were V70 <15–30% and Dmax of 80 Gy. For the brachytherapy series, ^{125}I LDR was most commonly used with a PTV2 dose of 145 Gy, a PTV1 dose of 217 Gy (150%) and Dmax to urethra of <130–150%. Median follow-up ranged from 3–66 months. Outcomes reported included biochemical control in 4 series and toxicity in 10. Grade 4 toxicity was reported in 4 patients (3 rectovesical fistula, 1 hematuria) [17,20,23]. The series with the highest boost differentials [22,23] included 66 patients with reported late Grade 3 or greater toxicities that ranged from 0 to 10% including one patient with fistula formation.

Discussion

Histopathologic studies and patterns of recurrence after external beam radiotherapy suggest that many men may have a dominant focus of disease in the prostate that is a key driver of cancer biology and treatment success [2,30]. Evolution of prostate cancer imaging [4–6] and radiation treatment [7] has driven the exploration of focal intra-prostatic dose escalation. Consensus statements and prospective trials regarding the implementation of therapies based on the identification of focal intra-prostatic lesions are emerging [31–33]. Concerns regarding therapies addressing the focal lesion only are the difficulty in identifying men with truly focal disease [2] and the high risk of recurrence noted to date when less than whole gland treatment is attempted based on