Prostate International xxx (2018) 1–13

Contents lists available at ScienceDirect

Prostate International

journal homepage: https://www.journals.elsevier.com/prostate-international

Review Article

Prostate irradiation with focal dose escalation to the intraprostatic dominant nodule: a systematic review

Thomas Feutren [a, b], Fernanda G. Herrera [a, *]

[a] Department of Radiotherapy, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland
[b] Current Position Department of Radiotherapy, Institut de Cancérologie de Lorraine, Nancy, France

ARTICLE INFO

Article history:
Received 15 December 2017
Received in revised form
10 February 2018
Accepted 21 March 2018
Available online xxx

Keywords:
Boost
Brachytherapy
Dominant intraprostatic lesion
Hypofractionated radiotherapy
Localized prostate cancer
Review
Stereotactic body radiation therapy

ABSTRACT

Radiation therapy (RT) is a curative treatment option for localized prostate cancer. Prostate irradiation with focal dose escalation to the intraprostatic dominant nodule (IDN) is an emerging treatment option that involves the prophylactic irradiation of the whole prostate while increasing RT doses to the visible prostatic tumor. Because of the lack of large multicentre trials, a systematic review was performed in an attempt to get an overview on the feasibility and efficacy of focal dose escalation to the IDN.

A bibliographic search for articles in English, which were listed in MEDLINE from 2000 to 2016 to identify publications on RT with focal directed boost to the IDN, was performed. The review was completed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

Twenty-two articles describing 1,378 patients treated with RT using focal boost were identified and fulfilled the selection criteria. Intensity-modulated radiation therapy (IMRT) was used in 720 patients (52.3%), volumetric modulated arc therapy was used in 45 patients (3.3%), stereotactic body radiation therapy (SBRT) in 113 patients (8.2%), and low–dose rate and high–dose rate brachytherapy (BT) were used in 305 patients (22.1%) and 195 patients (14.1%), respectively. Use of androgen deprivation therapy varied substantially among series. Biochemical disease-free survival at 5 years was reported for a cohort of 812 (58.9%) patients. The combined median biochemical disease-free survival for this group of patients was 85% (range: 78.8–100%; 95% confidence interval: 77.1–82.7%).

The average occurrence of grade III or worse gastrointestinal and genitourinary late toxicity was, respectively, 2.5% and 3.1% for intensity-modulated RT boost, 10% and 6% for stereotactic body RT, 6% and 2% for low–dose rate BT, and 4% and 4.3% for high–dose rate BT.

This review shows encouraging results for focal dose escalation to the IDN with acceptable short- to medium-term side effects and biochemical disease control rates. However, owing to the heterogeneity of patient population and the short follow-up, the results should be interpreted with caution. Considering that the clinical endpoint in the studies was biochemical recurrence, the use and duration of androgen deprivation therapy administration should be carefully considered before driving definitive conclusions. Randomized trials with long-term follow-up are needed before this technique can be generally recommended.

1. Introduction

Prostate cancer (PCa) is among the third most common malignancy in Europe. An estimated 417,000 PCa cases were diagnosed in Europe in 2012[1] and 1.4 million cases of PCa worldwide with 293,000 deaths in 2013[2]. Traditionally, PCa patients have been considered for active surveillance programs or radical whole-gland therapies such as prostatectomy, external beam radiotherapy (EBRT), or brachytherapy (BT)[3]. In the case of EBRT, the advent of more sophisticated treatment plans yields better dose conformity to the target, allowing for dose escalation and better biochemical disease control, although not without toxicity because of the close proximity of organs at risk (OARs), particularly bladder and rectum[4–10].

* Corresponding author. Rue du Bugnon 46, 1011, Lausanne, Switzerland.
E-mail address: Fernanda.Herrera@chuv.ch (F.G. Herrera).

https://doi.org/10.1016/j.prnil.2018.03.005

Abbreviations

ADT	Androgen deprivation therapy
ADC	Apparent diffusion coefficient
BED	Biological equivalent dose
bDFS	Biological disease-free survival
BT	Brachytherapy
CTCAE	Common Terminology Criteria for Adverse Events
CBCT	Cone-beam Computed tomography
DWI	Diffusion-weighted imaging
DCE	Dynamics contrast enhancement
DSS	Disease-specific survival
EBRT	External beam radiotherapy
ERC	Endorectal coil
GI	Gastrointestinal
GU	Genitourinary
Gy	Gray
GTV	Gross tumor volume
HDR	High−dose rate brachytherapy
IMRT	Intensity-modulated radiation therapy
IGRT	Image-guided radiation therapy
IDN	Intraprostatic dominant nodule
KVCT	Kilovoltage Computed tomography
LDR	Low dose rate
LC	Local control
MRSI	Magnetic resonance spectroscopy imaging
MVCT	Megavoltage computed tomography
mpMRI	Multiparametric Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
OAR	Organs at risk
OS	Overall survival
PET CT	Positron emission computed tomography
PCa	Prostate cancer
PSA	Prostatic Specific Antigen
PTV	Planning Target Volume
PTVb	PTV boost
PTVpr	PTV prostate
SIB	Simultaneous integrated boost
SPECT	Single-Photon Emission Computed Tomography
SUV	Standard Uptake Value
SBRT	Stereotactic body radiation therapy
T2W	T2-weighted sequence
US	Ultrasound
VMAT	Volumetric modulated arc therapy

Randomized data comparing different methods of dose escalation are sparse, with three randomized trials comparing EBRT plus whole prostate BT boost with EBRT alone. These trials have demonstrated improved biochemical disease-free survival (bDFS) using distinct BT boost regimens, but only the Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) trial has shown significantly greater urinary side effects[11–14].

Importantly, studies of patterns of failure after conventionally fractionated EBRT show that the area responsible for local recurrence is the intraprostatic dominant nodule (IDN) in 90% of cases[15–18]. The IDN is defined as the largest nodule in a multifocal disease which harbors in more than 80% of the cases the most aggressive biological behavior and therefore dictates the overall clinical prognosis of PCa[19].

Retrospective studies compared the site of the primary tumor on pre- and post-EBRT magnetic resonance images (MRIs), and by using large block pathology sections of the salvage radical prostatectomy specimen as the reference gold standard, they mapped the position of the recurrent tumor within the prostate showing that the pre-EBRT intraprostatic dominant nodule visible on the MRI was responsible for the local recurrence and could be specifically targeted to receive higher doses of radiation[15–18].

Intraprostatic dose escalation requires advanced imaging capabilities, which can detect intraprostatic tumor deposits with acceptable sensibility and specificity. Nowadays, it is possible to identify the IDN by using multiparametric magnetic resonance image (mpMRI), which uses various T1 and T2 sequences, dynamic contrast enhancement to assess perfusion, and diffusion-weighted imaging to calculate the different diffusion capability of PCa versus normal tissue[20]. Other imaging methods to detect the IDN such as ^{11}C-choline-positron emission computed tomography (PET/CT), ^{68}Ga-prostate-specific membrane antigen (PSMA) PET/CT, and newer generation ultrasound equipment are also under evaluation[21–24].

Furthermore, highly conformational EBRT techniques with improvement in patient positioning during treatment, such as image-guided radiation therapy (IGRT) and the use of fiducial markers to track prostate movements during a radiotherapy session, are needed for safe and effective treatment delivery[25–27].

Because of the lack of large multicentric trials, a systematic review was performed in an attempt to get an overview on the feasibility and efficacy of focal dose escalation to the IDN, with special attention to gastrointestinal (GI) and genitourinary (GU) toxicity as well as clinical efficacy.

2. Materials and methods

2.1. Literature search strategy

The literature review included a search in MEDLINE from 2000 to 2016, using the terms “intraprostatic” OR “intra-prostatic” OR “dominant intraprostatic lesion” OR “intraprostatic lesion” OR “gross tumor volume (GTV)” OR “simultaneous integrated boost” AND “radiation” OR “radiation therapy” OR “brachytherapy” OR “stereotactic body radiation therapy (SBRT)” OR “intensity modulated radiation therapy (IMRT)” OR “volumetric arc therapy (VMAT)” AND “prostate cancer”.

2.2. Assessment of study quality and inclusion criteria

The search results were assessed on content before inclusion into the review. The selection criteria for inclusion in the systematic review were accessible fully published articles in English, which reported the treatment outcome of PCa patients who received a boost to the IDN either by BT or EBRT. The primary endpoint was treatment-related side effects and efficacy outcome.

Articles dealing with case reports, recurrent disease, or planning studies were not included. Reports from conference proceedings were excluded. All authors participated in the design of the search strategy and inclusion criteria.

The following data were extracted from each study: predefined eligibility criteria, year of report, sample size, type of treatment, histology Gleason score, TNM stage, National Comprehensive Cancer Network cancer risk classification, median prostate-specific antigen, median time of follow-up, pretreatment diagnostic tools, such as imaging techniques used to localize the disease, radiotherapy technique and dose, use of androgen deprivation therapy (ADT), follow-up duration, acute

Please cite this article in press as: Feutren T, Herrera FG, Prostate irradiation with focal dose escalation to the intraprostatic dominant nodule: a systematic review, Prostate International (2018), https://doi.org/10.1016/j.prnil.2018.03.005