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Tumour Review

Hypofractionated radiotherapy for prostate cancer in the postoperative setting: What is the evidence so far?

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ABSTRACT

Postoperative external beam radiation therapy (EBRT) is a validated treatment option in the adjuvant setting for prostate cancer patients with aggressive pathological features following radical prostatectomy (RP) or as salvage modality in patients with biochemical recurrence after RP. Contemporary randomized phase III trials have provided evidence for using hypofractionation in the definitive treatment setting as an alternative to standard fractionated regimens.

Biomathematical modeling for prostate cancer fractionated EBRT associated with widely available refined treatment delivery techniques such as volumetric modulated-arc therapy with image-guided RT may improve the therapeutic ratio. Nevertheless, the role of hypofractionation in the postoperative setting still remains investigational.

In this systematic review of the literature we reviewed the role of hypofractionation for postoperative EBRT in the adjuvant or salvage setting in prostate cancer patients previously treated by RP. A favorable acute toxicity profile with, at least, as good biochemical control rates with hypofractionation has been suggested. And yet conflicting results have been reported concerning long-term genitourinary late toxicity. Prospective studies are eagerly awaited to assess the role of hypofractionation in the postoperative setting.

Introduction

Radical prostatectomy (RP) is a state of the art curative treatment in the management of localized prostate cancer [1–3]. And yet up to 1/3 of prostate cancer patients will later relapse [4]. Postoperative external beam radiotherapy (EBRT) is a validated treatment option in an adjuvant or salvage setting to prevent or treat biochemical recurrences following RP. A better overall survival has been demonstrated with adjuvant EBRT among prostate cancer patients with high-risk factors for relapse such as extracapsular extension, seminal vesicles invasion, and/or positive margins treated after RP [5].

Assuming that the α/β value of prostate cancer is somewhere between 1–2 Gy and yet lower than the surrounding organs at risk [6–8] hypofractionation has gained popularity in the treatment of prostate cancer in the last years. By delivering fewer but large-size fractions (i.e., >2.5 Gy) compared to conventional fractionated schedules (i.e., 1.8–2.0 Gy), the therapeutic index may potentially be improved by increasing the tumor cell kill while reducing toxicity to the surrounding healthy tissues [9]. A better outcome with a lower or equal toxicity profile, while preserving quality of life and reducing overall treatment time and improving logistics may therefore be expected [10].

Contemporary randomized phase III trials have provided evidence favoring hypofractionation in the definitive treatment setting as an alternative to standard fractionated regimens for localized prostate cancer [11–14] though no evidence exists to support hypofractionation in the postoperative setting.

The aim of the present review is to present a critical analysis on prospective and retrospective published clinical trials using hypofractionated radiotherapy schedules in the postoperative setting after RP.

Material and methods

A systematic review of the literature was performed in the *PubMed Web of Science* and *Embase* database according to *Preferred Reporting Items for Systematic Reviews and Meta-analysis* (PRISMA) guidelines [15]. English language articles reporting on hypofractionation for prostate cancer in the postoperative setting were

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identified and analyzed. Only full-text articles were considered. The following keywords were entered to identify potential articles: (“prostate” OR “prostate cancer”) AND (“radiotherapy” OR “radiation”) AND (“hypofractionation” OR “hypofractionated”) AND (“postprostatectomy” OR “radical prostatectomy” OR “postoperative” OR “adjuvant” OR “salvage”). 108 articles were identified and screened. The final reference list was generated based on originality and relevance to the broad scope of this review and 14 full-text papers including prospective and retrospective trials was found matching the terms of the research and included in the qualitative synthesis. A final list of 13 papers was included in the quantitative analysis. No meta-analysis was carried out. The PRISMA flowchart is presented in Fig. 1.

Results

Among the 14 studies included in the analysis ten were prospective and four retrospective. A total of 918 patients were included and analyzed. Most studies included patients treated after the 2000s with a minority of trials that recruited patients already in the 1990s [16,17]. The oldest trial, included in our study, recruited patients from 1984 to 1989 [18]. One prospective trial concerned patients treated only in an adjuvant setting [19], while three other studies reported on patients treated with salvage EBRT [16,20,21]. All other trials included a mixture of patients treated either with adjuvant or salvage EBRT.

The different fractionation schedules used in the corresponding studies are presented in Table 1. The total dose to the prostate bed ranged from 72.8 Gy in 29 fractions to 50 Gy in 20 fractions thus a delivered median dose per fraction of 2.5 Gy (range, 2.3–3.4 Gy). Assuming an α/β value of 3 Gy for late toxicity, the normalized total dose in 2 Gy/fraction (NTD_{2Gy}) ranged from 55 Gy to 80 Gy, while the corresponding values for an α/β value = 1.5 Gy for prostate cancer cells ranged from 57 Gy to 83 Gy.

The Radiation Therapy Oncology Group (RTOG) guidelines were used in the majority of the studies to define the prostatic bed [19–25]. Excluding six reports without pelvic nodal irradiation in the treatment volume [16–18,24,26], the whole pelvis was irradiated in all but one study using normofractionated schedules (1.8–2 Gy per fraction). Only in the series from Koukourakis et al., the whole pelvis was treated with 2.7 Gy/fraction up to a total dose of 37.8 Gy [26]. All but three studies, using 2D or conformal 3D techniques [16,18,26], used complex irradiation techniques such as intensity-modulated (IMRT), volumetric modulated-arc RT (VMAT), or helical tomotherapy.

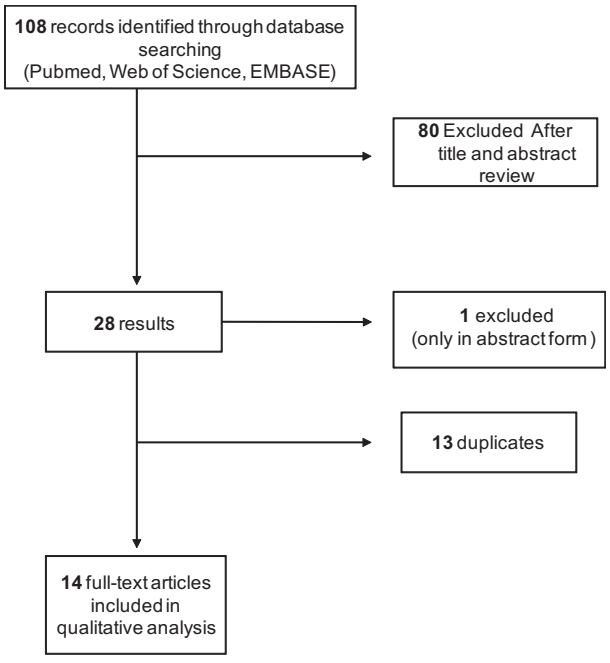

Fig. 1. PRISMA flow diagram of systematic literature review of eligible studies.

In order to assure reproducibility and to minimize irradiation to surrounding healthy tissues (e.g., rectal wall and bladder) measures were undertaken by most authors employing pretreatment rectal cleaning and bladder filling protocols [16,19–24,27–29]. Image-guided radiotherapy (IGRT) techniques with daily CBCT's or kV/MV images were performed for most patients. Gladwish et al., implanted three fiducial markers in the prostate bed aiming to help daily image guidance [22], while an endorectal balloon was used by some authors for intra-fractional immobilization purposes [20,21]. Table 1 presents the summary of the different treatment techniques used. Androgen deprivation therapy, when combined to EBRT, was not always reported, and yet when mentioned, timing (neo-adjuvant, adjuvant or concomitant) and duration were very heterogeneous among series.

Genitourinary (GU) and gastrointestinal (GI) acute toxicity was mild to moderate with similar rates across the studies (Table 2). Indeed, ≤ grade-2 changes in urinary frequency, nicturia, or proctitis were reported in the majority of the series [23]. Acute grade-3 urinary toxicity events were unusual (<3%) of the cases overall [20,22,25,27]. A single acute GU grade 4 toxicity event (acute bladder obstruction) was reported by Massaccesi et al. [29]. However, the later authors reported the highest GI toxicity rates among all series with 33% of the patients experiencing grade-2 GI toxicity [29].

In all but three series, late toxicity was reported albeit marked follow-up differences, ranging from 6 to 98 months (median, 36 months), were observed. In most series the reported late toxicity was mild (i.e., grade 1–2): episodes of macrohematuria or changes in urinary frequency, urgency, or proctitis with rates ranging between 0% and 39%. Yet, the most relevant and exhaustive data about long-term GU toxicity was reported by Cozzarini et al. [17]. Indeed, 1176 postoperative patients were treated either with conventionally fractionated EBRT (n = 929), mainly using 3D-conformal techniques (n = 657), or hypofractionated helical tomotherapy (n = 247). After a median follow-up time of 68 months (range, 54–81), the 5-year risk for ≥grade-3 late GU toxicity was significantly higher in the hypofractionated group (18.1%) compared to patients treated with conventional EBRT (6.9%). Among the group of 115 patients with late grade-3 GU toxicity, 68 required surgical corrections of urethral stenosis and/or bladder neck strictures, 30 patients underwent blood transfusions and/or hyperbaric oxygen therapy for severe and persistent gross haematuria, and 47 patients reported a post-irradiation onset or worsening of grade 3 urinary incontinence. Salvage cistectomy was undertaken in 5 additional patients who suffered of grade-4 GU toxicity.

Two more studies reported severe long-term toxicity with hypofractionated EBRT. In the first study, 89 and 26 patients received either adjuvant or salvage EBRT with 2D-EBRT techniques for local recurrence, respectively (mean dose/fraction, 2.76 Gy). The incidence of grade-3/4 late GU toxicity was 19% (adjuvant) and 26% (salvage) [18]. In the second study, a cohort of 56 men was treated with 65 Gy in 2.5 Gy/fraction. Fifteen out of 56 patients (27%) presented with grade-3 gross haematuria; two presented with late grade-3 GI toxicity (rectal fistula requiring surgical correction) [24].

Three papers reported on quality of life (QoL) using two validated international QoL questionnaires, the EPIC (Expanded Prostate Cancer Index Composite) and the EORTC QLQ-C30 [22–24].