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Review – Prostate Cancer

A Systematic Review of Hypofractionation for Primary Management of Prostate Cancer

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Abstract

Context: Technological advances in radiation therapy delivery have permitted the use of high-dose-per-fraction radiation therapy (RT) for early-stage prostate cancer (PCa). Level 1 evidence supporting the safety and efficacy of hypofractionated RT is evolving as this modality becomes more widely utilized and refined.
Objective: To perform a systematic review of the current evidence on the safety and efficacy of hypofractionated RT for early-stage PCa and to provide in-context recommendations for current application of this technology.
Evidence acquisition: Embase, PubMed, and Scopus electronic databases were queried for English-language articles from January 1990 through June 2014. Prospective studies with a minimum of 50 patients were included. Separate consideration was made for studies involving moderate hypofractionation (doses of 2.5–4 Gy per fraction) and extreme hypofractionation (5–10 Gy in 4–7 fractions).
Evidence synthesis: Six relatively small superiority designed randomized trials of standard fractionation versus moderate hypofractionation in predominantly low- and intermediate-risk PCa have been published with follow-up ranging from 4 to 8 yr, noting similar biochemical control (5-yr freedom from biochemical failure in modern studies is >80% for low-risk and intermediate-risk patients) and late grade ≥2 genitourinary and gastrointestinal toxicities (between 2% and 20%). Noninferiority studies are pending. In prospective phase 2 studies, extreme hypofractionation has promising 2- to 5-yr biochemical control rates of >90% for low-risk patients. Results from a randomized trial are expected in 2015.
Conclusions: Moderate hypofractionation has 5-yr data to date establishing safety compared with standard fractionation, but 10-yr outcomes and longer follow-up are needed to establish noninferiority for clinical effectiveness. Extreme hypofractionation is promising but as yet requires reporting of randomized data prior to application outside of a clinical protocol.
Patient summary: Hypofractionation for prostate cancer delivers relatively high doses of radiation per treatment. Prospective studies support the safety of moderate hypofractionation, while extreme fractionation may have greater toxicity. Both show promising cancer control but long-term results of noninferiority studies of both methods are required before use in routine treatment outside of clinical protocols.

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1. Introduction

The standard external-beam radiation therapy (EBRT) regimen for localized prostate cancer (PCa) is delivered in 1.8- to 2-Gy fractions 5 d per week over 7–9 wk. This prescription is based on classical radiobiology experiments in which this relatively small dose per treatment allowed preferential recovery of radiation-induced damage within normal tissues compared with fast-growing tumors. Recent advances in radiation therapy (RT) technologies have sparked interest in hypofractionation, a highly conformal RT delivering daily fractions of 2.5–10 Gy, utilizing targeting to minimize normal tissue injury rather than dose modulation.

The biologic rationale for applying hypofractionation to PCa is based on the theory that the slow proliferation of PCa cells leads to a biologic radiation response in PCa that differs from most other cancers. Traditional fractionation causes the accumulation of DNA damage, ultimately causing apoptosis, mitotic catastrophe, or senescence [1]. A slow proliferation rate results in a high reparation ability of radiation damage over time, such that standard fractionation given in small increments over a long time period may be suboptimal for PCa for which a high total dose is required for effective control [2]. For slowly proliferating cells, high doses per fraction may be more effective because immediate cell death is instigated due to the high number of DNA double-strand breaks caused by each fraction.

Radiobiology has developed a concept to explain how fraction size and total dose interact to compare differing treatment regimens, described as the α/β. General radiobiology teaches that tumors with high α/β values are less able to repair injury between fractions than normal tissues with low α/β values, such that small fractions to high doses will allow preferential recovery of low α/β tissues while still killing cancer cells. Alternatively, if tumor cells have a lower α/β than nearby normal tissues, low-dose long treatment courses will require higher total doses than a few large fractions given over a short time. Thus hypofractionation using a few large fractions may result in the same tumor cell kill with lower total doses achieving comparable normal tissue toxicity. It is believed that PCa has a low α/β of approximately 1.5 Gy. Retrospective data from 11 330 patients with PCa treated with EBRT of varying fraction size supports this theory [3].

The α/β can also be used as a conversion constant to compare different hypofractionation schemes, converting each scheme to a biologically equivalent dose (BED) in 2-Gy fractions. This conversion is helpful when designing treatment protocols, but it should be recognized that there is concern within the radiobiology community that dose conversion may not be accurate when dealing with large doses per fraction because of differences in types of cell death that occur at high versus low fraction size. This complicates the application of extreme hypofractionation because the theory of converting a conventional fractionation course to a hypofractionated course with expected similar toxicities and efficacy may not result as expected [4].

Beyond biology, hypofractionation for PCa has the advantages of increased convenience for the patient and a lower cost burden for the health care system. In multiple cost-effectiveness comparisons, it was believed that hypofractionation was overall a lower direct, indirect, and migratory cost burden than intensity-modulated radiation therapy (IMRT) with standard fractionation [5,6]. However, these assessments were based on estimates of toxicity garnered from studies to date and may need reevaluation as long-term toxicities are better understood. Nevertheless, there has been significant clinical interest in applying hypofractionation to PCa.

In recent years, there has been a flurry of both randomized and nonrandomized publications regarding the application of hypofractionation for clinically localized PCa. Consequently, we sought to provide a systematic review of this literature, with special attention to clinical outcomes including toxicity. For the purposes of this review, we have divided hypofractionation studies into those of *moderate* hypofractionation (2.5–4 Gy per fraction) and *extreme* hypofractionation (5–10 Gy per fraction).

2. Evidence acquisition

We conducted a systematic review of the literature using Embase, PubMed, and Scopus electronic databases for English-language articles from January 1990 through June 2014 in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement. Search terms included *prostate hypofractionated, prostate hypofractionation, prostate stereotactic, prostate CyberKnife*, and *prostate randomized hypofractionated*. Identified literature reviews were examined to identify additional articles appropriate for inclusion.

Two categories were considered separately: moderate hypofractionation (2.5–4 Gy per fraction) and extreme hypofractionation (5–10 Gy per fraction). For the first, eligibility criteria included only published phase 3 clinical trials. Extreme hypofractionation is a more recent development, so both clinical trials and prospectively collected institutional series were included. A minimum volume of 50 cases was required to adjust for the learning curve in treatment delivery. Finally, studies were excluded if they used a combination of EBRT and brachytherapy, used a simultaneous integrated boost delivering different doses concurrently within one treatment plan, or used hypofractionation only in part of the overall radiation treatment. Figure 1 details how studies were selected for inclusion in this review.

3. Evidence synthesis

3.1. Technological requirements for prostate hypofractionation

Hypofractionation has arisen in the setting of an increased ability to plan and target RT conformal to a given target. In the case of definitive PCa RT, the use of IMRT has allowed highly conformal treatment plans where the dose gradient is quite steep, allowing for reduced dose to nearby normal

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