Hypofractionated Radiation Therapy for Prostate Cancer: Risks and Potential Benefits in a Fiscally Conservative Health Care System

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Introduction

Given that prostate cancer is the most common non-cutaneous cancer among men in the Western world, its treatment is of great medical and public significance.[1] Despite its high incidence, the relative 10-year survival following treatment is 98%.[1] A variety of treatment modalities exist, including surgery, external beam radiotherapy, brachytherapy, proton therapy, and other novel methods of treatment.[2]

Currently, standard external beam radiotherapy for prostate cancer consists of 75.6 to 81.0 Gy of radiation separated into 1.8- to 2-Gy doses (or “fractions”) given daily for 7 to 9 weeks. The prolonged length of this standard course of prostate radiation, coupled with advances in radiation therapy technologies, have stimulated interest in delivering more radiation per fraction for the purpose of reducing the overall length of treatment.[3] This type of shorter treatment regimen, involving larger doses of radiation per fraction, is known as “hypofractionation” or “hypofractionated” radiotherapy. Although hypofractionation has been proposed for a variety of cancer types, such as breast and early-stage lung cancer, the utilization of hypofractionation in prostate cancer treatment remains controversial because of concerns regarding clinical efficacy and the potential for increased bowel and urinary toxicity. This potential increased toxicity represents the response of normal tissue to radiation doses and varies based on the amount of radiation delivered per fraction. Furthermore, because hypofractionated radiotherapy is an emerging technique, the National Comprehensive Cancer Network (NCCN) prostate cancer guidelines currently give no recommendations concerning hypofractionated treatment schedules. Compared to conventional fractionation, hypofractionation allows for a smaller number of treatment visits. Depending on the reduction in the number of treatment visits, the overall cost of a treatment course is proportionally reduced. This is of particular importance in a financially constricted health care system. The challenge remains to investigate the potential benefits in terms of cost and convenience while optimizing clinical outcomes.

Prostate Hypofractionation: History and Theoretical Rationale

In radiation therapy, the alpha/beta (α/β) ratio is a theoretical measure of a tissue’s predicted response to a dose of radiation, relative to the size of the dose delivered per fraction.[4] Conventional daily doses of radiation are normally between 1.8 and 2.0 Gy and are based on the presumed high α/β ratios of most malignant tumors. Higher α/β ratios mean that tumor response is less dependent on the amount of radiation administered with each fraction, and therefore that a lower radiation dose per treatment can typically be used.[5] Lower tumor α/β ratios, conversely, mean that a larger dose of radiation per treatment can provide improved efficacy in terms of tumor control. Although controversial and contested,[6] a large body of work theorizes that the α/β ratio for prostate cancer is low, implying that a hypofractionated schedule (fraction sizes greater than 2.0 Gy) could improve prostate cancer control.[4]

Controversy concerning prostate hypofractionation stems from uncertainties not only about the radiobiology of prostate cancer,[6] but also regarding the effect of hypofractionated treatment on the nearby tissues of the rectum and bladder. In particular, radiation toxicity that manifests in the months and years following treatment, known as “late” toxicity, is known to be especially sensitive to fraction size. Because parts of the rectum and bladder may receive the same dose of radiation as
the prostate itself, the difference in the sensitivity of the rectum and bladder to variations in radiation fraction size, compared with the sensitivity of the prostate cancer itself, is what results in potential harm from hypofractionated treatment. Proponents of hypofractionated treatment argue that the rectum and bladder are less sensitive to increases in dose per fraction than prostate cancer and that therefore hypofractionation should yield negligible increases in late toxicity while providing improved cancer control. Continued study as to the balancing of toxicity and efficacy is needed.

Different Clinical Approaches to Hypofractionation

Three clinical approaches to hypofractionated radiotherapy have been proposed. The first attempts to maintain the same level of tumor control with modestly shorter treatment times while maintaining similar radiation-related toxicity compared with a conventional fractionation schedule.[5] The second approach exploits the radiosensitivity of the prostate to increase tumor control while maintaining accepted levels of adverse effects.[5] The third technique, known as “extreme hypofractionation,” is synonymous with stereotactic body radiotherapy (SBRT), and involves the administration of only five total fractions, with doses between 5.5 and 10 Gy per fraction. Because of the delivery of large doses per fraction, extreme hypofractionation requires the use of stereotactic techniques that minimize prostate movement and maximize accuracy of treatment.[7] Like modestly hypofractionated treatment regimens, extreme hypofractionation remains under scrutiny due to the uncertainties surrounding its execution and effects. Fortunately, several prospective studies investigating extreme hypofractionation in prostate cancer treatment have been performed, although the number of patients and length of follow-up are modest.[7,8]

Potential Benefits of Hypofractionation: Clinical Trial Results

TABLE

Significant Trials Studying Prostate Hypofractionation

The scope and number of clinical trials investigating prostate hypofractionation have increased substantially in the last decade. It is clear that prostate hypofractionation has varying effects on tumor control, acute toxicity, quality of life, treatment cost, and convenience. Many trial findings show evidence of efficacy in terms of survival or biochemical relapse-free survival. However, the overall number of patients studied is low, and the length of follow-up remains relatively short. The Table summarizes studies investigating hypofractionated radiotherapy for prostate cancer.

Tumor control

Yeoh et al evaluated hypofractionated schedules in patients with low-risk, localized prostate cancer.[9] The randomized trial consisted of 217 men who were enrolled either in a hypofractionated arm (55 Gy in 20 fractions over 4 weeks) or a conventional arm (64 Gy in 32 fractions over 6.5 weeks). The prostate-specific antigen (PSA) relapse-free survival at 90 months was significantly better in the hypofractionated group than in the conventional group. The most recent toxicity data show no difference in late gastrointestinal (GI) and genitourinary (GU) effects between the hypofractionated and the standard fractionated arm at 5 years. Although this report is one of the first studies to show a long-term therapeutic advantage to prostate hypofractionation, the patient base consisted only of men with localized, early-stage prostate carcinoma, and the total dose of radiation on the conventional arm was relatively low.

Most recently, Pollack et al reported on the results of the Fox Chase Cancer Center (FCCC) randomized trial of 307 patients comparing conventionally fractionated intensity-modulated radiation therapy (IMRT) involving 76 Gy of radiation in 38 fractions of 2.0 Gy each to a modestly hypofractionated regimen involving 70.2 Gy of radiation delivered in 2.7-Gy fractions. There was no difference in 5-year biochemical disease-free survival or metastasis-free survival between the two arms.[10]
Kruser et al reported the retrospective results of “salvage hypofractionation” in a specific subgroup of prostate cancer patients who had experienced biochemical recurrence after prostatectomy.[11] This analysis found that modestly hypofractionated radiotherapy was associated with a 4-year biochemical disease-free survival of 67% ± 5%, which compares favorably to standard fractionated series. Additionally, investigators found that a hypofractionated treatment plan reduces the length of treatment by 1.5 to 3 weeks compared with conventionally fractionated schedules. To date, no randomized trial has compared conventional and hypofractionated salvage schedules; however, evidence suggests equivalent GI/GU toxicities and biochemical response between hypofractionated and conventionally fractionated treatments.[12]

A trial conducted by King et al utilized extreme hypofractionation to treat 65 patients with low-risk prostate adenocarcinoma and found a 4-year biochemical control rate of 94% among the entire cohort, with a median follow-up of 2.7 years.[13] Like the study by King et al, other trials that involved treatment of low-risk patients have showed similar, positive results. Boike et al treated 45 low-risk prostate adenocarcinoma patients with extreme hypofractionation (45 Gy, 47.5 Gy, or 50 Gy in 5 fractions) and found no biochemical failure and declining or stable PSA levels at 30 months, 18 months, and 12 months for the 45-Gy, 47.5-Gy, and 50-Gy groups, respectively.[14] McBride et al found no biochemical failures at a median survival of 44.5 months for 45 low-risk patients treated with extreme hypofractionation. Furthermore, progression-free survival at 3 years was 97.7%.[7] It is important to note that although this trial, and the trial by King et al, shows that extreme hypofractionation is effective, the treatments were confined to patients at low risk for treatment failure, and follow-up was short.

Acute and late toxicity

A number of clinical trials report the results of moderate hypofractionation vs standard fractionation with respect to outcomes such as acute and late toxicity (see the Table). Most trials show similar toxicity between moderately hypofractionated therapy and standard fractionated therapy.[6,15] Other trials have shown less long-term toxicity[16,17] and greater short-term toxicity[9,18] for hypofractionated radiotherapy compared to standard fractionated radiation. Nonetheless, since radiation-related complications often take many years to become fully manifest, further long-term follow-up is needed before a definitive judgment can be made with regard to the toxicity of moderately hypofractionated treatment relative to that of standard fractionated treatment.

Quality of life

In addition to assessing medical treatment–related outcomes, a few recent trials have also assessed patient-reported quality of life (QOL) for prostate hypofractionation treatment schedules with androgen deprivation therapy. A prospective phase 1/II study in Canada included patients with high-risk prostate cancer and administered a hypofractionated regimen of 67.5 Gy (2.7 Gy per fraction) in 25 fractions over 5 weeks.[2] The investigators used the Expanded Prostate Cancer Index Composite (EPIC) tool to measure four primary domains (urinary, bowel, sexual, and hormonal) and found modest declines in urinary and bowel QOL at 24 months that caused mild distress to patients. However, severe changes to baseline QOL were not found. These results suggest similar QOL outcomes between hypofractionated treatment and previously published standard fractionated treatment schedules.[19,20]

McBride et al[7] studied extreme hypofractionation in patients with low-risk prostate adenocarcinoma, and as in the Canadian study, they used the EPIC instrument. Overall, they did not observe a statistically significant decrease in sexual function. Furthermore, the reported magnitude of decline in sexual health for potent patients was similar to that reported in patients with low baseline sexual morbidity who received standard fractionation.[7] Nevertheless, additional follow-up is still needed to examine long-term effects on QOL.

Convenience

Compared to standard fractionated schedules, hypofractionation has also been associated with improved convenience because patients on this abbreviated regimen undergo fewer treatments. Several studies have reported increased convenience associated with hypofractionation at other disease sites. For example, a Greek trial compared a hypofractionated schedule to a standard fractionated schedule in the treatment of 92 patients with locally advanced non–small-cell lung cancer (NSCLC). Not only did the investigators find increased efficacy with the hypofractionated schedule, they also reported that the hypofractionated schedule offered more convenience to their
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Reasons for Concern

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...the push for financially conservative health care models, the high cost of treating prostate cancer ...

...the patient.

Cost-effectiveness

With approximately 180,000 new diagnoses per year, prostate cancer treatment remains a significant cost burden to the US health care system.[23] In radiation therapy, standard fractionated IMRT has been adopted as the current standard of external beam radiotherapy. When treatment preoperative evaluation, imaging, laboratory tests, and treatment complications are all accounted for, radiation therapy to treat prostate cancer with IMRT is estimated to cost between $31,574 and $37,125.[23] Moreover, new technologies such as proton therapy are associated with even further increases in the cost of treating prostate cancer compared to external beam radiotherapy.[24] Given the push for financially conservative health care models, the high cost of treating prostate cancer with IMRT and proton therapy has led to investigation of the comparative effectiveness of the various prostate cancer treatment modalities, and of ways to reduce the overall cost of treatment. Because the cost of radiation therapy is largely driven by total treatment time, calculated as the daily treatment time multiplied by the number of fractions, hypofractionation serves as a potentially more cost-effective method that can curtail rising prostate cancer treatment costs.[25] Although there is little research specifically evaluating the cost-effectiveness of prostate cancer hypofractionation compared to standard fractionated schedules, there is evidence suggesting that hypofractionation reduces treatment costs in other disease sites.

In a breast cancer treatment study at the Leuven Radiotherapy Department in Belgium, there was a 60% decrease in total treatment cost with hypofractionated treatment compared to standard treatment schedules in the Belgian health care system. The decrease was a direct consequence of the reduction in daily irradiation cost. An Australian study reported a 24% reduction in treatment costs in the Australian health care system for breast cancer patients on a hypofractionated schedule.[26] Variations in cost reductions are dependent on the number by which the hypofractionated schedule reduces the total number of fractions, as well as on the payment structure of the particular health care system involved. Along with demonstrating a reduction in total treatment costs, all cost analyses for standard breast, chest wall, or loco-regional lymph node irradiation with hypofractionated schedules have shown the costs of these regimens to be well below the currently accepted willingness-to-pay thresholds of various countries.[25] However, it is important to note that the cost of treatment preparation becomes proportionally more important when hypofractionated schedules are used.

There are also reports of lower costs with hypofractionation in the palliative treatment of lung cancer with radiotherapy. Van den Hout et al performed an extensive cost-utility analysis of short- vs long-course schedules and compared quality-adjusted life-years, an overall measure of the patients’ quantity and quality of life, to the total cost of disease treatment, including the costs of radiation as well as the various other costs incurred by patients during their remaining lifetime. Hypofractionated treatment schedules for these poor-prognosis patients reduced costs by approximately 52%. However, in contrast, in the Greek study that looked at locally advanced NSCLC, hypofractionated treatment schedules were also associated with a 39% decrease in life expectancy, suggesting that they may not be as clinically efficacious for the palliative treatment of lung cancer and that the benefit from hypofractionated treatment may not be uniform across disparate groups of patients.[28]

Van den Hout et al also conducted a cost-analysis of single- vs multiple-fraction radiation treatment in patients with painful bone metastases.[29] Single-fraction radiotherapy was associated with a 27% reduction in cost and was associated with equivalent palliation and quality of life. Because single- and multiple-fraction radiotherapy were shown to provide equal palliation, the authors strongly suggested the adoption of single-fraction treatment because of its lower societal and medical costs. Although provocative, the results of these studies are difficult to apply to prostate radiotherapy, since patients with localized prostate cancer on average live much longer than patients with bone metastases. Therefore, each incremental difference in quality of life must be multiplied by many years of survival.

Reasons for Concern
Despite the large body of data showing the potential biological and economic benefits of prostate hypofractionation, there are causes for concern. Although there are many researchers who feel that the $\alpha/\beta$ ratio for prostate cancer is low, there is no definitive conclusion as to exactly how the $\alpha/\beta$ ratio for prostate cancer compares to that of nearby late-responding normal tissues, such as the rectum and bladder.[6] Additionally, those advocating the widespread adoption of hypofractionation have typically only relied on imprecise modeling assumptions and an imprecise biologically effective dose (BED) equation.[6]

Most importantly, the exact therapeutic gain is not known. Although many trials report favorable outcomes for patients with prostate cancer who have undergone hypofractionation, there are a number of trials that report conflicting evidence. With regard to tumor control, a Canadian multicenter study found that the estimated 5-year biochemical or clinical failure rate was higher in the hypofractionated arm than in the standard treatment arm.[6]

A number of trials have also reported negative acute toxicity outcomes associated with prostate hypofractionation, as noted previously. A Fox Chase Cancer Center randomized trial reported a small but significantly higher level of GI toxicity (grade ≥ 2) in the hypofractionated arm, but a lower grade of GU toxicity compared with the normofractionated arm.[6] Canadian and Australian randomized trials found a significant increase in GI and GU toxicity in the hypofractionated group when comparing symptoms at the end of radiotherapy with patients’ baseline.[6] These results, considered together with other studies showing no major differences in toxicity, suggest a relative lack of consensus regarding the risks and benefits of hypofractionated treatment. It is hoped that the controversies and questions regarding hypofractionated treatment for prostate cancer will be addressed by ongoing clinical trials.

**Ongoing Studies**

Because there remains considerable debate regarding the therapeutic advantage of prostate hypofractionation, there is a strong need to assess the efficacy and safety of hypofractionation in future trials. Several recently closed and ongoing trials aim to provide information that will further inform the development of this treatment. A recently closed Radiation Therapy Oncology Group (RTOG) phase III randomized trial (0415) aims to compare the disease-free survival of patients with favorable-risk stage II prostate cancer treated with hypofractionated three-dimensional conformal radiotherapy (3D-CRT) or IMRT vs standard fractionated 3D-CRT or IMRT.[8] The investigators also will determine whether the incremental gains in disease-free survival outweigh effects on such QOL domains as mobility, self-care, ability to perform usual activities, pain/discomfort, and anxiety/depression. This trial closed to accrual in 2009. Following the close of RTOG 0415, the multicenter RTOG 0938 trial opened; RTOG 0938 seeks to demonstrate that 1-year health-related QOL for at least one hypofractionated arm (of two hypofractionated regimens being studied) is not significantly lower than baseline as measured by the bowel and urinary domains of the EPIC instrument.[8] This trial will only include men with favorable-risk prostate cancer. Additionally, the Proton Collaborative Group has undertaken a phase III clinical trial comparing standard vs hypofractionated treatment with proton therapy in men with low-risk prostate adenocarcinoma.[8] Because proton therapy is growing in popularity, the results of this trial will be instructive. All of the aforementioned trials will further illuminate the effectiveness of prostate hypofractionation and provide information that will potentially change the way in which clinicians treat prostate cancer.

**Conclusion**

Hypofractionation for the treatment of prostate cancer remains a growing area of research. Many trials illustrate the significant risks and benefits associated with this treatment modality. Because this treatment modality has the potential to lower overall treatment costs and increase patient convenience, prostate hypofractionation is of interest in a fiscally conservative health care system. Depending on the results of future trials, prostate hypofractionation could serve as a resource-efficient and well-tolerated treatment modality that will prove effective in the long-term management of prostate cancer worldwide.

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