Practical Radiation Oncology (2014) **xx**, xxx–xxx

practical radiation oncology
pro
www.practicalradonc.org

Special Article

Stereotactic body radiation therapy for prostate cancer: Rational and reasonable

Patrick Kupelian MD [a,*], Niraj H. Mehta MD [b], Chris King MD, PhD [a], Michael Steinberg MD [a], Steven E. Finkelstein MD [b], Eduardo Fernandez MD, PhD [b]

[a]*University of California at Los Angeles, Los Angeles, California*
[b]*21st Century Oncology, Fort Myers, Florida*

Received 23 July 2014; revised 15 August 2014; accepted 21 August 2014

Abstract Stereotactic body radiation therapy (SBRT), a treatment procedure that uses large doses per fraction, is currently being used to treat prostate cancer with external radiation therapy in 4 to 5 treatments. Published series in the clinical use of SBRT in patients with localized prostate cancer demonstrate high efficacy within the available follow-up time periods. Rectal and sexual toxicity profiles have been favorable compared with other radiation techniques and surgery. Urinary toxicity profiles might be more comparable to those observed with brachytherapy, more pronounced in the acute setting. SBRT is technically more challenging, requiring precise geometric targeting with in-room image guidance. The use of large doses per fraction potentially provides unique biological effects on both tumor and normal tissues. Immunologic responses in normal tissues, local stromal microenvironment, and specific antigen-presenting cells induced by such high doses likely contribute to effective tumor kill. Ultimately, SBRT for prostate cancer offers significant logistical advantages, with increased convenience to patients and decreased overall cost to the health care delivery system.

Introduction

Stereotactic body radiation therapy (SBRT) is characterized by short treatment courses of 5 fractions or less using larger than conventional dose fraction sizes. In the treatment of localized prostate cancers, SBRT is typically delivered in 5 fractions of approximately 7.5 to 8 Gy per fraction, with 1 study using doses as high as 10 Gy per fraction. Building on the existing and ever-more-moderate hypofractionation schemes that use fractions between 2 and 5 Gy, prostate SBRT is attractive because of the perceived increased biologic effectiveness of large fractions caused by alpha/beta ratio differentials for prostate cancer and possibly other unique impacts of large fractions on tumor immune responses and/or vascular effects.[1-6]

The biology of large fraction sizes

High intratumoral dose exposures with SBRT might optimize antitumor mechanisms by stimulating local and direct immune responses in the local microenvironment and antigen-presenting cells (APCs).[7] Exposure to such high doses of radiation can induce changes in the tumor

Conflicts of interest: None.

* Corresponding author. Department of Radiation Oncology, UCLA Jonsson Comprehensive Cancer Center, David Geffen School of Medicine at UCLA, 200 UCLA Medical Plaza, Suite B265, Los Angeles, CA 90025.

E-mail address: pkupelian@mednet.ucla.edu (P. Kupelian).

http://dx.doi.org/10.1016/j.prro.2014.08.018
1879-8500/

stroma in vitro through activation of vascular endothelial cell apoptosis pathways.[8,9] In addition to specific biochemical regulatory pathways, pathologic observations after radiosurgery also demonstrate greater obliteration of abnormal vasculature with high single doses, such as those used for managing arteriovenous malformations.[10] Evidence also indicates that direct immune modulation, through the stimulation of toll-like receptors on APCs and alteration of tumor cell characteristics, renders them more vulnerable to T-cell killing via vaccines.[7,11,12]

Higher doses per fraction, as opposed to conventional 2-Gy doses, can also prime T cells in lymphatic tissue, leading to more significant CD8+ T-cell–dependent eradication of disease, as well as the induction and expression of effector cytokines and other inflammatory mediators.[13] Such a proinflammatory environment laden with cytokine production can increase permeability of local vasculature and stimulate APCs to mature more effectively. Immune responses have been documented in the context of prostate cancer treatments.[14] SBRT therefore appears to be able to induce abscopal effects, costimulatory molecules, cellular adhesion molecules, and death receptors to augment anticancer immune responses.[7,13] As a result of tumor-specific T-cell responses and antigen-specific cellular immunity, innovative radiation dose–delivery strategies can be combined with modern immunotherapeutic interventions in the clinic.[7]

Clinical experience with SBRT for prostate cancer

Modern hypofractionation for prostate cancer has its clinical roots in both high-dose-rate brachytherapy and external radiation therapy, yielding acceptable toxicity profiles and durable biochemical control rates with moderately hypofractionated schedules.[15-19] This has generated significant discussion concerning whether moderately hypofractionated schedules should be favored over traditional schedules in the treatment of localized prostate cancers if they are either equivalent or superior to conventional schedules.[20-22] Following that trend of shortening treatment duration and increasing fraction sizes, the use of SBRT for prostate cancer started tentatively approximately 10 years ago.[23] A number of single institution trials have reported results on both toxicity and outcome of SBRT for prostate cancer, although equipment, technique, image guidance, and dose prescriptions can vary. Table 1 summarizes reported biochemical control and genitourinary and gastrointestinal toxicity in treated patients. A recent pooled analysis of 1100 patients from prospective phase II trials using SBRT techniques demonstrated a 95% 5-year biochemical relapse-free survival rate for low-risk patients, with excellent long-term patient-reported outcomes with respect to urinary and bowel function.[37,38] On the basis of the Stanford experience, recent fractionation regimens used are typically in the range of 35 to 40 Gy in 5 fractions with image guided radiation therapy delivered every other day.[27] When the linear quadratic model is applied and one assumes an alpha/beta ratio of 2 for prostate cancer, the biologically equivalent dose (BED) for a dose of 40 Gy delivered in 5 fractions (8 Gy per fraction) is 200 Gy, a substantially higher BED than with conventionally fractionated schedules and similar to BED levels achieved with brachytherapy. The limit of dose per fraction escalation appears to have been reached: As reported by Boike et al, in the lone study that tested doses up to 50 Gy delivered in 5 fractions, toxicity (particularly rectal) was excessive, clearly demonstrating that SBRT with current techniques should be kept lower than 50 Gy in 5 fractions.[30,39] For patient series treated to doses in the 35- to 45-Gy range in 4 to 5 fractions, with follow-up exceeding 5 years, the freedom from biochemical failure for low-risk patients alone is in the range of 94% to 99%, comparing favorably with the best results of image-guided intensity modulated radiation therapy (IMRT), high-dose-rate monotherapy, low-dose-rate permanent brachytherapy, and surgical series.[27] Although the majority of patients treated to date have been at low to low-intermediate risk, SBRT as monotherapy or as a boost has been incorporated recently for various intermediate- and high-risk patients with or without androgen-deprivation therapy, with promising short-term results.[26,40] This is reflected in the most recent American Society for Radiation Oncology statement as of April 2013, which states that the "data supporting the use of SBRT for prostate cancer have matured to a point where SBRT could be considered an appropriate alternative for select patients with low to intermediate risk disease."

With respect to cost, a comparison of SBRT versus IMRT in Medicare beneficiaries $\geq$ 66 years old treated between 2008 and 2011 documented lower treatment costs; mean treatment cost was $13,645 for SBRT versus $21,023 for IMRT. With respect to quality of life (QOL) after SBRT, given the convenience and efficacy of SBRT, patient-based QOL concerns have been the subject of much debate, especially with respect to late side effects.[41] Initial clinical trials have shown favorable late gastrointestinal and genitourinary toxicity in the range of 1% to 3%.[37] In a recent analysis using Medicare claims, toxicity outcomes with SBRT were reported to be somewhat worse than with IMRT; Medicare claims based on certain procedures or diagnoses were the proxies for toxicity.[42] Although this methodology could be criticized as not equivalent to physician- or patient-reported toxicity assessments, only minor differences were observed between IMRT and SBRT, all in urinary toxicity; when results were examined 6 months after treatment initiation, 16% of SBRT patients versus 13% of IMRT patients experienced genitourinary toxicity. At 24 months after