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Critical Review

Whole-Pelvic Nodal Radiation Therapy in the Context of Hypofractionation for High-Risk Prostate Cancer Patients: A Step Forward

Orit Kaidar-Person, MD,* Mack Roach, III, MD,† and Gilles Créhange, MD, PhD‡

**Division of Oncology, Rambam Health Care Campus, Haifa, Israel; †Department of Radiation Oncology, University of California, San Francisco, San Francisco, California; and ‡Department of Radiation Oncology, Georges-François Leclerc Cancer Center, Dijon, France*

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Given the low α/β ratio of prostate cancer, prostate hypofractionation has been tested through numerous clinical studies. There is a growing body of literature suggesting that with high conformal radiation therapy and even with more sophisticated radiation techniques, such as high-dose-rate brachytherapy or image-guided intensity modulated radiation therapy, morbidity associated with shortening overall treatment time with higher doses per fraction remains low when compared with protracted conventional radiation therapy to the prostate only. In high-risk prostate cancer patients, there is accumulating evidence that either dose escalation to the prostate or hypofractionation may improve outcome. Nevertheless, selected patients who have a high risk of lymph node involvement may benefit from whole-pelvic radiation therapy (WPRT). Although combining WPRT with hypofractionated prostate radiation therapy is feasible, it remains investigational. By combining modern advances in radiation oncology (high-dose-rate prostate brachytherapy, intensity modulated radiation therapy with an improved image guidance for soft-tissue sparing), it is hypothesized that WPRT could take advantage of recent results from hypofractionation trials. Moreover, the results from hypofractionation trials raise questions as to whether hypofractionation to pelvic lymph nodes with a high risk of occult involvement might improve the outcomes in WPRT. Although investigational, this review discusses the challenging idea of WPRT in the context of hypofractionation for patients with high-risk prostate cancer. © 2013 Elsevier Inc.

Introduction

In recent years the treatment of prostate cancer has evolved, as shown by the accumulating evidence from clinical trials: dose escalation to the prostate (1-5), androgen deprivation treatment combined with radiation therapy (6, 7), prostate hypofractionation (8), and elective pelvic node irradiation for high-risk patients (6-9). Radiation-induced toxicity is most often associated with high total and daily doses, a short recovery time, and the amount of irradiated tissues (ie, surrounding organs at risk [OARs]). Toxicity to OARs has become a major concern: data suggest that even in prostate-only radiation therapy, toxicity to OARs was more prevalent in the "high-dose" group (1-5).

Hypofractionation has been proposed as an additional strategy to optimize the therapeutic ratio by taking advantage of the assumption that prostate cancer is more sensitive than normal surrounding tissues to fractionation (low α/β ratio) (10-13). However, higher fraction sensitivity of prostate cancer may result in late effects of other pelvic organs, such as the rectum, bladder, and urethra.

Miralbell et al (13) published a large retrospective study that included data from 7 worldwide databases of almost 6000 patients. The study evaluated the radiobiology characteristics of prostate cancer according to clinical outcomes and confirmed the

Note—An online CME test for this article can be taken at http://astro.org/MOC.

Reprint requests to: Gilles Créhange, MD, PhD, Georges-François Leclerc Cancer Center, Radiotherapy Department, 1 rue du Professeur Marion, 21000 Dijon, France. Tel: +33 380 737 517; E-mail: gcrehange@cgfl.fr

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relatively low α/β ratio for prostate cancer control, ranging between 0.9 and 2.2 Gy, which is lower than the corresponding spectrum of α/β ratios for late-responding tissues (3-5 Gy). The study results imply that hypofractionation for prostate cancer will benefit all risk groups. However, none of the included trials (except one) evaluated pelvic node irradiation (13). It is important to state that there is no absolute α/β ratio and that most data came from retrospective studies, some of which had a wide 95% confidence interval. A recently published meta-analysis supported the view that the α/β ratio was low even when the time factor was included, but this value was derived mainly from the results of a single study. If this study is excluded and the outcomes of other published studies are taken into account, an α/β ratio exceeding 4 Gy can still not be ruled out (14), thus challenging the role of hypofractionation.

Even though hypofractionation to the prostate only is now accepted as a therapeutic alternative for high-risk patients, there is weaker evidence from retrospective or phase 1/2 data that concomitant pelvic node irradiation can be performed safely. Some claim that the careful use of such modern technologies might allow radiation oncologists to treat larger volumes of critical structures such as the bowel, rectum, and bladder with hypofractionation (15, 16). By combining modern advances in radiation oncology (high-dose-rate prostate brachytherapy, intensity modulated radiation therapy [IMRT] with improved image guidance for soft-tissue sparing), it is hypothesized that whole-pelvic radiation therapy (WPRT) could take advantage of recent results from hypofractionation trials.

In the setting of high-risk prostate cancer patients, the purpose of this article is to review the growing body of literature concerning the safety of combining WPRT with a hypofractionated scheme of radiation therapy delivered to the prostate.

The references for this review were identified through a search of the PubMed database, using the search terms “prostate” and “cancer” and “radiation therapy” or “radiation” or “irradiation” and “hypofractionation” and “pelvis” or “pelvic” for the Title/Abstract section. The search was limited to clinical studies published in English and unlimited to publication year. A Google Scholar search was conducted using the terms as listed above. The articles were first evaluated by title and thereafter by abstract. Full-text articles were retrieved and reviewed for the selected titles and abstracts. Reference lists of the retrieved articles were searched for additional publications. Data from international meetings (such as the American Society for Radiation Oncology) published in English were also reviewed. The final reference list was generated on the basis of relevance to the subject of the review.

Conventionally Fractionated WPRT Combined With Hypofractionation to the Prostate

The Italian phase 3 trial on hypofractionation radiation therapy reported by Arcangeli et al (17) showed a significant benefit of hypofractionation to the prostate only (ie, without whole pelvis) in high-risk patients. In such high-risk patients there is still considerable controversy in the literature regarding the place of pelvic node irradiation. The large phase 3 trial (protocol 9413) from the Radiation Therapy Oncology Group (RTOG) demonstrated the role of WPRT on progression-free survival in patients with a high risk of nodal involvement using the Roach formula (9). The controversy still exists because the Groupe d’Etude des Tumeurs Uro-Génitales (GETUG)-01 trial did not support these observations (18-20). Nevertheless, from the outset, GETUG-01 was far more likely to be a negative study: it was a smaller study that included more favorable patients with smaller pelvic fields. This argument was supported by Arcangeli et al (21), who pointed out that a failure to demonstrate the benefits of elective nodal irradiation might be due to a number of reasons, including the inclusion of very-low-risk patients, the inclusion of very-high-risk patients in whom systemic spread has already occurred, inadequate coverage (small field), inadequate doses to the prostate and/or pelvic nodes, and the fact that the radiation benefit might have been hidden by the concurrent hormone therapy. Young, otherwise healthy men with no comorbidities are also more likely to benefit from WPRT. Some of these arguments were supported by RTOG 9413 and provide a possible explanation for the conflicting results of GETUG-01 and RTOG 9413 (19, 20). Surgical staging data based on a standard lymph node dissection may underestimate the true incidence of lymph node involvement. Elective nodal irradiation should thus be considered in a selected group of patients (19). To this end, RTOG launched a larger phase 3 trial (RTOG 0924), which will include roughly 2500 patients to conclusively address the impact of WPRT on overall survival. Dose escalation to the prostate in RTOG 0924 is given with either IMRT, prostate seed implants, or a hypofractionated high-dose-rate boost.

Technical challenges of elective nodal irradiation and hypofractionated radiation therapy

Preliminary results from a randomized, phase 3 trial testing hypofractionation in intermediate- and high-risk patients who underwent WPRT with IMRT have been recently reported (22). In their study, Pollack et al (8) randomized 303 patients either to 76 Gy in 2-Gy fractions over 7.5 weeks or to 70.2 Gy in 2.7-Gy fractions while the pelvis was treated at 50 Gy in 26 fractions in the hypofractionated arm and $\geq$56 Gy in 38 fractions in the conventional arm. Grade $\geq$2 gastrointestinal toxicities were seen in 5% and 6.8% of the conventional and hypofractionated groups, respectively, but genitourinary grade $\geq$2 toxicities occurred in 8.3% and 18.3%, respectively ($P = .028$). The rates of local regional failure or distant metastasis for the high-intensity radiation and the conventional radiation groups were 1.3% and 1%, respectively, at 5 years (22). Note should be taken that, because of the natural course of the disease, a 5-year follow-up is not enough to evaluate the true treatment benefit in the case of prostate cancer.

Whole-pelvis irradiation by image-guided IMRT is challenging, because the target encompasses 2 independent target volumes, one of which is more mobile than the other.

Theoretically, if daily repositioning is performed according to bone anatomy, wider margins should be considered around the prostate to take into account daily variations of prostate position (up to 1.5 cm). If daily repositioning is performed on the prostate or on implanted fiducial markers in an attempt to protect mostly the rectum, then margins around the pelvic and/or para-aortic nodes should be increased. This dilemma is of paramount importance when considering hypofractionation to the prostate. To circumvent this obstacle, the University of California, San Francisco (UCSF) proposed an alternative strategy, which is referred to as multiple adaptive plans (MAP) IMRT (23); MAP-IMRT provides a feasible solution for tracking 2 concomitant targets independently. In other circumstances than MAP-IMRT, physicians have to choose which target volume to refer to for repositioning on a daily basis. In hypofractionation, the prostate should