Urologic Oncology: Seminars and Original Investigations 37 (2019) 579−581

UROLOGIC ONCOLOGY

Seminars Article

Radiation therapy for prostate cancer: An evolving treatment modality

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Received 26 May 2019; accepted 31 May 2019

Abstract

Radiation therapy for prostate cancer is evolving rapidly with advancing technology and with results from many clinical trials. This article summarizes highlights from the 5 articles published in this issue of Seminars on the current state of radiation treatment and areas of continued development. © 2019 Elsevier Inc. All rights reserved.

Keywords: Prostate cancer; Radiation therapy; Brachytherapy; Salvage; Proton

The ProtecT randomized trial showed indistinguishable cancer control, metastasis, and survival outcomes between radical prostatectomy and radiation therapy (RT). It also showed favorable quality of life outcomes, with most measures at 6 years similar between patients randomized to RT and active monitoring [1]. For nonradiation oncologists, the treatment used in ProtecT is what they know about RT in prostate cancer. However, ProtecT started in 1999 and used 3D conformal RT. Now 20 years later, radiation technology is 2 to 3 generations (intensity-modulated RT, volumetric arc therapy, and stereotactic body RT) after ProtecT radiation treatment. In the past 20 years, numerous randomized trials and other well-conducted studies involving various uses of RT for prostate cancer have been published. Articles in this issue of *Seminars* summarize several areas where RT has evolved and continues to evolve.

The article by Beckta et al. [2] summarizes arguably the biggest change in RT for prostate cancer: shortening the duration of treatment. Historically, a relatively small dose of RT is given daily (1.8−2.0 Gy/d), and prostate cancer required a treatment duration of 7 to 9 weeks to a total dose of 74 to 80 Gy (ProtecT used 74 Gy delivered over 7.5 weeks). Today, this is called "conventional fractionation;" in my own practice, very few patients receive this long course of treatment anymore. Moderate hypofractionation delivers a higher dose of daily RT and shortens the treatment course to 4 to 6 weeks. As the article describes, 9 randomized clinical trials have shown similar oncologic and toxicity results from moderate hypofractionation vs. conventional fractionation. In fact, moderate hypofractionation gives less radiation dose to the patient overall, demonstrating the radiobiological principle that when a higher daily dose is used, less total dose is required to cure prostate cancer. This strong body of Level 1 evidence has led the American Society for Radiation Oncology to recommend moderate hypofractionation as a standard of care [3]. Rapidly accumulating long-term data for extreme hypofractionation is making this treatment option increasingly popular. Extreme hypofractionation uses the stereotactic body RT technology to deliver prostate cancer treatment in 1 to 2 weeks, using about one-half the total dose of conventional RT. Beckta et al. [2] describe an overall trend of less RT dose, shorter treatment (which is also less costly) − without compromising curative or quality of life outcomes. In oncology overall where healthcare costs are increasing steadily, prostate cancer RT bucks this trend.

Another way to deliver radiation treatment is using brachytherapy. Many nonradiation oncologists are less familiar with this, a technique sometimes called "internal" RT to contrast with external beam RT. As with any

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https://doi.org/10.1016/j.urolonc.2019.05.023

procedure, brachytherapy outcomes (including cancer control and toxicity) are likely highly dependent on the experience of each physician. As the article by Dess et al. [4] describes, use of brachytherapy is decreasing over time partly due to insufficient training and experience. The article summarizes published randomized trials involving brachytherapy for prostate cancer. There are some details which require further study: temporary vs. permanent (i.e., high-dose rate vs. low-dose rate) brachytherapy, and type of radioisotope used in permanent brachytherapy. Several trials have now studied adding brachytherapy to external beam RT as a way to deliver a higher dose to the prostate than is feasible with external beam RT alone (due to concerns about excess dose to normal tissue including bladder and rectum). Even more than proton therapy, brachytherapy minimizes radiation dose to organs and tissues outside the prostate. In these trials, combination treatment (external beam RT plus brachytherapy) improved biochemical control compared to RT alone but also increased toxicity [5−7]. Additional clinical trial data suggest that for patients with favorable risk disease, brachytherapy alone results in similar oncologic outcomes as brachytherapy plus external beam RT; for these patients, brachytherapy is less costly and results in better quality of life [8,9].

Another major area of continued RT development for prostate cancer relates to the incorporation of advanced (and advancing) imaging. The article by Xu et al. [10] summarizes the rapidly emerging literature on the use of multiparametric MRI and PET scan with an increasing number of tracers (including sodium fluoride, choline, prostate-specific membrane antigen, and fluciclovine). Novel imaging holds promise to improve the precision in detecting cancer in the prostate as well as nodal and distant metastatic disease, which can directly impact the design of RT. Research by Jani et al. have shown that with use of fluciclovine PET scan, radiation target volumes changed in the majority of patients [11]. The high likelihood of more accurate targeting of prostate cancer leading to improved patient outcomes seems intuitive, but will require longer term follow-up data to prove.

Improved imaging also leads to increased detection of visible recurrences after primary therapy. Specifically, for patients who received primary RT, detection of a local (prostate) recurrence − which is potentially curable − has historically posed a clinical challenge. As the article by Steele and Holmes describes [12], salvage radical prostatectomy after prostate RT carries a higher risk for morbidity (e.g., rectal injury) compared to primary prostatectomy. However, there is an increasing list of local salvage options after primary RT, including brachytherapy (high-dose rate and low-dose rate), stereotactic body RT, cryotherapy, and high intensity-focused ultrasound. The article summarizes existing data on the efficacy and side effects of each of these salvage treatment options. Indeed, if improving imaging leads to more accurate definitions of local recurrence, the potential exists for partial gland salvage therapy. Another exciting area of development is the treatment of oligometastatic disease, which will be increasingly diagnosed with improving imaging. Early efficacy data are now available with multiple ongoing trials exploring whether this aggressive approach leads to improved patient outcomes.

Finally, proton therapy for prostate cancer remains a controversial topic. Based on several decades of published data, there is no question that proton therapy is safe and effective for prostate cancer. But the controversy centers on the issue of whether proton therapy results in better patient outcomes (i.e., reduced side effects) compared to more commonly available photon-based RT to justify its higher cost. As the article by Royce and Efstathiou [13] summarizes, radiation planning studies have shown that proton vs. photon radiation reduces the amount of normal tissue that receives low to moderate radiation doses; there is one notable exception which is that proton therapy actually delivers more dose to the femoral heads than photon radiation. Whether these dosimetric differences will lead proton patients to have less bowel/bladder toxicity but more hip fractures compared to photon patients continues to be a subject of debate and research. Existing published studies, as a whole, have found no major differences in patient outcomes between proton and photon radiation. Two ongoing and complementary studies, including a 400-patient randomized trial [NCT 01617161] and a 3,000-patient nonrandomized prospective trial [NCT 03561220], hope to provide a more definitive answer to this debate.

"RT" for prostate cancer includes both external beam RT and internal radiation (brachytherapy). The former varies by the particle used (photon and proton), treatment planning and delivery technology (3D conformal, intensity-modulated RT, and stereotactic body RT) and dose/fractionation. The latter includes permanent and temporary options, and varies by the type of radioisotope used and how brachytherapy combines with external beam RT. Patients treated today are not receiving the same RT as patients in the ProtecT randomized trial. Continued rigorous research on how to best use the various types of radiation therapy for prostate cancer, as well as continued developments in imaging and salvage treatment options, means that patients treated 5 to 10 years from now will not be receiving the same "radiation therapy" as patients today.

Conflict of interest

Blue Earth, Inc.

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