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Review article

What is the best way to radiate the prostate in 2016?

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Abstract

Prostate cancer treatment with definitive radiation therapy (RT) has evolved dramatically in the past 2 decades. From the initial 2-dimensional planning using X-rays, advances in technology led to 3-dimensional conformal RT, which used computerized tomography-based planning. This has allowed delivery of higher doses of radiation to the prostate while reducing dose to the surrounding organs, resulting in improved cancer control. Today, intensity-modulated RT (IMRT) is considered standard, where radiation beams of different shapes and intensities can be delivered from a wide range of angles, thus further decreasing doses to normal organs and likely reducing treatment-related toxicity. In addition, image guidance ascertains the location of the prostate before daily treatment delivery.

Brachytherapy is the placement of radioactive seeds directly in the prostate, and has a long track record as a monotherapy for low-risk prostate cancer patients with excellent long-term cancer control and quality of life outcomes. Recent studies including several randomized trials support the use of brachytherapy in combination with external beam RT for higher-risk patients.

RT for prostate cancer continues to evolve. Proton therapy has a theoretical advantage over photons as it deposits most of the dose at a prescribed depth with a rapid dose fall-off thereafter; therefore it reduces some doses delivered to the bladder and rectum. Prospective studies have shown the safety and efficacy of proton therapy for prostate cancer, but whether it leads to improved patient outcomes compared to IMRT is unknown.

Hypofractionated RT delivers a larger dose of daily radiation compared to conventional IMRT, and thus reduces the overall treatment time and possibly cost. An extreme form of hypofractionation is stereotactic body radiation therapy where highly precise radiation is used and treatment is completed in a total of 4 to 5 sessions. These techniques take advantage of the biological characteristic of prostate cancer, which is more sensitive to larger radiation doses per fraction, and therefore could be more effective than conventional IMRT. Multiple randomized trials have demonstrated noninferiority of moderately hypofractionated RT compared to conventional fractionation. There is also a growing body of data demonstrating the safety and efficacy of stereotactic body radiation therapy for low- and intermediate-risk prostate cancer.

Keywords: Prostate cancer; Radiation therapy; Intensity-modulated radiation therapy (IMRT); Image-guided radiation therapy (IGRT); Proton therapy; Hypofractionation; Stereotactic body radiation therapy (SBRT); Brachytherapy

1. Introduction: Historical perspective

Radiation therapy (RT) has a long track record as a curative treatment modality for localized prostate cancer. Overall, 2 large randomized trials compared androgen deprivation therapy (ADT) vs. ADT plus RT for patients with high-risk/locally advanced prostate cancer, and both showed that RT improves overall survival by an absolute difference of 8% to 10% [1,2]. Radiation delivered in the form of X-rays or protons causes DNA damage, which is preferentially repaired in the normal tissue compared to cancer cells, creating a therapeutic ratio [3]. The goal of RT is to deliver sufficiently high doses of radiation to achieve complete tumor kill while minimizing the dose and damage to the surrounding normal structures.

RT technology has made dramatic developments over the past 25 years. Before the 1990s, external beam RT for

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prostate cancer was delivered with 2-dimensional (2D) techniques; that is, treatment planning only used X-ray films and radiation fields were designed based on pelvic bony landmarks. During this time, doses to organs surrounding the prostate (such as bladder and bowel) could not be calculated accurately, and treatment was associated with significant gastrointestinal (GI) toxicities such as diarrhea or proctitis and genitourinary (GU) toxicities such as dysuria, urgency, and urinary strictures. In prospective studies, acute and late ≥grade 2 GI toxicities were reported in 15% to 41% and 14% to 15% of patients, respectively; whereas acute and late ≥grade 2 GU toxicities were seen in 23% to 65% and 20% to 23% of patients, respectively [4,5]. Owing to a significant dose response of GI toxicities in particular, prescribed radiation dose for prostate cancer treatment was limited to 64 to 70 Gy [6,7].

The 3-dimensional (3D) radiation treatment planning for prostate cancer became routinely used in the 1990s. Using computerized tomography scans for radiation planning allowed direct visualization of the RT target (prostate) and surrounding organs, not previously possible with 2D/X-ray planning, and more precise calculations of doses delivered to each. Indeed, acute and late toxicity rates published from the 3D conformal RT (3DCRT) era were lower than those from the prior 2D era [4,8,9].

Over time, research efforts led to correlations between doses received by organs with GI and GU toxicities, which have helped define "safe" dose guidelines for each organ to be followed during 3D treatment planning. Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) was a multi-institutional effort analyzing published radiation dose, volume, and toxicity outcomes data. For prostate cancer treatment, rectal radiation dose constraints were defined to minimize ≥grade 2 late GI toxicity, and bladder constraints defined to minimize ≥grade 3 late GU toxicity [10].

2. Current standards

In addition to the decreased rates of toxicities, the use of more conformal radiation treatment techniques also enabled safer delivery of higher doses of radiation to the prostate. At least 5 randomized trials have compared traditional radiation doses (64–70 Gy) to dose-escalated RT (74–80 Gy) [11–15], and all consistently demonstrated improved disease-free survival with escalated doses, and this has become current standard of care (Table 1). By 2011, 90% of patients in the United States receiving definitive RT for prostate cancer received dose-escalated treatment [16]. However, the trials that used 3DCRT techniques also showed that dose-escalated RT increased ≥ grade 2 acute and late GI toxicity [11,12,15,17] and ≥ grade 2 late urinary toxicity [14] compared to lower doses. For example, in the dose escalation trial conducted at MD Anderson Cancer Center, 10-year incidence of ≥grade 2 GI toxicity was 13% for patients treated to 70 Gy compared to 26% for those treated to 78 Gy ($P = 0.013$) [11].

Table 1
Randomized trials evaluating external beam radiotherapy dose escalation for localized prostate cancer

Study	*N*	Doses, Gy	Median f/u, mo	bDFS	OS	≥Grade 2 late toxicity	
						GI	GU
MD Anderson [11]	301	78 vs. 70	104	78% vs. 59% $P = 0.004$	78% vs. 79% $P = 0.32$	26% vs. 13% $P = 0.001$	13% vs. 8% $P = 0.69$
PROG 95-09 [12]	393	79.2 vs. 70.2	107	83% vs. 68% $P < 0.001$	83% vs. 78% $P = 0.41$	24% vs. 13% $P = 0.09$	29% vs. 25% $P = 0.79$
MRC RT01 [13]	843	74 vs. 64	120	55% vs. 43% $P = 0.003$	71% vs. 71% $P = 0.96$	33% vs. 24% $P = 0.005$	11% vs. 8% $P = 0.14$
GETUG 06 [14]	306	80 vs. 70	61	72% vs. 61% $P = 0.036$	NR	20% vs. 14% $P = 0.22$	18% vs. 10% $P = 0.046$
Dutch CKVO96-10 [15]	669	78 vs. 68	70	54% vs. 47% $P = 0.04$	75% vs. 77% $P = 0.96$	35% vs. 25% $P = 0.04$	40% vs. 41% $P = 0.6$

bDFS = biochemical disease-free survival; f/u = follow-up; NR = not reported; OS = overall survival.