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Review Article

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Abstract: Radiation therapy (RT) is a curative treatment modality for localized prostate cancer. Over the past two decades, advances in technology and imaging have considerably changed RT in prostate cancer treatment. Treatment has evolved from 2-dimensional (2D) planning using X-ray fields based on pelvic bony landmarks to 3-dimensional (3D) conformal RT (CRT) which uses computed tomography (CT) based planning. Despite improvements with 3D-CRT, dose distributions often remained suboptimal with portions of the rectum and bladder receiving unacceptably high doses. In more recent years, intensity-modulated radiation therapy (IMRT) has become the standard of care to deliver external beam RT. IMRT uses multiple radiation beams of different shapes and intensities delivered from a wide range of angles to 'paint' the radiation dose onto the tumor. IMRT allows for a higher dose of radiation to be delivered to the prostate while reducing dose to surrounding organs. Multiple clinical trials have demonstrated improved cancer outcomes with dose escalation, but toxicities using 3D-CRT and escalated doses have been problematic. IMRT is a method to deliver dose escalated RT with more conformal dose distributions than 3D-CRT and has been associated with improved toxicity profiles. IMRT also appears to be the safest method to deliver hypofractionated RT and pelvic lymph node radiation. The purpose of this review is to summarize the technical aspects of IMRT planning and delivery, and to review the literature supporting the use of IMRT for prostate cancer.

Keywords: Prostate cancer; intensity-modulated radiation therapy (IMRT)

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Introduction

Prostate cancer is the most common malignancy in men (1). Patients with localized prostate cancer have multiple treatment options including active surveillance, prostatectomy, brachytherapy, and external beam radiation therapy (EBRT). A patient's preference toward a specific treatment is often driven by the invasiveness of the treatment modality and the expected side effects from that particular intervention. EBRT, considered as one of the least invasive treatments, has changed drastically over the past several decades with the ultimate goal of improving survival outcomes with decreasing toxicity. Older techniques were replaced with 3-dimensional (3D) conformal radiation therapy (CRT), and further technological advancements in radiation imaging, planning, and delivery has allowed the introduction and wide adoption of intensity-modulated radiation therapy (IMRT). IMRT uses 3D imaging to guide beams of radiation to the tumor from many different angles while changing (modulating) the intensity and shape of the beam to match the shape of the tumor. These adjustments of the radiation allow for the prescribed amount of radiation to be delivered to each part of the tumor while minimizing the amount of radiation normal surrounding healthy tissue

receives. For prostate cancer, multiple randomized and nonrandomized series have shown improved tumor control with the use of dose escalated therapy (2-7). The enhanced conformality of IMRT allow for dose escalation to the prostate while reducing dose to the bladder and rectum, and trials have demonstrated reduced toxicity with IMRT (8,9). In addition to the fundamental principles of the IMRT technique, there are numerous biologic, anatomic, and clinical features which also make prostate cancer a model site for implementation of IMRT. In this review, we describe the evolution of EBRT to IMRT, describe the specific features of prostate cancer which make this disease an ideal site for implementation and routine use of IMRT, comparisons between IMRT and 3D-CRT including genitourinary (GU) and gastrointestinal (GI) toxicities, clinical outcomes of IMRT including dose escalation, and future directions utilizing this technology.

Evolution of external beam radiation to IMRT

Historically, definitive radiation for prostate cancer was accomplished using 2-dimensional (2D) or 3D-CRT. The most common conventional beam arrangement was a "four field box" arrangement consisting of a pair of anterior-posterior and posterior-anterior (AP-PA) beams, as well as a pair of lateral opposed beams. This approach was commonly used into the early 1990s, until 3D-CRT became more widely adopted. 3D-CRT takes advantage of sophisticated computer software, and included computed tomography (CT) simulation to integrate volumetric data regarding the patient's tumor and organs at risk to allow for beam angles and radiation portals that were difficult to implement using conventional 2-dimensional planning.

Dearnaley *et al.* conducted a randomized study of conventional *vs.* 3D-CRT to a dose of 64 Gy in 2 Gy fractions, which at that time was a standard dose for prostate cancer (10). Of the 225 men treated, significantly fewer men developed radiation proctitis and bleeding in the 3D-CRT group compared to the conventional group (5% *vs.* 15% grade 2+) and there was no difference in tumor control. As toxicity was reduced with 3D-CRT, several groups conducted studies to escalate the radiation dose to the prostate tumor. The outcomes of dose escalation with 3D-CRT have been summarized in several other review articles (11-14). In general, they observed that the radiation dose could be escalated from the range of 64–68 Gy to the range of 74–81 Gy using 3D-CRT, and resulted in improved biochemical progression free survival rates. These results are summarized by a meta-analysis conducted by Viani *et al.*, which pooled seven randomized trials with a total patient population of 2,812 (15). They identified that dose-escalated radiation resulted in significant reductions in biochemical failure, but there were no differences in the rate of all-cause or prostate cancer specific mortality. Furthermore, there were also more cases of late grade 2+ GI toxicity in the high-dose radiation groups, with the absolute difference typically ranging between 5–10% between the study arms.

In particular, the Radiation Therapy Oncology Group (RTOG) conducted protocol 9406 which used 3D-CRT to sequentially increase the radiation dose to several levels including 68.4 (1.8 Gy per fraction), 73.8 (1.8 Gy per fraction), 79.2 (1.8 Gy per fraction), 74.0 (2.0 Gy per fraction), and 78.0 (2.0 Gy per fraction) (16). These regimens resulted in disease free and biochemical progression free survival rates which compared favorably with historical data. Additionally, the toxicity results with 3D-CRT, including the maximum dose levels of 79.2 Gy in 1.8 Gy per fraction and 78.0 Gy in 2.0 Gy per fraction were low compared to historical controls (17). However, the 78 Gy in 2.0 Gy fractions dose level was ultimately associated with a greater incidence of late grade 2+ toxicity compared to 79.2 Gy in 1.8 Gy per fraction (30–33% *vs.* 9–13%). These results established a dose of 79.2 Gy in 1.8 Gy fractions for prostate cancer that is commonly used at Washington University in St. Louis.

An additional refinement on 3D-CRT is a technique known as IMRT. IMRT uses beam modulation and "field in field" techniques made possible by multi-leaf collimators combined with sophisticated inverse planning software. The IMRT approach allows the radiation oncologist to prescribe doses to target structures such as the prostate and proximal seminal vesicles and dose constraints to nearby normal structures such as the rectum and bladder. The computer software then determines the beam modulation to optimally achieve the radiation prescription. The resulting radiation distribution appears "sculpted" to cover the target and to avoid normal structures in a way that would typically not be achievable using conventional planning methods as seen in *Figure 1*. Although the mathematics underlying IMRT were published in the late 1980s and early 1990s, clinical IMRT systems were not implemented until the mid to late 1990s and commercial systems were not in common use until the early 2000s.

There are no randomized controlled trials directly comparing dose escalated IMRT and 3D-CRT in prostate

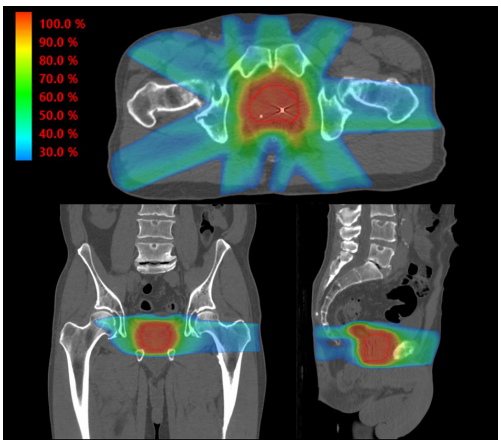

Figure 1 Illustrative IMRT plan treating the prostate and proximal seminal vesicles. The images show the radiation dose distribution in the axial (top center), coronal (bottom left), and sagittal (bottom right) orientations. The dose color-wash shows the radiation dose distribution as percentage of the prescription dose. Regions outside of the color-wash received less than 20% of the radiation prescription dose. The treatment plan encompasses the prostate (red structure) and proximal seminal vesicles (green structure) and avoids nearby regions such as the bladder, rectum, penile bulb, and femoral heads. The dense structures inside the prostate are fiducial markers placed for image guidance. The radiation plan includes seven beam angles and uses beam energy of 10 mega-volts (MV). IMRT, intensity-modulated radiation therapy.

cancer. However, several single institution retrospective studies have demonstrated improved biochemical control and/or reduced GI toxicity with IMRT as compared to 3D-CRT (18-20). Additionally, in RTOG 0126, a randomized study of dose escalation in intermediate risk prostate cancer, a reduction in late grade 2+ GI toxicity of 15% *vs.* 22% was observed with IMRT compared to 3D-CRT in the 79.2 Gy high dose arm (8). These studies will be discussed in detail later in this review.

The reduction in toxicity of IMRT as compared to 3D-CRT has led to its rapid adoption in the United States. In a SEER-Medicare study, IMRT use increased substantially as a proportion of patients treated with radiation from 28% in 2002 to 82% in 2005 (21). According to the most recent 2016 American College of Radiology Appropriateness Criteria, the use of 3D-CRT for dose escalated treatment of prostate cancer is typically no longer appropriate if other options, such as IMRT, are available (22).

Table 1 Target and normal structure constraints used for prostate IMRT optimization at Washington University in St. Louis. For example, the interpretation of the constraint "Rectum V65 Gy <17%" can be explained as: limit volume of rectum receiving 65 Gy or greater to less than 17 percent of the total volume of the structure

Structure	Optimization parameter
Planning target volume (PTV)	Cover 98% of PTV with 100% of prescription dose
Rectum	V65 Gy <17% and V40 Gy <35%
Bladder	V65 Gy <25% and V40 Gy <50%
Femoral heads	V50 Gy <10% for each femoral head
Penile bulb	Mean dose <52 Gy

IMRT, intensity-modulated radiation therapy.

Anatomic and biologic features which make prostate cancer a model site for implementation of IMRT

The prostate is located in close proximity to the rectum, bladder, penile bulb, and femoral heads which are at risk of receiving radiation dose and subsequent toxicity due to prostate cancer treatment. IMRT has been shown in dosimetric studies to substantially decrease the amount of unintentional radiation delivered to these normal structures. In RTOG 0126, a comparison of the dosimetry of IMRT and 3D-CRT plans in the 79.2 Gy arm showed that the percent of the rectum treated to at least 75 Gy (rectum V75) was reduced from 15.8% to 13.0%, and the V65 was reduced from 27.4% to 23.0% (8). The bladder V75 was reduced from 17.7% to 13.1% and the V65 was reduced from 25.3% to 19.7%. A dosimetric study by Hardcastle *et al.* showed similar findings suggesting a reduction in the rectum V75 from 23.2% to 9.9%, resulting in an estimated reduction in rectal complication rates from 14% to 5% (23). Luxton *et al.* have estimated that the mean dose to the femoral heads can be approximately halved by using IMRT over 3D-CRT (24). Additional studies have shown the possibility of IMRT in reducing radiation dose to the penile bulb (mean dose 33 *vs.* 49 Gy for IMRT *vs.* 3D-CRT) (25) The normal structure dose constraints used for IMRT plan optimization used at Washington University in St. Louis are listed in *Table 1*. The ability of IMRT to reduce dose to nearby normal structures without sacrificing dose coverage of the target makes it an ideal treatment modality for prostate cancer.

There may be additional radiobiological considerations that make prostate cancer a good target for IMRT, due to the alpha/beta ratio of the tumor and the use of hypofractionated radiation treatments. The response of tumor cells and normal tissue to therapeutic doses of radiation can be characterized by the alpha/beta ratio (α/β). This radiobiologic parameter is useful in determining the effect of various dose and fractionation schemes on the tissue. In this model, α represents the cells that die after one "hit" of radiation and β represents the cells that die after two "hits", representing the ability to repair sublethal damage. The ratio of these two parameters, α/β, represents the "sensitivity" of a tissue to radiation. Rapidly proliferating cells, such as most tumors, are characterized by a α/β of ≥10 whereas most normal tissues, which are comprised of slower proliferating cells, have an α/β of 2–3. Tissues with low α/β are thought to be more sensitive to radiation given in large doses per treatment (large fraction sizes), while tissues with high α/β are thought to be more responsive to smaller fraction sizes. The combination of α/β ratio, dose per fraction, and number of fractions in a radiation treatment course can be used to calculate the biologically effective dose (BED), which is a measure of damage to tumor cells that can be calculated from many different radiation regimens.

Surprisingly, while most tumors have high α/β values, radiobiological models based on clinical data suggest that prostate cancer has a low α/β ratio of about 1.5 Gy, which is actually lower than that of many normal tissues in the pelvis (26,27). This finding implies that although dose escalation using conventional fractionation (1.8–2.0 Gy per fraction) has been effective for prostate cancer, an alternative method of improving the therapeutic ratio may include hypofractionation, the use of doses >2.0 Gy per radiation treatment (28).

The efficacy and toxicity of moderate hypofractionation has been tested in several studies (29). The United Kingdom CHHiP study randomized patients to 74 Gy in 2 Gy fractions *vs.* two hypofractionated regimens of 60 Gy in 20 fractions or 57 Gy in 19 fractions (29). IMRT was mandated in this study, and there were no differences in toxicity or cancer-related outcomes (29,30). The RTOG conducted a randomized study comparing a dose of 73.8 Gy in 1.8 Gy fractions to moderate hypofractionation to a dose of 70 Gy in 28 fractions (31). This study of 1,092 men with low risk prostate cancer established that the hypofractionated regimen was non-inferior in efficacy compared to the conventional regimen (31). However, there was an increase in late GI/GU adverse events with hypofractionated treatment. Both 3D-CRT and IMRT was allowed on this study. The Dutch HYPRO study also randomized patients between a conventional and hypofractionated dose regimen, and there was a ~95% utilization of IMRT in both arms (32). The late toxicity results of this study showed that the incidence of grade 3+ GI toxicity between the two regimens were not different (2.6% *vs.* 3.3%), but the late grade 3+ GU toxicity was not non-inferior between the conventional and hypofractionated treatments (13% and 19% respectively) (32). Five-year rates of treatment failure and relapse free survival were not significantly different between the two groups (32).

Although further analysis and reporting of the data is needed, the evidence above may suggest that IMRT is important to the delivery of moderate hypofractionation without excess GI toxicity. However, the ability of IMRT to reduce GU toxicity is limited as a portion of the bladder and prostatic urethra are necessarily within the treatment volume. Future studies will better define the appropriate tissue constraints to use for hypofractionated radiation, and the full benefit of IMRT in this setting.

Technical aspects of IMRT

IMRT combines inverse treatment planning and computer-controlled intensity modulation of the radiation to deliver 3D-CRT. Since the introduction of IMRT, many techniques for IMRT treatment of the prostate have been implemented (33). A common approach is the use of multiple coplanar fields arranged at equal or nearly equal spacing around the patient (33). Usually between 5 to 9 static fields are used for this approach, and in general, dose homogeneity and conformality improve as the number of treatment fields increases, however the benefit with field numbers beyond 7 to 9 diminishes (33,34). Noncoplanar beam arrangements, volumetric-modulated arc therapy (VMAT) and tomotherapy have been developed in attempts to further improve the dose distribution and are commonly used at many institutions.

IMRT treatment plans are designed by using specialized computer algorithms commonly termed "inverse treatment planning and optimization" systems (33). The user selects objectives, usually termed constraints and goals, that describe the desired dose to each target and organ at risk, and penalties are assigned based on the relative importance of each objective (33). These constraints and penalties are then combined into the mathematical

Table 2 Randomized trials evaluating external beam radiation therapy dose escalation for localized prostate cancer

Study	Patients	Dose (Gy)	Median follow-up (months)	bDFS	Grade 2+ GI toxicity
MD Anderson	301	78 *vs.* 70	104	78% *vs.* 59%*	26% *vs.* 13%*
PROG 95-09	393	79.2 *vs.* 70.2	107	83% *vs.* 68%*	24% *vs.* 13%
MRC RT01	843	74 *vs.* 64	120	55% *vs.* 43%*	33% *vs.* 24%*
GETUG 06	306	80 *vs.* 70	61	72% *vs.* 61%*	20% *vs.* 14%
Dutch CKVO96-10	669	78 *vs.* 68	70	54% *vs.* 47%*	35% *vs.* 25%*

*, P<0.05. bDFS, biochemical disease-free survival; GI, gastrointestinal.

algorithm according to a cost function and the intensity of beamlets within each field are adjusted iteratively until the cost function is minimized and thereby determining the intensity of each beam that leads to the closest profile as stated in the objective goals (33). Optimization objectives are both planning system and patient specific, therefore many institutions have developed institutional constraint templates that are used as a starting point for the planning process (33). The delivery of IMRT is than achieved by using either sequential delivery of multiple static apertures from a multileaf collimator (MLC) termed "step and shoot", or as dynamic multileaf movement termed "sliding window" (35). Other techniques for delivery are available, but these two methods remain the most common.

After an acceptable IMRT plan has been generated, it is important to ensure the plan is properly implemented. Delivery of the complex intensity profiles created during the IMRT optimization process is performed by sophisticated mechanical and computerized delivery systems on a linear accelerator. Quality assurance is an integral part of this process and is typically performed with dosimetric verification of the leaf motion and sequencing for each field as well as computer based verification of the dose distribution and monitor unit settings for each field.

Outcomes with IMRT

Evidence from several single institution studies and multiple randomized control trials demonstrate a dose-response relationship with doses above 68 Gy associated with improved local and biochemical control (4,7,36). A summary of randomized dose escalation trials is found in *Table 2*. Additionally, dose-volume toxicity relationships have also been established for rectal bleeding and other GI and GU toxicities with increased high dose associated with increased risk of toxicity (4,37-40). IMRT is a method to escalate dose while achieving safe dose-volume constraints to organs at risk.

Published in 2007, Vora *et al.* evaluated biochemical control rates and prognostic factors for patients with localized prostate cancer treated with either high-dose IMRT or conventional-dose 3D-CRT. A total of 271 patients received 3D-CRT with a median dose of 68.4 Gy (range, 66.0–71.0 Gy), and 145 patients received IMRT with a median dose of 75.6 Gy (range, 70.2–77.4 Gy). Using the ASTRO Phoenix definition, the 5-year biochemical control rate was 74.4% for 3D-CRT and 84.6% with IMRT (P=0.033). On both univariate and multivariate analysis, increased dose was associated with improved biochemical control (19).

Despite improvements in prostate RT and increased dose conformity, rectal complications have not been eliminated and rectal toxicity remains a major concern for men undergoing EBRT. Giordano *et al.* (41) performed a population based analysis using the SEER database to determine the rates and predictors of late lower GI toxicity after prostate radiation prior to the IMRT era. They compared a group of men with prostate cancer treated with EBRT (n=24,130) compared to those treated without RT (n=33,835) from 1992 to 1999. For patients with a minimum of 5 years follow-up, the rates of GI diagnoses were 19.4% higher in the radiation group (41). Hemorrhage was the most common complication, and was increased by 19% for patients treated with radiation (39.6% of RT patients *vs.* comparison rates of 18.2% in patients treated with radical prostatectomy and 20.7% in patients with no local therapy) (41). Several single institutional series have reported a reduction in late toxicity since the introduction of IMRT as compared to conventional RT.

Jani *et al.* reviewed the records of 461 patients with localized prostate who received either IMRT (n=106) or conventional RT defined as 4- or 6-field conformal therapy

(n=355) from 1998 to 2005 (42). Late GI toxicities were found to be lower with IMRT (P<0.001) and regression analyses demonstrated that IMRT was the only factor predictive of late GI toxicity. On analysis of the DVH data, it was hypothesized that the GI toxicity rates were lower for the IMRT group due to lower mid-to-high range rectal dosimetric metrics (V40, V50, V60, and V70). There was no association of decreased GU complications with IMRT compared to conventional treatment (42).

Sanguineti *et al.* compared the late rectal toxicity rates after 3D-CRT to the prostate alone and whole-pelvis IMRT along with a prostate boost to the same nominal total dose to the prostate in both groups (43). Sixty-eight patients were treated to the prostate alone using 3D-CRT to a total dose of 76 Gy. A second group of patients consisted of 45 patients treated with IMRT covering the pelvic lymph nodes and seminal vesicles to 54 Gy in 1.8 Gy fractions and the prostate to 60 Gy in the same 30 fractions followed by a boost to the prostate alone to 76 Gy (43). Planning was similar for both groups, with both receiving 76 Gy to the prostate, with the main difference being the inclusion of the pelvic lymph nodes in the IMRT group (43). Late toxicity was prospectively scored using the RTOG scale and all patients had a minimum of 12 months follow-up. At 2-years, the cumulative incidence of grade 2 late rectal toxicity was greater for the group receiving 3D-CRT (21.2%±6%) compared to IMRT (6%±4%) despite the IMRT group receiving treatment to the pelvic lymph nodes. On multivariate analysis the difference was statistically in favor of IMRT [hazard ratio (HR): 0.1; 95% CI, 0.0–0.6; P=0.01]. No patients in either group developed grade 3+ toxicity (43).

Wortel *et al.* analyzed the late side effects after treatment with image-guided (IG)-IMRT or 3D-CRT, evaluating 2 prospective cohorts of men treated with localized prostate cancer to investigate hypothesized reductions in toxicity (44). Patients from two Dutch randomized trials were treated with 3D-CRT (n=189) or IG-IMRT (n=242) to 78 Gy in 39 fractions with identical toxicity scoring protocols (modified RTOG-EORTC scoring criteria). The 5-year cumulative incidence of grade ≥2 GI toxicity was 24.9% for IG-IMRT and 37.6% following 3D-CRT (adjusted HR: 0.59, P=0.005). There was significant reduction in proctitis (HR: 0.37, P=0.047) and increased stool frequency (HR: 0.23, P<0.001). GU grade ≥2 toxicity remained comparable between the two groups. Other predictors of late grade ≥2 complications were baseline complaints, acute toxicity, and age (44).

The RTOG 0126 was a prospective randomized phase III trial comparing escalated high dose RT to conventional dose RT for localized early stage intermediate risk prostate cancer which opened in March 2002 and closed to accrual in 2008. The primary endpoint of the study was to determine whether 3D-CRT or IMRT to 79.2 Gy in 44 fractions would lead to improved overall survival in patients with intermediate risk prostate cancer compared to those patients treated with the same techniques to 70.2 Gy in 39 fractions. The protocol initially included only 3D-CRT, however, in September 2003 the trial was amended to allow IMRT, and treatment modality was added as a stratification variable in order to help avoid treatment arm modality imbalances. Of the 1,532 patients enrolled on the trial, 763 were randomized to the high dose treatment arm. In this arm, patients treated with 3D-CRT received 55.8 Gy to a planning target volume that included the prostate and seminal vesicles, and then a 23.4 Gy boost to the prostate alone. Patients receiving IMRT were treated to the prostate and seminal vesicles to 79.2 Gy. In 2013, a preliminary toxicity analysis of 3D-CRT versus IMRT was published reporting acute and late effects between the two techniques (8). 748 of the 763 patients were eligible of whom 491 received 3D-CRT and 257 received IMRT. After dosimetric analysis, the median % of the bladder receiving at least xGy (pVx equals partial volume receiving 'x' Gray) for pV65, pV70 and pV75 were 25.3%, 22.2%, and 17.7% for 3D-CRT and 19.7%, 16.6% and 13.1% for IMRT. The median rectum pV65, pV70 and pV75 were 27.4%, 21.7%, and 15.8% for 3D-CRT and 23.0%, 18.2% and 13.0% for IMRT. For both the bladder and rectum, the volumes receiving 65, 70, and 75 Gy were significantly lower in the IMRT cohort (all P<0.0001). For grade 2+ acute GI/GU toxicity, both univariate and multivariate analyses showed a significant decrease in collective GI/GU toxicities in favor of IMRT. There was no significant difference between 3D-CRT or IMRT for acute or late grade 2+ or 3+ GU toxicities. Univariate analysis indicated a statistically significant decrease in late grade 2+ GI toxicity for IMRT (P=0.039). In multivariate analysis, IMRT had a 26% reduction in late grade 2+ GI toxicity compared to 3D-CRT (P=0.099). Additionally, small volumes of the rectum exceeding high threshold radiation doses (i.e., >70 Gy) were associated with nearly a two-fold risk of late grade 2 or greater toxicity. If more than 10% or 15% of the rectum volume exceeded 75 or 70 Gy, respectively, patients had a significantly greater risk of late GI toxicity. After both modality and the dose thresholds were included in the GI toxicity analysis, there was still a separation between the 3D

and IMRT arms at each dose constraint level with a larger, however not statistically significant, separation for the >10% dose constraint groups. Based on these preliminary findings of RTOG 0126, IMRT is associated with a significant reduction in acute grade 2+ GI/GU toxicity and there is a trend for a clinically meaningful reduction in late grade 2+ GI toxicity with IMRT. The occurrence of acute GI toxicity and large (>15%) volumes of rectum >70 Gy are associated with late rectal toxicity. The final results of this trial are pending publication this year.

In September 2017, a national population based study was performed comparing treatment-related toxicity in men who received IMRT versus 3D-CRT for prostate cancer (45). Patients treated for prostate cancer between January 2010 and December 2013 in the English National Health Service were included (N=23,222). A total of 16,289 patients treated with 3D-CRT and 6,933 patients with IMRT. Patients with severe toxicity, defined as at least grade 3 according to the National Cancer Institute Common Terminology Criteria for Adverse Events scoring system were identified. A competing risks regression analysis was used to estimate HRs, comparing the incidence of severe GI and GU complications after IMRT and 3D-CRT, adjusting for patient, disease, and treatment characteristics. The use of IMRT, as opposed to 3D-CRT, increased from 3.1% in 2010 to 64.7% in 2013 in this cohort. Patients who received IMRT were less likely than those receiving 3D-CRT to experience severe GI toxicity [4.9 *vs.* 6.5 per 100 person-years; adjusted HR: 0.66; 95% confidence interval (CI), 0.61–0.72]. Similar rates of GU toxicity were observed (2.3 *vs.* 2.4 per 100 person-years; adjusted HR: 0.94; 95% CI, 0.84–1.06) (45).

Lastly, a meta-analysis of 23 studies (n=9,556) comparing the clinical outcomes, including GI toxicity, GU toxicity, biochemical control and overall survival was performed (46). IMRT was significantly associated with decreased grade 2–4 acute GI toxicity (risk ratio =0.59 (95% CI, 0.44–0.78), late GI toxicity (risk ratio =0.54, 95% CI, 0.38–0.78), late rectal bleeding (risk ratio =0.48, 95% CI, 0.27–0.85), and achieved better bio-chemical control (risk ratio =1.17, 95% CI, 1.08–1.27) in comparison with 3D-CRT (46). IMRT and 3D-CRT remained the same in regard to grade 2–4 acute rectal toxicity (risk ratio =1.03, 95% CI, 0.45–2.36), late GU toxicity (risk ratio =1.03, 95% CI, 0.82–1.30) and overall survival (risk ratio =1.07, 95% CI, 0.96–1.19), while IMRT slightly increased the morbidity of grade 2–4 acute GU toxicity (risk ratio =1.08, 95% CI, 1.00–1.17) (46).

IMRT for pelvic lymph node radiation

A subset of patients with prostate cancer, typically those with high risk disease, may benefit from radiation to the pelvic lymph nodes in addition to the prostate and proximal seminal vesicles. In these situations, the use of IMRT might also be beneficial in reducing toxicity in comparison to 3D-CRT. Although no randomized study has been conducted in prostate cancer comparing 3D-CRT and IMRT techniques in treating the pelvic lymph nodes, some insight can be gained from extrapolating from other disease sites in which pelvic nodal coverage is indicated. For instance, the multi-national TIME-C study enrolled 278 patients with endometrial or cervical cancer and randomized the patients after surgery to IMRT or four-field pelvic radiation treatment and evaluated patients using the Expanded Prostate Cancer Index Composite (EPIC) (47). A preliminary presentation of the toxicity outcomes at ASTRO in 2016 suggested that IMRT reduced GI toxicity including diarrhea and fecal incontinence compared to 3D-CRT (47). Patients receiving IMRT also had smaller declines in EPIC urinary domain scores. Limitations in extrapolating data from this study to patients with prostate cancer includes the fact that patients in TIME-C received prior surgery, a subset received concurrent chemotherapy, and the volumes treated with radiation for gynecological tumors may differ from that for prostate cancer.

Additional insight on IMRT to the pelvic volume may be gained by examining retrospective and single arm prospective studies in prostate cancer. A dosimetric study by Guckenberger *et al.* compared the risk of toxicity using normal tissue complication probability (NTCP) calculations after IMRT to the prostate only compared to additional irradiation of the pelvic lymphatic region in a retrospective cohort of 10 patients (48). They concluded from this planning study that the NTCP model predicted similar risks of rectal (5–8%) and bladder (1%) toxicity after prostate-only or prostate and pelvis IMRT. However the risk of toxicity to the small bowel was estimated to be increased with inclusion of the pelvic volume IMRT to 0.8–3.2%. Deville *et al.* retrospectively compared patients treated with dose-escalated IMRT to 79.2 Gy to the prostate alone or also with 45 Gy by IMRT to the pelvis (49). Although the acute grade 2+ GI toxicity was greater with the inclusion of pelvic radiation (50% *vs.* 13%), there was no difference in late GI or GU toxicity with the addition of pelvic IMRT (49). These estimated risks are also similar to

the observed toxicity reported in a phase 1–2 study of dose-escalated IMRT to the prostate and pelvic nodes reported by Reis Ferreira *et al.* (50). They enrolled 447 patients with locally advanced prostate cancer and treated with IMRT of 70–74 Gy to the prostate and dose escalated IMRT to the pelvic lymph nodes to 50–60 Gy. The 2-year rates of grade 2+ bowel and bladder toxicity in patients receiving conventionally fractionated pelvic IMRT ranged from 8.3–13.2% and 2.9–5.9% respectively. The importance of reducing toxicity is especially important as it is becoming recognized that larger radiation fields such as those extending to L4/L5 may be necessary to adequately cover the lymph node regions commonly involved with prostate cancer metastasis (51).

In the setting of modern dose escalation and androgen depravation therapy, the benefit of pelvic nodal irradiation in patients with unfavorable intermediate risk and high risk prostate cancer is still debatable. RTOG 0924 is an ongoing study investigating the benefit of pelvic radiation in addition to ADT and prostate dose escalation (52). Although both 3D-CRT and IMRT is allowed for the pelvic field, it is expected that most of the patients will be treated with IMRT. Outcomes and toxicity data from this randomized study will better define the benefit and risks of covering the nodal regions with IMRT in prostate cancer.

Future directions

As described above, clinical studies suggest that prostate cancer has biologic characteristics which may make it more sensitive to larger doses per fraction (i.e., hypofractionation) (27,53). These higher doses per fraction may lead to better tumor kill compared to conventional fractionation while offering increased patient convenience from a shorter course of treatment and also fewer burdens on the health care system with decreased treatment costs. The CHHiP trial (a randomized, phase 3, non-inferiority trial) demonstrated that hypofractionated radiotherapy with IMRT using 60 Gy in 20 fractions is non-inferior to conventional fractionation using 74 Gy in 37 fractions and is recommended as a new standard of care for external-beam radiotherapy of localized prostate cancer (54). Further hypofractionation, specifically stereotactic body radiation therapy (SBRT) which uses even larger doses per fraction, are currently under investigation. RTOG 0938 is a randomized phase II trial of hypofractionated radiation therapy for favorable risk prostate cancer in which patients are assigned to either 36.25 Gy in 5 fractions (7.25 Gy per fraction) versus 51.6 Gy in 12 fractions (4.3 Gy per fraction) (55). This protocol requires the use of IMRT or related technologies (i.e., Tomotherapy/VMAT/Cyberknife and proton therapy) given the large doses per fraction and risk to healthy pelvic organs (55).

Additional methods to improve the toxicity profile of IMRT for prostate cancer are the use of a hydrogel spacer. Given that the prostate and rectum are often in immediate physical contact, even the most conformal IMRT plan cannot always spare high dose radiation being delivered to the rectum. An absorbable hydrogel injected between the prostate and rectum has been shown in a randomized trial to have a clinically significant 25% reduction in the rectal V70 Gy in >97% of men, correlating with a reduction in rectal toxicity, improvement in bowel quality of life, and improved sexual function (56-59).

Conclusions

Radiation therapy for prostate cancer has evolved dramatically over the past 2 decades. Treatment has evolved from X-ray fields based on bony anatomy to dose escalated radiation therapy with image-guidance and IMRT. Published dose-volume constraints that can reduce or prevent rectal injury have been established and are achievable with IMRT. Multiple randomized, retrospective, and population based studies have shown that men who receive radiation therapy using IMRT were less likely to experience severe GI toxicity compared with those who received 3D-CRT. The radiobiology of prostate cancer also suggests it may be more responsive to hypofractionated treatment, and IMRT is a method to deliver higher doses per fraction while minimizing dose to organs at risk. Randomized trials investigating extreme hypofractionation (SBRT) are underway.

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Footnote

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