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Original Article

Dose escalation (81 Gy) with image-guided radiation therapy and volumetric-modulated arc therapy for localized prostate cancer: A retrospective preliminary result

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Abstract

Objectives: The objective of the study is to report the acute and late toxicity and preliminary results of localized prostate cancer treated with high-dose radiation therapy (RT). **Materials and Methods:** Between March 2010 and October 2018, a total of 53 patients with clinically localized prostate cancer were treated with definitive RT at our institution. All patients were planned to receive a total dose of 81 Gy with the volumetric-modulated arc therapy technique. Patients were stratified by prognostic risk groups based on the National Comprehensive Cancer Network risk classification criteria. Acute and late toxicities were scored by the Radiation Therapy Oncology Group morbidity grading scales. The definition of biochemical failure was using the 2005 ASTRO Phoenix consensus definition. Median follow-up time was 46.5 months (range: 4.7–81.0 months). **Results:** The 3-year biochemical failure-free survival rates for low-, intermediate-, and high-risk group patients were 100%, 87.5%, and 84%, respectively. The 3- and 5-year overall survival rates were 83% and 62%, respectively. Three (5.6%) patients developed Grade II acute gastrointestinal (GI) toxicity. Four (7.5%) patients developed Grade II acute genitourinary (GU) toxicity, and none experienced Grade III or higher acute GI or GU symptoms. One (1.8%) patient developed Grade II or higher late GI toxicity. Six (11.3%) patients experienced Grade II late GU toxicity. No Grade III or higher late GI and GU complications have been observed. **Conclusions:** Data from the current study demonstrated the feasibility of dose escalation with image-guided and volumetric-modulated arc therapy techniques for the treatment of localized prostate cancer. Minimal acute and late toxicities were observed from patients in this study. Long-term prostate-specific antigen controls are comparable to previously published results of high-dose intensity-modulated RT for localized prostate cancer. Based on this favorable outcome, dose escalation (81 Gy) has become the standard treatment for localized prostate cancer at our institution.

Keywords: *Dose escalation, Image-guided radiation therapy, Prostate cancer, Volumetric modulated arc therapy*

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Introduction

Prostate cancer is one of the most common cancers in males. The incidence and prevalence remain number one in the ranking of male malignancies worldwide. Apart from surgical intervention, external beam radiation therapy (EBRT) is also one of the primary treatment modalities for localized prostate cancer. Several randomized and nonrandomized studies have shown an improvement of tumor local control with the use of higher dose levels when treating prostate cancers [1-6].

Over the years, many studies had reported that intensity-modulated radiation therapy (IMRT) possesses a greater dosimetric advantage in dose conformity while comparing to conventional EBRT treatment such as three-dimensional conformal radiation therapy (3D-CRT) [7,8]. This improvement of dose conformity in treatment planning allowing more sparing for organs at risk (OARs). The avoidance of excessive

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radiation dose to normal tissues or organs not only yields less treatment-related toxicities [9] but also provides possibilities for further dose escalation. Clinical treatment outcomes may improve with IMRT [10-16] and dose escalation due to better tumor control capability. Volumetric-modulated arc therapy or the so-called RapidArc is the latest development in radiation therapy (RT). VMAT allows the RT to be delivered more efficient by utilizing more beam angles hence making reductions in treatment time comparing to IMRT. Studies have also shown that VMAT enables treatment-related side effects to be kept at a reasonable minimum extent [17].

Here, we tried to report the preliminary results of clinical outcomes, treatment-related toxicities, and prostate-specific antigen (PSA) control in patients treated with high-dose (81 Gy) volumetric-modulated arc therapy for localized prostate cancer at our hospital as a single institution's experience.

Materials and methods

Between March 2010 and October 2018, 53 patients with clinically localized prostate cancer were treated with definitive RT at our institution. The median follow-up time for the cohort was 46.5 months (range: 4.7–81.0 months). The median age for this patient cohort was 76 years (range: 56–93 years). Pretreatment diagnostic evaluations include pelvic magnetic resonance imaging, chest X-ray, digital rectal examination, serum PSA concentration, bone scan, transrectal ultrasonography, prostate biopsy, and blood profile. All patients had a histologic diagnosis of prostate adenocarcinoma confirmed by a pathologist at our institution. Patients were stratified by prognostic risk group based on the National Comprehensive Cancer Network (NCCN) risk classification criteria (http://www.nccn.org).

All patients were treated with Varian's RapidArc. Patients were simulated in the supine position. A computed tomography scan was obtained at the time of simulation and images were then transferred to the treatment planning system. Our planning system uses Eclipse anisotropic analytical dose algorithm. The radiation dose delivery uses Varian Trilogy linear accelerator. Treatments were planned with an inverse planning approach with progressive resolution optimizer. All patients received one full arc from 185º to 175º clockwise, and two partial arcs from 90º–185º to 185º–0º counterclockwise. Once the intensity profiles of the VMAT beams were determined, leaf motion files were created, and dose distributions were generated. The treatment was delivered with 10-MV photons in daily fractions of 1.8 Gy. Patient's positions were verified with daily on-board-image, and weekly cone-beam computed tomography. The total RT dose of 81Gy was prescribed to the high-risk region and 45 Gy to the subclinical regional lymphatic drainage area. A clinical target volume includes prostate gland, seminal vesicles, and pelvic regional lymph nodes. Pelvic regional lymph nodes were contoured for patients who have ≥15% of pelvic lymph node risk, which was calculated by Roach's formula [18]. A planning target volume (PTV) was contoured with a 0.7 cm margin in all directions except posterior margin at the prostate-rectal interface, where the margin was reduced to 0.5 cm. The bowels, rectum, bilateral femoral heads, and bladder were contoured as critical normal organ structures. Patients should evacuate bladders before their treatments. Dose constraints were placed on the following normal organ structures: bowels, rectum, bladder, bilateral femoral heads, and PTV. Maximum point dose was limited to 53 Gy for the small bowel, 60 Gy for the large bowel, 68 Gy for the bilateral femoral heads, ≤103.5% of total volume for the rectal wall, and ≤107% of total volume for the bladder wall. We limited no more than 30% of the rectal wall to 75.6 Gy (V75.6 ≤30%) and no more than 53% of the bladder wall to 47 Gy (V47 ≤53%). The dose distributions were normalized such that the maximum dose to the PTV did not exceed 110% of the prescribed dose.

Acute gastrointestinal (GI), genitourinary (GU), and skin toxicities were scored by RT Oncology Group Acute Radiation Morbidity Scoring Criteria (http://www.rtog. org/researchassociates/adverseeventreporting/acuteradiationm orbidityscoringcriteria. aspx). Late GI and GU toxicities were scored by RTOG/EORTC Late Radiation Morbidity Scoring Schema (http://www.rtog.org/ResearchAssociates/AdverseEventReporting/RTOGEORTCLateRadiationMorbidityScoringSchema.aspx). Acute toxicities were defined as beginning from the start of treatment and lasting until 3 months' post-RT. Late toxicities were defined as occurring after 3 months' post-RT. Late toxicity was scored according to the RTOG morbidity grading scale.

The database was closed for analysis in October 2018. All endpoints were calculated from the date of radiation treatment completion. Biochemical failure was defined using the 2005 RTOG-ASTRO Phoenix Consensus definition of the nadir PSA concentration plus 2 ng/mL [19-21]. The cause of death was recorded for all patients who died during the analysis. If death was secondary to prostate cancer with clear evidence or the patient had metastatic disease with elevation of PSA at the time of death, then it is denoted as prostate cancer-specific death, or it will be referred to as sensor.

Androgen deprivation therapy (ADT) was prescribed at the discretion of the treating physician and/or the conclusion of tumor board conference. In general, a 6-month course of ADT (3 months' neoadjuvant + 3 months' concurrent) was given to patients in intermediate-risk groups. A 6-month–2-year ADT course was given to patients in high or greater risk groups. Six patients in the entire cohort study did not show any records of ever receiving ADT at any time. With majority (47 patients; 88.6%) of the patients received ADT, most of them received ADT for more than 6 months. Patients lost follow-up were censored at the time of their last follow-up observation. Biochemical relapse-free survival rates were defined as surviving without biochemical relapse and calculated using actuarial analyses. Those people whose death was not related to cancer would count as censored. Biochemical relapse-free survival curves were assessed using the Kaplan–Meier method. Predictors of treatment outcome examined by univariate and multivariate analyses with the Cox proportional hazards regression model. Statistical significance was achieved when $P < 0.05$. We used Rstudio 1.1.463 for all statistics.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of the institute. Written informed consent

was obtained from all patients before their enrollment in this study. The protocol is approved by the Research Ethics Committee of Hualien Tzu Chi Hospital, Buddhist Tzu Chi Foundation on October 31, 2018. The committee is under, and operates in accordance with, the Good Clinical Practice Guidelines and government laws and regulations (REC No. IRB 107-216-B).

Results

Fifty-three patients with clinically localized prostate cancer between March 2010 and October 2018 were treated with definitive RT at our institution [Table 1]. Majority (51 patients; 96.2%) of the patients in this cohort were older than the age of 60 years when diagnosed of prostate cancer. Thirteen and sixteen patients have T stage 2b-2c and tumor T stage ≥3a, respectively, whereas 24 (45.3%) patients have tumor T stage ≤2a. For Gleason Score classification, 32 (60.3%) patients have scores below 7, and 12 (22.6%) patients have scores above 7. More than half (52.8%) of the patients had pretreatment PSA over 20 ng/mL. Five (9.4%) patients, 9 (16.9%) patients, and 39 (73.5%) patients belong to low-, intermediate-, and high-risk group according to the NCCN classification, respectively. With the majority (47 patients; 88.6%) of the patients received ADT, most (43 patients; 81.1%) of them received ADT for more than 6 months.

Overall survival/cancer-specific survival

A total of 13 patients passed away during this retrospective study. Prostate cancer-related deaths were noted on four patients, one of them belongs to intermediate risk, and the rest belong to high. The 3- and 5-year overall survival rates for all patients are 83% and 68%, respectively [Figure 1]. The 3- and 5-year cancer-specific survival rates for all patients are 97.7% and 90.7%, respectively [Figure 2].

Biochemical failure-free survival

The 3-year biochemical failure-free survival according to the 2005 RTOG-ASTRO Phoenix consensus definition of the nadir PSA concentration plus 2 ng/mL was 100%, 87.5% and 84% for the low-, intermediate-, and high-risk groups, respectively [Figure 3].

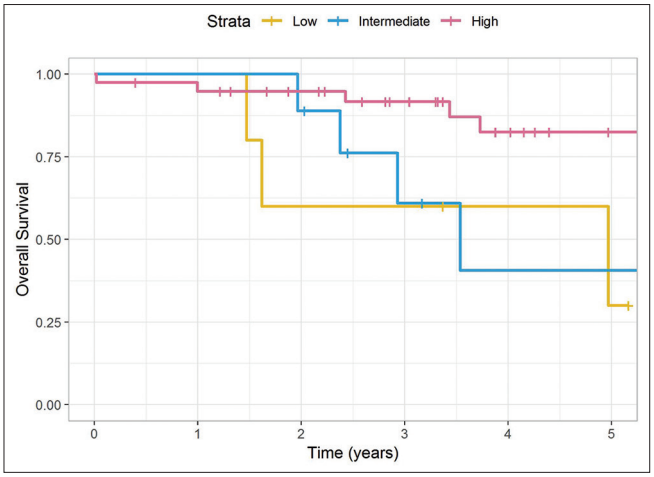

Figure 1: Overall survival according to low-, intermediate-, and high-risk prostate cancer. Univariate analysis showed a significant difference (P = 0.03), while multivariate analysis did not

Acute and late toxicity

The acute side effects of radiotherapy in this cohort were well tolerated. Acute grade I GU toxicity occurred in 10 (18.8%) patients, whereas 4 (7.5%) patients experienced Grade II GU toxicity. There were no patients experienced Grade III or higher acute GU side effects. Acute Grade I and Grade II GI toxicities were noted in 11 (20.7%) and 3 (5.6%) patients, respectively. No patient suffered from acute GI toxicity more severe than Grade II. Grade I skin toxicity occurred in 3 (5.6%) patients, whereas no patient experienced Grade II or higher skin toxicity [Table 2].

According to late toxicity, the result was also acceptable. Forty-one (77.3%) and 46 (86.7%) patients experienced no late GI or GU toxicity, respectively. Grade I late GI toxicity was identified in 6 (11.3%) patients, and 1 patient had Grade II late GI toxicity. No patients experienced GI side effects beyond Grade II. Six (11.3%) patients with Grade I late GU toxicity were noted, and another 6 (11.3%) patients experienced Grade II late GU toxicity. One of the patients with Grade II late GU toxicity had intermittent macroscopic hematuria, where others had experienced only moderate frequency. The volume of the bladder wall to receive a dose of 47 Gy for this patient was 59.3%, and the maximum point dose of total volume for the rectal wall was 107.7%, which were both beyond the dose constraint from our institute. There was no late GU toxicity beyond Grade II [Table 2]. Intermittent macroscopic hematuria usually resolved after medication or sometimes relieved spontaneously.

Table 1: Patient characteristics

Patient characteristics	*n* (%)
Age (y/o) (year)	
Median	75
Range	56-93
T stage	
≤T2a	22 (47.8)
T2b-T2c	12 (26.1)
≥T3a	12 (26.1)
Gleason score	
≤6	30 (65.2)
7	5 (10.9)
≥8	11 (23.9)
Pretreatment PSA (ng/mL)	
<10	11 (23.9)
10-20	25 (54.3)
>20	10 (21.8)
Risk group	
Low	6 (13)
Intermediate	5 (10.9)
High	35 (76.1)
Androgen deprivation therapy	
Yes	38 (82.6)
No	8 (17.4)

PSA: Prostate-specific antigen

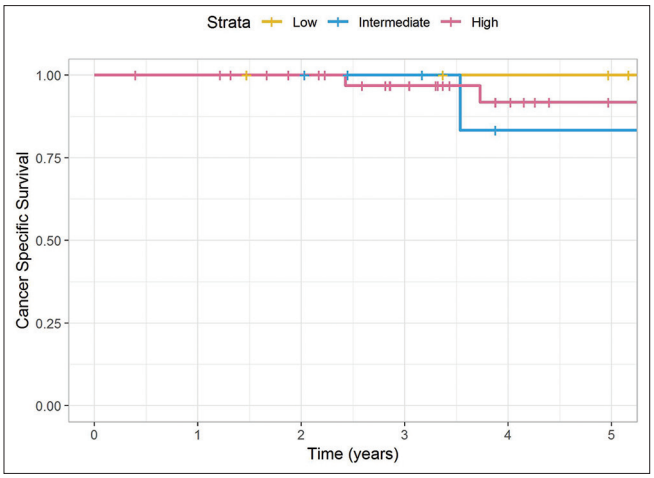

Figure 2: Cancer-specific survival according to low-, intermediate-, and high-risk prostate cancer. Univariate analysis showed no significant difference

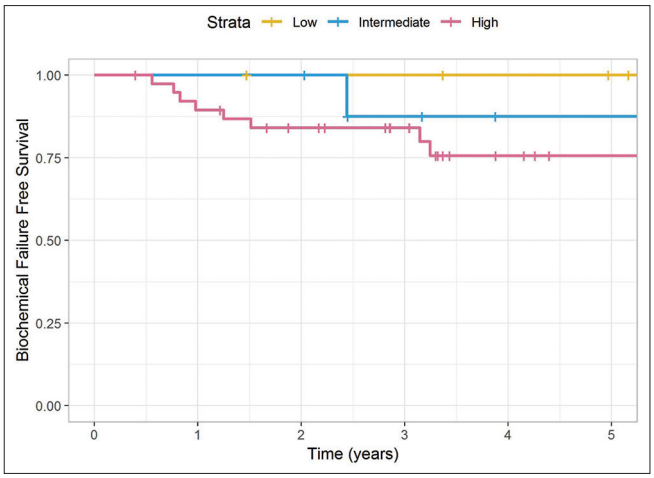

Figure 3: Biochemical failure-free survival according to low-, intermediate-, and high-risk prostate cancer. Univariate analysis showed no significant difference

Table 2: Toxicity by grade according to skin, genitourinary, and gastrointestinal

	Grade 0 (%)	Grade I (%)	Grade II (%)	Grade III (%)	Grade IV (%)	Grade V (%)
Acute toxicity						
Skin	50 (94.3)	3 (5.6)	0 (0)	0 (0)	0 (0)	0 (0)
GU	39 (73.5)	10 (18.8)	4 (7.5)	0 (0)	0 (0)	0 (0)
GI	39 (73.5)	11 (20.7)	3 (5.6)	0 (0)	0 (0)	0 (0)
Late toxicity						
Skin	53 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
GU	41 (77.3)	6 (11.3)	6 (11.3)	0 (0)	0 (0)	0 (0)
GI	46 (86.7)	6 (11.3)	1 (1.8)	0 (0)	0 (0)	0 (0)

GU: Genitourinary, GI: Gastrointestinal

Univariate and multivariate analyses showed no factors statistically significant for overall survival, cancer-specific survival, and biochemical failure-free survival. The hazard ratio for intermediate risk to low risk is 0.44, and for high risk to low risk is 0.11, though *P* value showed no statistically significant [Table 3].

Discussion

This study is the first time in Taiwan to evaluate the feasibility of dose escalation using VMAT with image-guided RT (IGRT) for localized prostate cancer. This report represents the preliminary result of our experience over the past years. There are a few of institutions in Taiwan utilizing definitive RT to treat prostate cancers for a total dose beyond 80 grays. Our data showed that dose escalation to a level of 81 Gy with VMAT and IGRT for localized prostate cancer is well-tolerated with acceptable treatment-related toxicities.

By choosing more conformal techniques, a higher dose of radiation may be feasible for treating prostate cancer. In a prospective dose escalation trial conducted by the RTOG using 3D-CRT (RTOG 9406), the incidence of late toxicity was significantly lower than expected based on controls with conventional 2D techniques. IMRT employ variable intensity across multiple radiation beams leading to the construction of highly conformal dose distributions. This technique is achieved by further dividing each radiation beam into smaller radiation beamlets and varying the individual intensities of these beamlets. IMRT also can produce inhomogeneous dose distributions, which allows the simultaneous delivery of different doses per fraction to separate areas within the target volume. IMRT could facilitate localized dose escalation strategies without increasing total treatment time, which may have the potential radiobiological benefit of reducing the impact of accelerated repopulation in tumor clonogen [22,23]. One of the most common tumor sites treated with IMRT worldwide is prostate cancer. The use of IMRT allows dose escalation, which has been shown to improve clinical outcomes while simultaneously reducing toxicity by improved OAR sparing [1,8,11,24-30].

More recently, there has been increasing interests in a novel radiation technique called arc-based or rotational therapies in the attempt to overcome some of the limitations associated with fixed-field IMRT. The basic concept of arc therapy is the delivery of radiation from a continuous rotation of the radiation source and allows the patient to be treated from full 360º beam angles. Arc therapy such as VMAT can achieve highly conformal dose distributions with improved target volume coverage and more sparing of nearby normal organs and/or tissues comparing to conventional radiotherapy techniques (3D-CRT or IMRT). VMAT also has the potential to offer additional advantages including greatly reduced treatment delivery time when comparing with conventional static field radiotherapy such as IMRT, thus serves as an alternative form to IMRT. IGRT involves the incorporation of image-checking before and/or during treatment to enable more precise position verification

Table 4: The treatment outcome and toxicities comparing with previous study

Study	Free from failure/biochemical-free survival (%)	Overall survival (%)	Toxicity (Grade II or greater) (%)
Thames *et al*. (2003) 78 Gy [20]	5-year 78	5-year 78	GI 26
			GU 13
Peeters *et al*. (2006) 78 Gy [3]	5-year 66	5-year 83	GI 32
			GU 39
Pollack *et al*. (2004) 78 Gy [30]	5-year 79	5-year 91	-
Zelefsky *et al* (2008) 81 Gy [36]	5-year 66	7-year 84	-
Shiraishi *et al* (2014) 76 Gy [29]	5-year	-	GI 4
	Low 100		GU 10
	Intermediate 91.8		
	High 85.3		
Huang *et al*. 81 Gy	3-year	3-year 83	GI 1.8
	Low 100	5-year 68	GU 11.3
	Intermediate 87.5		
	High 84		

GU: Genitourinary, GI: Gastrointestinal

and to allow improvement for the treatment target accuracy. Since VMAT can shorten the treatment delivery time substantially, employing IGRT techniques has become more feasible during daily busy clinical settings.

Shiraishi *et al*. had reported preliminary data regarding their experience in using VMAT for the treatment of localized prostate cancer at the University of Tokyo Hospital in Japan [29]. In their study, they divided patients into two-dose groups (≤72 Gy and 76 Gy). Their results showed 2 (1%) patients developed acute Grade II or higher GI toxicity. Thirty-nine (19%) patients developed acute Grade II GU symptoms. Six (3%) patients developed late Grade II GI toxicity such as rectal bleeding. Two (1%) patients experienced Grade III GI toxicity requiring either one or more blood transfusions or a laser cauterization procedure. No Grade IV or higher GI complications have been observed. Twenty (10%) patients experienced late Grade II GU toxicity, and no one developed Grade III GU toxicity. The 5-year actuarial PSA relapse-free survival rate for low-, intermediate-, and high-risk group was 100%, 91.8%, and 85.3%, respectively [Table 4].

In our preliminary report, most patients treated at our institution belonged to high-risk group with a total of 73.5% belonged to this group. The 3- and 5-year overall survival rate for our entire cohort was 83% and 62%, respectively. The 3-year actuarial PSA relapse-free survival rate for low-, intermediate-, and high-risk group was 100%, 87.5%, and 84%, respectively.

It has been reported that excellent long-term PSA control could be achieved when using the dose between 78 and 81 Gy. The average 5-year actuarial PSA relapse-free survival rates according to the nadir plus 2 ng/mL definition were around 100%, 87.5%, and 76.5% for the low-, intermediate-, and high-risk groups, respectively. Initial studies had suggested that higher doses were only being advantageous for intermediate- and high-risk patients [4]. However, some investigators have shown that low-risk patients may also be beneficial from dose escalation [2,6,30-34]. Our report shows excellent PSA control across all the risk groups.

Eade *et al*. have actively advocated for the use of doses exceeded 80 Gy for localized prostate cancer [35]. They believed that when total doses exceeded 80 Gy could result in better local control and ultimately lead to less chance of distant failures than those who received below 80 Gy. In their report, an additional Gy in this dose range could decrease the risk of PSA relapse by 2.2%. Cahlon *et al*. reported that most patients could benefit from treatment when doses were at least 80 Gy and that the plateau on the dose-response curve for prostate cancer lies well above 80 Gy [16].

Table 3: Univariate and multivariate analysis for overall survival

Variable	Univariate analysis		Multivariate analysis	
	OR	*P*	OR	*P*
Risk				
Low	1.00	0.03		0.1
Intermediate	0.71		0.44	
High	0.21		0.119	
Age (years-old)				
<80	1.00	0.2	1.00	0.28
≥80	2.17		1.92	
Gleason score				
≤7	1.00	0.8		-
>7	1.19			
Stage group				
Stage I-IIB	1.00	0.2	1.00	0.69
Stage III-IV	0.28		1.28	
Biochemical failure				
Yes	1.00	0.6		-
No	1.36			

OR: Odds ratio

As a retrospective study, we acknowledged that there may have some selection biases. Patients with a poorer general condition or higher risk of developing comorbidities may have been advised to receive other treatment modalities or may have been treated to a more conventional dose range. Furthermore, toxicity was evaluated by an individual physician's discretion, which has some inherent limitations. Longer follow-up period will be needed to determine the durability of tumor control and the full extent of late effects in this cohort of patients. Only by conducting a randomized trial for such a dose range may be

able to determine the real possible benefit of dose escalation for localized prostate cancer patients.

Conclusions

With VMAT technique and IGRT, dose escalation for prostate cancer treatment not only can maintain its advantage of treatment outcome but also can increase patients' quality of life during treatment. The VMAT and IGRT techniques should become a trend for dose-escalating treatment in prostate cancer, while further outcome should be confirmed in randomized control trial.

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Conflicts of interest

There are no conflicts of interest.

References

1. Dearnaley DP, Sydes MR, Graham JD, Aird EG, Bottomley D, Cowan RA, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: First results from the MRC RT01 randomised controlled trial. Lancet Oncol 2007;8:475-87.
2. Hanks GE, Hanlon AL, Epstein B, Horwitz EM. Dose response in prostate cancer with 8-12 years follow-up. Int J Radiat Oncol Biol Phys 2002;54:427-35.
3. Peeters ST, Heemsbergen WD, Koper PC, van Putten WL, Slot A, Dielwart MF, et al. Dose-response in radiotherapy for localized prostate cancer: Results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. J Clin Oncol 2006;24:1990-6.
4. Pollack A, Zagars GK, Smith LG, Lee JJ, von Eschenbach AC, Antolak JA, et al. Preliminary results of a randomized radiotherapy dose-escalation study comparing 70 Gy with 78 Gy for prostate cancer. J Clin Oncol 2000;18:3904-11.
5. Zelefsky MJ, Leibel SA, Gaudin PB, Kutcher GJ, Fleshner NE, Venkatramen ES, et al. Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. Int J Radiat Oncol Biol Phys 1998;41:491-500.
6. Zietman AL, DeSilvio ML, Slater JD, Rossi CJ Jr., Miller DW, Adams JA, et al. Comparison of conventional-dose vs. high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: A randomized controlled trial. JAMA 2005;294:1233-9.
7. Ling CC, Burman C, Chui CS, Kutcher GJ, Leibel SA, LoSasso T, et al. Conformal radiation treatment of prostate cancer using inversely-planned intensity-modulated photon beams produced with dynamic multileaf collimation. Int J Radiat Oncol Biol Phys 1996;35:721-30.
8. De Meerleer GO, Vakaet LA, De Gersem WR, De Wagter C, De Naeyer B, De Neve W. Radiotherapy of prostate cancer with or without intensity modulated beams: A planning comparison. Int J Radiat Oncol Biol Phys 2000;47:639-48.
9. Zelefsky MJ, Fuks Z, Happersett L, Lee HJ, Ling CC, Burman CM, et al. Clinical experience with intensity modulated radiation therapy (IMRT) in prostate cancer. Radiother Oncol 2000;55:241-9.
10. Jani AB, Su A, Correa D, Gratzle J. Comparison of late gastrointestinal and genitourinary toxicity of prostate cancer patients undergoing intensity-modulated versus conventional radiotherapy using localized fields. Prostate Cancer Prostatic Dis 2007;10:82-6.
11. De Meerleer GO, Fonteyne VH, Vakaet L, Villeirs GM, Denoyette L, Verbaeys A, et al. Intensity-modulated radiation therapy for prostate cancer: Late morbidity and results on biochemical control. Radiother Oncol 2007;82:160-6.
12. Teh BS, Mai WY, Uhl BM, Augspurger ME, Grant WH 3rd, Lu HH, et al. Intensity-modulated radiation therapy (IMRT) for prostate cancer with the use of a rectal balloon for prostate immobilization: Acute toxicity and dose-volume analysis. Int J Radiat Oncol Biol Phys 2001;49:705-12.
13. Vora SA, Wong WW, Schild SE, Ezzell GA, Halyard MY. Analysis of biochemical control and prognostic factors in patients treated with either low-dose three-dimensional conformal radiation therapy or high-dose intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2007;68:1053-8.
14. Kupelian PA, Willoughby TR, Reddy CA, Klein EA, Mahadevan A. Hypofractionated intensity-modulated radiotherapy (70 Gy at 2.5 Gy per fraction) for localized prostate cancer: Cleveland clinic experience. Int J Radiat Oncol Biol Phys 2007;68:1424-30.
15. Zelefsky MJ, Chan H, Hunt M, Yamada Y, Shippy AM, Amols H, et al. Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. J Urol 2006;176:1415-9.
16. Cahlon O, Zelefsky MJ, Shippy A, Chan H, Fuks Z, Yamada Y, et al. Ultra-high dose (86.4 Gy) IMRT for localized prostate cancer: Toxicity and biochemical outcomes. Int J Radiat Oncol Biol Phys 2008;71:330-7.
17. Pesce GA, Clivio A, Cozzi L, Nicolini G, Richetti A, Salati E, et al. Early clinical experience of radiotherapy of prostate cancer with volumetric modulated arc therapy. Radiat Oncol 2010;5:54.
18. Roach M 3rd, DeSilvio M, Lawton C, Uhl V, Machtay M, Seider MJ, et al. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. J Clin Oncol 2003;21:1904-11.
19. Consensus statement: Guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel. Int J Radiat Oncol Biol Phys 1997;37:1035-41.
20. Thames H, Kuban D, Levy L, Horwitz EM, Kupelian P, Martinez A, et al. Comparison of alternative biochemical failure definitions based on clinical outcome in 4839 prostate cancer patients treated by external beam radiotherapy between 1986 and 1995. Int J Radiat Oncol Biol Phys 2003;57:929-43.
21. Roach M 3rd, Hanks G, Thames H Jr., Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO phoenix consensus conference. Int J Radiat Oncol Biol Phys 2006;65:965-74.
22. Wu Q, Mohan R, Morris M, Lauve A, Schmidt-Ullrich R. Simultaneous integrated boost intensity-modulated radiotherapy for locally advanced head-and-neck squamous cell carcinomas. I: Dosimetric results. Int J Radiat Oncol Biol Phys 2003;56:573-85.
23. Mohan R, Wu Q, Manning M, Schmidt-Ullrich R. Radiobiological considerations in the design of fractionation strategies for intensity-modulated radiation therapy of head and neck cancers. Int J Radiat Oncol Biol Phys 2000;46:619-30.
24. Guerrero Urbano MT, Nutting CM. Clinical use of intensity-modulated radiotherapy: Part I. Br J Radiol 2004;77:88-96.
25. Zelefsky MJ, Fuks Z, Hunt M, Yamada Y, Marion C, Ling CC, et al. High-dose intensity modulated radiation therapy for prostate cancer: Early toxicity and biochemical outcome in 772 patients. Int J Radiat Oncol Biol Phys 2002;53:1111-6.
26. Zelefsky MJ, Levin EJ, Hunt M, Yamada Y, Shippy AM, Jackson A, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2008;70:1124-9.
27. Zelefsky MJ, Yamada Y, Fuks Z, Zhang Z, Hunt M, Cahlon O, et al. Long-term results of conformal radiotherapy for prostate cancer: Impact of

dose escalation on biochemical tumor control and distant metastases-free survival outcomes. Int J Radiat Oncol Biol Phys 2008;71:1028-33.

28. Kupelian PA, Reddy CA, Carlson TP, Altsman KA, Willoughby TR. Preliminary observations on biochemical relapse-free survival rates after short-course intensity-modulated radiotherapy (70 Gy at 2.5 Gy/fraction) for localized prostate cancer. Int J Radiat Oncol Biol Phys 2002;53:904-12.
29. Shiraishi K, Yamamoto K, Haga A, Sakumi A, Nakagawa K. Volumetric modulated arc therapy (VMAT) in the treatment of localized prostate cancer: Initial experience in 200 patients. Int J Radiat Oncol Biol Phys 2014;90(Suppl 2564):S436.
30. Pollack A, Hanlon AL, Horwitz EM, Feigenberg SJ, Uzzo RG, Hanks GE, et al. Prostate cancer radiotherapy dose response: An update of the fox chase experience. J Urol 2004;171:1132-6.
31. Zelefsky MJ, Fuks Z, Hunt M, Lee HJ, Lombardi D, Ling CC, et al. High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer. J Urol 2001;166:876-81.
32. Kuban DA, Thames HD, Levy LB, Horwitz EM, Kupelian PA, Martinez AA, et al. Long-term multi-institutional analysis of stage T1-T2 prostate cancer treated with radiotherapy in the PSA era. Int J Radiat Oncol Biol Phys 2003;57:915-28.
33. Kupelian PA, Buchsbaum JC, Reddy CA, Klein EA. Radiation dose response in patients with favorable localized prostate cancer (Stage T1-T2, biopsy Gleason < or = 6,, and pretreatment prostate-specific antigen < or = 10). Int J Radiat Oncol Biol Phys 2001;50:621-5.
34. Symon Z, Griffith KA, McLaughlin PW, Sullivan M, Sandler HM. Dose escalation for localized prostate cancer: Substantial benefit observed with 3D conformal therapy. Int J Radiat Oncol Biol Phys 2003;57:384-90.
35. Eade TN, Hanlon AL, Horwitz EM, Buyyounouski MK, Hanks GE, Pollack A, et al. What dose of external-beam radiation is high enough for prostate cancer? Int J Radiat Oncol Biol Phys 2007;68:682-9.
36. Zelefsky MJ, Yamada Y, Fuks Z, Zhang Z, Hunt M, Cahlon O, Park J, Shippy A, et al. Long-term results of conformal radiotherapy for prostate cancer: Impact of dose escalation on biochemical tumor control and distant metastases-free survival outcomes. Int J Radiat Oncol Biol Phys. 2008 Jul 15;71:1028-33.