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Scientific Article

A Phase I/II Trial of Fairly Brief Androgen Suppression and Stereotactic Radiation Therapy for High-Risk Prostate Cancer (FASTR-2): Preliminary Results and Toxicity Analysis

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Abstract

Purpose: FASTR was designed to provide a compact treatment course for high-risk prostate cancer patients but was discontinued because of excess toxicity. We present the results of FASTR-2, which used a lower dose to the prostate (35 Gy vs 40 Gy), smaller posterior PTV margin (4 mm vs 5 mm) and omitted nodal radiation to lower the volumes of rectum receiving high and intermediate doses compared with FASTR. Gastrointestinal (GI) and genitourinary (GU) toxicities at baseline, 6 weeks, 6 months, and 1 year and biochemical control rates are presented.

Methods and Materials: Eligibility included high-risk prostate cancer (cT3/4, prostate-specific antigen >20 or Gleason Score ≥8), age ≥70 or refused standard treatment, and no evidence of metastatic disease. Patients received 18 months of androgen deprivation therapy starting 2 months before radiation. Clinical target volume was defined as prostate plus proximal 1-cm seminal vesicles. PTV was a nonuniform expansion around clinical target volume (4 mm posteriorly, 5 mm in all other directions). Volumetric arc therapy was used for treatment delivery (35 Gy delivered in 5 weekly fractions of 7 Gy each), and cone beam computed tomography with soft tissue matching (no fiducial placement) was used for daily image guidance. Toxicity was assessed at 6 weeks, 6 months, and 1 year according to Common Toxicity Criteria.

Results: In the study, 30 patients were enrolled in FASTR-2 between 2015 and 2017. Two patients were withdrawn owing to ineligibility after enrollment. One patient (3.7%) reported grade 2 GI toxicity at 6 weeks. There was no reported grade ≥2 GI toxicity at 6 months or 1 year. There were no reported episodes of rectal bleeding. Four patients (14.8%), 5 patients (17.9%), and 5 patients (21.7%) reported grade 2 GU toxicity at 6 weeks, 6 months, and 1 year, respectively. There were no reported cases of grade ≥3 GU toxicity. The most common toxicities were nocturia and urinary frequency or urgency.

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Conclusions: FASTR-2 was more tolerable than FASTR, with no grade ≥3 toxicities reported, in keeping with expectations based on our previous FASTR analysis. Long-term follow-up is necessary to ensure disease control and toxicity outcomes are comparable to conventional high-risk treatment paradigms.

Introduction

Biochemical control and disease-free survival in high-risk prostate cancer are improved with radical radiation combined with adjuvant androgen deprivation compared with either treatment alone.[1,2] Although effective, this regimen can be very demanding, especially on elderly or frail patients. Growing evidence suggests that prostate cancer has a lower α-to-β ratio than most solid tumors and may benefit from hypofractionation.[3] Ultra-hypofractionation in the form of stereotactic ablative radiation (SABR) has been shown to be tolerable in the low- and intermediate-risk groups;[4-8] however, the optimal protocol for treating high-risk prostate cancer with SABR has yet to be established.

Short course radiation combined with androgen deprivation therapy (ADT) was explored in the FASTR trial,[9] where patients received 12 months of ADT along with radiation to the prostate (40 Gy/5 fractions delivered weekly) and pelvic lymph nodes (25 Gy/5 fractions delivered weekly). This study was discontinued after accrual of 16 patients owing to an unacceptable rate of acute and late toxicities including one grade 4 gastrointestinal (GI) toxicity. It was thought that the rate of toxicity likely reflected the high rectal, small bowel, and bladder doses secondary to the large prescription dose to prostate and the inclusion of pelvic nodal irradiation.

The present study was designed with consideration of these previous toxicities and used a lower dose to the prostate (35 Gy/5 weekly fractions). Given the uncertainty in survival benefit of pelvic nodal irradiation in prostate cancer,[10,11] it was decided to omit pelvic lymph node irradiation. Furthermore, recent evidence has shown equivalence of 18 months compared with 36 months of ADT,[12] and we decided to lengthen the duration of ADT to 18 months.

The aim of this phase I/II study is to prospectively establish the safety and side effect profile of a novel stereotactic, ultra-hypofractionated radiotherapy approach to the prostate alone combined with 18 months of ADT for the treatment of high-risk prostate cancer. The secondary outcome of biochemical disease-free survival is also examined.

Methods and Materials

Patients were eligible for the study if they had at least 1 high-risk feature as described by the National Comprehensive Cancer Network criteria for high-risk prostate cancer (cT3/4, prostate-specific antigen [PSA] >20 or Gleason Score ≥ 8 based on transrectal ultrasound guided biopsy), no evidence of metastatic disease on computed tomographic (CT) scan of the pelvis or on bone scan, and were willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures. Patients were considered for the trial if they met the aforementioned criteria and were over the age of 70 years or declined standard treatment, with standard treatment being defined as 70 Gy in 28 fractions to the prostate and proximal seminal vesicles plus 48 Gy in 28 fractions to the pelvic nodes or 44 Gy in 22 fractions to the prostate, seminal vesicles, and pelvic nodes with a high-dose rate brachytherapy boost of 15 Gy to the prostate. Patients were excluded from the study if they did not meet the eligibility criteria outlined earlier; had received prior pelvic radiotherapy or brachytherapy; were taking anticoagulation; had a history of inflammatory bowel disease, diverticulitis, or collagen vascular disease (other than rheumatoid arthritis); had previous treatment for malignancy (other than basal or squamous cell skin cancer) within 3 years of prostate cancer diagnosis; or were on ADT for >2 months before study enrollment.

Patients consenting for treatment received 18 months of ADT. The preferred regimen was 3, 6-month luteinizing hormone-releasing hormone (LHRH) agonist depot injections (3- or 4-month depots also allowed). Four weeks of antiandrogen therapy was given contemporaneously with the initiation of LHRH agonist. Radiation therapy began 2 months after ADT was initiated.

Patients were instructed on appropriate bowel and bladder preparation for simulation and each treatment to ensure an empty rectum and full bladder. Rectal spacers were not utilized in this study. CT simulation allowed for acquisition of images with a 3-mm slice thickness from L4 superiorly to the ischial tuberosities inferiorly. Resimulation was allowed in the case of unrepresentative anatomy (full rectum or empty bladder). The clinical target volume (CTV) was defined as the prostate plus the proximal 1 cm of the seminal vesicles (at a minimum, entire seminal vesicles could be included if clinically involved). The PTV was a nonuniform expansion around the CTV of 4 mm posteriorly and 5 mm in all other directions. Magnetic resonance imaging was not used for target delineation. The following organs at risk were contoured in keeping with the Radiation Therapy Oncology Group guidelines

Table 1 Planning dose constraints for FASTR-2 and FASTR

Volume	Dose constraint	
	FASTR-2	FASTR[9]
PTV prostate and seminal vesicle	D95 = 35 Gy D5 = 33 Gy Dmax = 38 Gy	D95 = 40 Gy D5 = 42 Gy Dmax = 43 Gy
PTV nodes		D95 = 25 Gy D5 = 28 Gy Dmax = 41 Gy (within 1 cm of high dose volume) Dmax = 28 Gy (outside 1 cm of high dose volume)
Bladder	V26 ≤ 50% V31 ≤ 30%	V29 ≤ 50% V35 ≤ 30%
Rectum	V20 ≤ 60% V24 ≤ 50% V32 ≤ 10% V35 ≤ 2 mL	V27 ≤ 50% V35 ≤ 20%
Small bowel	V27.5 ≤ 2 mL V25 ≤ 190 mL	V27.5 ≤ 2 mL V25 ≤ 190 mL

(www.rtog.org): anus (as a solid organ); rectum (as a solid organ); bladder (as a solid organ); bilateral femoral heads and proximal femurs to the level of the ischial tuberosities; penile bulb; and small bowel. Volumetric-modulated arc therapy was planned with the dose volume histogram (DVH) constraints outlined in Table 1, where the DVH constraints from the original FASTR trial were also listed for comparison. As shown in Table 1, the DVH constraints for organs at risk (OARs) are more restrictive in the FASTR-2 trial than those in the FASTR trial. The tighter DVH constraints for OARs were the results of lower prescription dose (35 Gy instead of 40 Gy), smaller target volume (not including pelvic nodes), smaller posterior PTV margin (4 mm instead of 5 mm), and the analysis of the previous FASTR trial.[13]

Treatments were delivered in 5 fractions, 1 fraction per week for 5 weeks. All plans were verified in phantom before the first treatment fraction with a tolerance of 95% passing rate using gamma parameters, 3% in dose difference, and 3 mm for distance to agreement.

Patients received treatment on a linear accelerator with cone beam CT (CBCT) capabilities. CBCT was obtained before each treatment with automatic and manual soft tissue registration to the prostate. The attending radiation oncologist was responsible for viewing and approving the registration for the first fraction of treatment.

Patients were assessed at baseline and at 6 weeks after treatment. They were assessed at 6 monthly intervals thereafter until 3 years, then yearly. Assessments included measurements of toxicity using the Common Toxicity Criteria version 4.0. Measurements of prostate-specific antigen (PSA) and testosterone were checked at baseline and at each of the postradiotherapy visits. Liver function tests were checked at baseline, 6 weeks, and 6 months after treatment. The study was approved by the university Research Ethics Board.

The primary outcome was the incidence of grade 3 genitourinary (GU) and GI toxicity at 6 weeks, 6 months, and 1 year. Secondary endpoints were biochemical disease-free survival at 1, 2, and 3 years.

An independent data safety monitoring committee reviewed the toxicity data for the initial 15 patients enrolled after 6 months of follow-up.

Dose-volume histogram (DVH) values for FASTR and FASTR-2 were compared using the Wilcoxon signed-rank test. All analyses were performed using R Studio (version 3.4.1). P values $< .05$ were considered statistically significant.

Results

Thirty patients were enrolled in the study between March 2015 and August 2017. Two patients were withdrawn from the study before treatment: 1 patient was found to have pelvic nodal involvement after enrollment and 1 patient had significant stool burden resulting in poor reproducibility of anatomy. Of the 30 patients enrolled, 26 were ≥70 years and 4 were <70 years but declined standard therapy. All patients had high-risk prostate cancer with a PSA >20 ng/mL (n = 12), Gleason grade ≥ 8 (n = 17), or clinical T3 or T4 disease (n = 6). Baseline characteristics are summarized in Table 2. All 28 patients that received treatment were treated according to

Table 2 Baseline patient characteristics

Variable	Total (n = 30)
Age at baseline	76.6 (61-89)
Clinical stage	
T1c	7 (23.3%)
T2	17 (56.7%)
T3	5 (16.7%)
T4	1 (3.3%)
PSA at baseline	25.56 (6.58-98.4)
Gleason score	
6	4 (13.3%)
7	9 (30.0%)
8	9 (30.0%)
9-10	8 (26.7%)
Risk category (based on NCCN criteria)	
High	23 (76.6%)
Very high	7 (23.3%)

Abbreviations: NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen.

Table 3 Summary of GU and GI toxicities

	Baseline (n = 28)	6 weeks (n = 27)	6 months (n = 28)	1 year (n = 23)
Grade 1 GU	10 (35.7%)	15 (55.5%)	17 (60.7%)	15 (65.2%)
Grade 2 GU	1 (3.6%)	4 (14.8%)	5 (17.9%)	5 (21.7%)
Grade 1 GI	3 (10.7%)	8 (29.6%)	12 (42.9%)	9 (39.1%)
Grade 2 GI	0	1 (3.7%)	0	0

Abbreviations: GI = gastrointestinal; GU = genitourinary.

protocol. Median follow-up was 28 months (range, 12-44) from the start of radiation.

In addition, 27 patients were available for toxicity analysis at 6 weeks, 28 patients were available for analysis at 6 months, and 23 patients were available for analysis at 1 year. No grade 3 or higher toxicities were reported at any time point. At baseline, 1 patient (3.5%) had moderate to severe nocturia and no patients had moderate or severe gastrointestinal symptoms. Five patients (18.5%) experienced grade 2 toxicity at 6 weeks after completion of radiation treatment (4 GU and 1 GI). Five patients (17.9%) experienced grade 2 GU toxicity at 6 months, and 5 patients (21.7%) experienced grade 2 GU toxicity at 1 year. There were no instances of grade 2 or higher GI toxicity at 6 months or 1 year. Toxicity data is summarized in Table 3. The most common toxicities experienced were nocturia and urinary frequency or urgency. There were no reported episodes of rectal bleeding at any time point. Of the 23 patients seen at 1-year follow-up, there were no cases of biochemical failure (mean PSA 0.05, maximum PSA 0.23).

Dosimetric constraints to OARs were met in all patients. The rectal maximum dose (D1), D20, and D50, decreased from 40.7 Gy, 29.6 Gy, and 20.8 Gy in FASTR to 35.0 Gy, 22.2 Gy and 11.1 Gy in FASTR-2 ($P < .001$), respectively. The bladder maximum dose (D1), D20 and D50, decreased from 40.9 Gy, 28.1 Gy, and 21.5 Gy in FASTR to 35.7 Gy, 15.7 Gy, and 6.3 Gy in FASTR-2 ($P < .001$), respectively. Dosimetric results are compared in Table 4 between the FASTR-2 and the FASTR trials.

Discussion

FASTR-2 was well tolerated, with no reported grade 3 or higher toxicities. This is in keeping with expectations based on our analysis of the FASTR trial where it was found that higher relative dose volumes to the rectum (V20-40 Gy) was most strongly associated with rectal bleeding.[13] The FASTR-2 protocol was created with stricter dosimetric constraints to the rectum and bladder compared with the original FASTR protocol, in addition to a lower prescribed dose to the PTV and elimination of nodal irradiation. With the implementation of these changes, there were no reported instances of rectal bleeding or of intermediate or late grade 2 or higher GI toxicities and only 1 reported instance of early grade 2 GI toxicity.

The majority of prostate SABR studies have looked at the role of ultra-hypofractionation in low or intermediate risk prostate cancer; only a few studies have looked at the role of SABR in patients with high-risk prostate cancer. The recently published results from the phase 3, randomized HYPO-RT-PC trial[14] show noninferiority of ultra-hypofractionated radiation compared with conventional fractionation for patients with intermediate and high-risk prostate cancer.[14] Patients in the conventional fractionation arm (n = 602) received 78 Gy in 39 fractions and patients in the ultra-hypofractionated arm (n = 598) received 42.7 Gy in 7 fractions delivered every other day. Treatment in both arms was prescribed to the

Table 4 Dosimetric outcomes for FASTR-2 and FASTR

	FASTR-2		FASTR[9]		
	Mean	Range	Mean	Range	P Value
D95 prostate and proximal SV	35.2 Gy	33.7-35.9 Gy	40.2 Gy	40.0-40.7 Gy	<.001
V100 prostate and proximal SV	96.4%	83.8-101.7%	96.3%	95.0-100.0%	.376
D95 nodes			25.2 Gy	24.7-25.4 Gy	n/a
V100 nodes			96.8%	85.1-100.0%	n/a
D1 rectum	35.0 Gy	31.2-36.1 Gy	40.7 Gy	39.7-41.5 Gy	<.001
D20 rectum	22.2 Gy	9.4-32.9 Gy	29.6 Gy	24.1-39.2 Gy	<.001
D50 rectum	11.1 Gy	4.0-22.4 Gy	20.8 Gy	15.3-25.2 Gy	<.001
D1 bladder	35.7 Gy	30.8-36.4 Gy	40.9 Gy	37.6-42.0 Gy	<.001
D20 bladder	15.7 Gy	2.5-33.3 Gy	28.1 Gy	23.5-36.5 Gy	<.001
D50 bladder	6.3 Gy	0.7-22.2 Gy	21.5 Gy	15.3-26.2 Gy	<.001

SV = Seminal vesicles.

prostate only with a 7-mm PTV expansion using fiducial markers for image guidance. Five year biochemical and clinical control rates were 83.8% and 83.7% for the conventional fractionation and ultra-hypofractionation arms, respectively. Furthermore, physician reported late grade 2 or higher toxicity was not significantly different between the 2 arms.

Two previous prospective phase I/II trials have explored the role of SABR to prostate and elective nodal volumes. Both the SATURN (Stereotactic Ablative Radiotherapy Including Regional Lymph Node Irradiation) and FASTR trials prescribed 40 Gy in 5 fractions to the prostate and 25 Gy in 5 fractions to the regional lymph nodes; however, these 2 studies had very different toxicity outcomes.[9,15] FASTR was terminated during phase I owing to excess late GI toxicities; whereas within SATURN, minimal GI toxicities were noted. A detailed dosimetric analysis of the 2 studies allowed for identification of a correlation between higher dose ($\geq$20 Gy/5 fractions) volumes to the rectum and GI toxicity.[13] FASTR defined the high-dose volume to include the prostate and the proximal 1 cm of seminal vesicle, with a 5-mm expansion from CTV to PTV. SATURN, on the other hand, defined their high dose volume to include only the prostate and used fiducial markers to allow for a 3-mm expansion from CTV to PTV. Furthermore, in FASTR, radiation was prescribed such that 95% of the high-dose PTV received at least 40 Gy; whereas in SATURN, radiation was prescribed such that 99% of the high-dose PTV received at least 33.25 Gy. These variations in protocol are thought to explain the increased rectal dose and increased rectal toxicity experienced in the FASTR trial.

Other prospective trials have explored the role of SABR for localized high-risk prostate cancer either as monotherapy or in combination with external beam radiotherapy to pelvic nodes.[16-19] Only one of these trials had any reported grade 3 or higher toxicity, with 2 of 18 patients with high-risk prostate cancer treated with EBRT to the pelvic nodes in addition to SBRT boost to the prostate experiencing grade 3 GU toxicity.[17] The 2 studies with the longest follow-up reported biochemical disease free survival of 65% at 8 years[16] and 91.9% at 4 years.[18] In all of these studies, fiducial markers were used for image guidance.

The role of ADT in combination with SABR has not been well established. Extrapolation from ablative dosing with brachytherapy for high-risk prostate cancer does indicate that there may be less benefit to ADT than conventional radiotherapy.[20] Current guidelines continue to recommend ADT in addition to radiation for patients with high-risk prostate cancer, although it is unclear whether this should apply.[21] It should be acknowledged that ADT may increase late GI toxicities.[22]

Limitations of this study include small sample size and lack of randomized control data. The dose prescription used in this study was 35 Gy in 5 fractions prescribed to 95% of the PTV. Although this is a lower dose than reported in similar trials, this dose is in keeping with the recently published American Society for Radiation Oncology (ASTRO)/American Society of Clinical Oncology (ASCO)/American Urological Association (AUA) guidelines on hypofractionated radiotherapy for localized prostate cancer, which recommends 35 to 36.25 Gy in 5 fractions for ultra-hypofractionated EBRT regimens as doses higher than this are associated with increased risk of late toxicity.[23] Pelvic nodes were not included in the treatment field in this study; however, the role of nodal irradiation in high-risk prostate cancer is controversial. The long-term results of the GETUG-01 and RTOG-9413 trials did not show benefit of pelvic nodal irradiation for high-risk prostate cancer patients who were also receiving adjuvant ADT.[10,11] This protocol uses a larger PTV expansion than some similar trials because image guidance was achieved using CBCT without the use of fiducial markers. Fiducial markers have been used in the vast majority of trials studying the use of SABR for prostate cancer; however, it has a number of limitations, including the requirement for local expertise in placing the markers, risks of infection associated with the transperineal procedure, and possibility of marker migration resulting in unreliable image registration and, as such, are not necessarily feasible for all centers or all patients. Biochemical control was achieved in all patients at 1-year follow-up; however, all patients remained on ADT at this timepoint, and therefore longer follow-up is required to determine whether the efficacy of this treatment regimen is comparable to standard treatment for high-risk prostate cancer.

Benefits of the FASTR-2 protocol include a weekly fractionation schedule with only 5 fractions, making this regimen especially appealing for frail patients or patients travelling a long distance for treatment. Prostate directed radical radiation has been shown to improve overall survival in men with low-volume metastatic disease treated with concurrent ADT.[24,25] The FASTR-2 treatment regimen should be similarly well tolerated in this patient population, and the small number of fractions would be desirable in a patient population with known metastatic disease.

Conclusion

The FASTR-2 protocol allows for safe delivery of ultra-hypofractionated radiotherapy to the prostate and seminal vesicles in patients with high-risk prostate cancer without the use of fiducial markers and using a weekly treatment schedule, which is more convenient for some patients. Long term follow-up is required to ensure disease control and toxicity outcomes are comparable to conventional high-risk treatment paradigms.

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References

1. Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): A phase III randomised trial. *Lancet*. 2002;360:103-106.
2. Warde P, Mason M, Ding K, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: A randomised, phase 3 trial. *Lancet*. 2011;378:2104-2111.
3. Miralbell R, Roberts SA, Zubizarreta E, Hendry JH. Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5,969 patients in seven international institutional datasets: $\alpha/\beta = 1.4$ (0.9-2.2) Gy. *Int J Radiat Oncol Biol Phys*. 2012;82:e17-e24.
4. Boike TP, Lotan Y, Cho LC, et al. Phase I dose-escalation study of stereotactic body radiation therapy for low- and intermediate-risk prostate cancer. *J Clin Oncol*. 2011;29:2020-2026.
5. Madsen BL, Hsi RA, Pham HT, Fowler JF, Esagui L, Corman J. Stereotactic hypofractionated accurate radiotherapy of the prostate (SHARP), 33.5 Gy in five fractions for localized disease: First clinical trial results. *Int J Radiat Oncol Biol Phys*. 2007;67:1099-1105.
6. King CR, Brooks JD, Gill H, Presti JC. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. *Int J Radiat Oncol Biol Phys*. 2012;82:877-882.
7. King CR, Freeman D, Kaplan I, et al. Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials. *Radiother Oncol*. 2013;109:217-221.
8. Tang CI, Loblaw DA, Cheung P, et al. Phase I/II study of a five-fraction hypofractionated accelerated radiotherapy treatment for low-risk localised prostate cancer: Early results of pHART3. *Clin Oncol (R Coll Radiol)*. 2008;20:729-737.
9. Bauman G, Ferguson M, Lock M, et al. A Phase 1/2 Trial of Brief Androgen Suppression and Stereotactic Radiation Therapy (FASTR) for High-Risk Prostate Cancer. *Int J Radiat Oncol Biol Phys*. 2015;92:856-862.
10. Pommier P, Chabaud S, Lagrange J-L, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Update of the long-term survival results of the GETUG-01 randomized study. *Int J Radiat Oncol Biol Phys*. 2016;96:759-769.
11. Roach M, Moughan J, Lawton CAF, et al. Sequence of hormonal therapy and radiotherapy field size in unfavourable, localised prostate cancer (NRG/RTOG 9413): Long-term results of a randomised, phase 3 trial. *Lancet Oncol*. 2018;19:1504-1515.
12. Nabid A, Carrier N, Martin AG, et al. Duration of androgen deprivation therapy in high-risk prostate cancer: A randomized phase III trial. *Eur Urol*. 2018;74:432-441.
13. Bauman G, Chen J, Rodrigues G, Davidson M, Warner A, Loblaw A. Extreme hypofractionation for high-risk prostate cancer: Dosimetric correlations with rectal bleeding. *Pract Radiat Oncol*. 2017;7:e457-e462.
14. Widmark A, Gunnlaugsson A, Beckman L, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *The Lancet*. 2019;394:385-395.
15. Musunuru HB, D'Alimonte L, Davidson M, et al. Phase 1-2 study of stereotactic ablative radiotherapy including regional lymph node irradiation in patients with high-risk prostate cancer (SATURN): Early toxicity and quality of life. *Int J Radiat Oncol Biol Phys*. 2018;102:1438-1447.
16. Katz A, Formenti SC, Kang J. Predicting Biochemical disease-free survival after prostate stereotactic body radiotherapy: Risk-stratification and patterns of failure. *Front Oncol*. 2016;6:168.
17. Jabbari S, Weinberg VK, Kaprealian T, et al. Stereotactic body radiotherapy as monotherapy or post–external beam radiotherapy boost for prostate cancer: Technique, early toxicity, and PSA Response. *Int J Radiat Oncol Biol Phys*. 2012;82:228-234.
18. Lin Y-W, Lin L-C, Lin K-L. The early result of whole pelvic radiotherapy and stereotactic body radiotherapy boost for high-risk localized prostate cancer. *Frontiers in Oncology*. 2014;4.
19. Oermann EK, Slack RS, Hanscom HN, et al. A pilot study of intensity modulated radiation therapy with hypofractionated stereotactic body radiation therapy (SBRT) Boost in the treatment of intermediate- to high-risk prostate cancer. *Technol Cancer Res Treat*. 2010;9:453-462.
20. Keyes M, Merrick G, Frank SJ, Grimm P, Zelefsky MJ. American Brachytherapy Society Task Group Report: Use of androgen deprivation therapy with prostate brachytherapy—a systematic literature review. *Brachytherapy*. 2017;16:245-265.
21. Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part II: Recommended Approaches and details of specific care options. *J Urol*. 2018;199:990-997.
22. Hanks GE, Pajak TF, Porter A, et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: The Radiation Therapy Oncology Group Protocol 92-02. *J Clin Oncol*. 2003;21:3972-3978.
23. Morgan SC, Rumble RB, Sandler H. Hypofractionated radiation therapy for localized prostate cancer: An ASTRO, ASCO, and AUA evidence-based guideline summary. *J Oncol Pract*. 2019;15:50-54.
24. Burdett S, Boevé LM, Ingleby FC, et al. Prostate radiotherapy for metastatic hormone-sensitive prostate cancer: A STOPCAP systematic review and meta-analysis. *Eur Urol*. 2019;76:115-124.
25. Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): A randomised controlled phase 3 trial. *Lancet*. 2018;392:2353-2366.