Radiotherapy and Oncology 141 (2019) 144–148

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

MRI assisted focal boost integrated with HDR monotherapy study in low and intermediate risk prostate cancer (MARS): Results from a phase II clinical trial

Yasir Alayed [a,b,c], Laura D'Alimonte [a], Joelle Helou [d], Ananth Ravi [a,b], Gerard Morton [a,b], Hans T. Chung [a,b], Masoom Haider [e], Merrylee McGuffin [a], Liying Zhang [a], Andrew Loblaw [a,b,*]

[a] Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto; [b] Department of Radiation Oncology, University of Toronto, Canada; [c] Division of Radiation Oncology, College of Medicine, King Saud University, Riyadh, Saudi Arabia; [d] Department of Radiation Oncology, University of Toronto, Princess Margaret Cancer Centre, Canada; and [e] Mount Sinai Hospital, Toronto, Canada

ARTICLE INFO

Article history:
Received 2 August 2019
Received in revised form 10 September 2019
Accepted 11 September 2019
Available online 26 September 2019

Keywords:
MRI
HDR
Monotherapy
Dose escalation
DIL

ABSTRACT

Purpose: There is growing concern that single-fraction HDR monotherapy to a dose of 19 Gy is suboptimal for the treatment of localized prostate cancer. We report the results of a phase II prospective trial of single-fraction 19 Gy HDR monotherapy with MRI-guided simultaneous focal boost.

Methods: Eligible patients had low or intermediate risk prostate cancer and an identified lesion on MRI. TRUS based single-fraction HDR monotherapy with MRI fusion was delivered. The dose prescribed was 19 Gy to the prostate and ≥23 Gy to the dominant intraprostatic lesion (DIL). ADT was not used. The purpose is to report early efficacy results.

Results: 60 patients were enrolled, with a median follow-up of 39 months. With MRI T-stage incorporated into the risk-group criteria, 8% had low-risk, 35% had favorable intermediate-risk and 57% had unfavorable intermediate-risk disease. The median dose to 90% of the DIL (D90) was 27.2 Gy, and the median prostate V100% was 96.9%. No acute or late grade ≥3 bowel or urinary toxicity was observed. The cumulative BF probability was 15.2% at 36 months and 31.6% at 48 months. All patients that were fully investigated had local failure only, and 88% of the local failures were at the site of original DIL. The median PSA nadir was 0.79 ng/ml, with a median time to nadir of 32 months.

Conclusions: Focal boost to the MRI-specified gross tumor was well tolerated, but did not adequately improve local control. Single-fraction HDR monotherapy to 19 Gy for prostate cancer provides suboptimal local control, and should not be offered outside of clinical trials.

There is now clear evidence of improved biochemical disease free survival (bDFS) with radiotherapy dose-escalation in all prostate cancer (PCa) risk groups [1,2]. Despite the advent of new techniques, external beam radiotherapy (EBRT) is limited in dose escalation due to the continuous change in the position, shape and volume of the target volume as well as the organs at risk (OARs). High-dose-rate brachytherapy (HDR) is a recommended treatment of eligible patients with prostate cancer as a method of dose escalation in conjunction with external beam radiation therapy according to the American Society of Clinical Oncology & Cancer Care Ontario guidelines [3]. Several studies reported the outcomes of HDR monotherapy in prostate cancer using anywhere between 2 to 6 fractions [4–12].

More recently, there is increasing interest in single-fraction HDR monotherapy which eliminates the need for multiple implants or protracted bedrest with interstitial needles placed in the prostate. A few studies recently reported the outcomes of single-fraction HDR monotherapy, highlighting the concern that 19 Gy in a single fraction is a suboptimal dose [13–18]. One logical solution is to further escalate the dose to the whole gland beyond 19 Gy, which can be limited by a potential increase in gastrointestinal (GI) and genitourinary (GU) toxicity. An alternative is to define a dominant intraprostatic lesion (DIL) for focal dose escalation. With the advent of multiparametric MRI (mpMRI), it is possible to combine information from standard T1-and T2-weighted imaging with diffusion-weighted imaging to reflect cell density and dynamic contrast–enhancement (DCE) to image the permeability of the microvasculature and blood flow [19]. This characterization of the functional parameters of the prostatic tissue allow us to identify areas of increased tumor cell density, especially lesions

* Corresponding author at: Sunnybrook Health Sciences Center, Rm T2-161, 2075 Bayview Avenue Toronto, ON M4N 3M5, Canada.
E-mail address: andrew.loblaw@sunnybrook.ca (A. Loblaw).

https://doi.org/10.1016/j.radonc.2019.09.011
0167-8140/

of higher grade [20–22]. We hypothesized that focal dose escalation to the DIL would potentially increase the effectiveness of HDR monotherapy with a minimal impact on toxicity. Therefore, our group conducted a phase II prospective trial of single-fraction HDR monotherapy treatment incorporating mpMRI-guided simultaneous DIL boost.

Patients and methods

The trial was approved by the Sunnybrook research ethics board and registered on clinical trials.gov (NCT02623933). Written, informed consent was obtained in all participants.

Patient selection and treatment details

Eligible patients had histologically confirmed diagnosis of adenocarcinoma of the prostate, low- or intermediate-risk disease (clinical stage T1-2b, Gleason Score $\leq$7, and PSA $\leq$20 ng/mL), prostate volume <60 cc, and an identified DIL on mpMRI (PIRADs 3–5). All imaging was performed on a 3 Tesla MRI system with a 32-channel surface coil (no endorectal coil). Axial, sagittal, and coronal T2-weighted, diffusion-weighted and DCE imaging was used to identify a predominant PIRADS 3–5 intraprostatic nodule, and either cognitive fusion (first 30 patients) or an in-house deformable, co-registration algorithm was used to co-register the mpMRI dataset to the TRUS at the time of implant [23]. Real-time, TRUS based single fraction HDR monotherapy was delivered as an outpatient procedure under general anesthesia using the Oncentra planning system (Elekta, Stockholm). The prescription dose was 19 Gy to the PTV with the following planning objectives: DIL D90% $\geq$23 Gy, prostate V100% >95%, V150% <35%, V200% <12%, urethra D10cc <118%, and rectum V80% <0.5 cc. Androgen deprivation therapy was not allowed. All patients were routinely prescribed an alpha-blocker after the implant for 4 weeks.

Study endpoints and follow-up

Patients were assessed at baseline, week 6, and at 3 and 6 months. In the late period (>6 months), patients were followed every 6 months for 5 years. Acute toxicities, late toxicities and quality of life (QOL) data was collected using Common Terminology Criteria for adverse events version 4.0 (CTCAE v4.0) and expanded prostate cancer index composite (EPIC) questionnaires, respectively up to 5 years [24,25]. The primary endpoint was Acute GU and GI toxicities. Secondary endpoints included QOL using the EPIC questionnaire, late GU and GI toxicities, biochemical disease-free survival, and the rate of salvage therapy (ADT, surgery or brachytherapy). Biochemical failure (BF) was defined as per the American Society for Therapeutic Radiology and Oncology Phoenix definition (nadir + 2.0 ng/ml) [26].

Statistical analysis

Demographic and tumor characteristics were summarized using mean, standard deviation (SD), median and range for continuous variables, and proportions for categorical variables. BF was calculated from the time of first radiation treatment to failure, last follow-up or death. The cumulative incidence of BF was estimated using Nelson-Aalen curves. PSA nadir was set to be the lowest PSA value following treatment completion. Three domains of EPIC scores and sub-scores were analyzed: urinary (function/bother), bowel (function/bother) and sexual (function/bother). The patient responses to questions were transformed to a scale from 0 to 100, with higher scales indicating better function and less bother. A minimally clinical important change (MCIC) was scored if the average EPIC QOL score (months 6–60) was >0.5 standard deviation (SD) of baseline scores for each domain score or sub-score in all patients. Overall survival was estimated using the Kaplan-Meier curve. All analyses were conducted using Statistical Analysis Software (SAS version 9.4 for Windows) and R package (version 3.4.2). P-values <0.05 were considered statistically significant.

Results

Demographic factors, implant dosimetry, and basic tumor characteristics are summarized in Table 1. 60 patients were enrolled, with a median follow-up of 39 months. With MRI T-stage incorporated into the risk-group criteria, 8% of patients had low-risk, 35% had favorable intermediate-risk and 57% had unfavorable intermediate-risk PCa [27]. The median DIL volume was 3.1 cc, and the median dose to 90% of the DIL (D90) was 27.2 Gy. The dosimetric parameters achieved are listed in Table 1.

Eleven patients (18.3%) had biochemical failure. The cumulative BF probability was 15.2% at 36 months (95% CI 4.6%–25.6%) and 31.6% at 48 months (95% CI 10.1%–53%) (Fig. 1). Of the 11 patients with BF, 8 had biopsy proven local failure only and 3 were awaiting further investigations at the time of this analysis. Seven of the 8 local failures were at the site of the original DIL. Of the 8 local failures, 7 had salvage focal HDR as part of a clinical trial and 1 had

Table 1
Demographics, dosimetric parameters, and basic tumor characteristics.

	Total (N = 60)
Age (years)	
Median (range)	65.6 (52.9, 77.6)
MRI T stage	
T2a	30 (50%)
T2b	14 (23.3%)
T2c	16 (26.6%)
Clinical T stage	
T1c	41 (68.3%)
T2a	13 (21.7%)
T2b	4 (6.6%)
T2c	2 (3.3%)
Gleason score	
6	8 (13.3%)
7	52 (86.6%)
PSA at baseline (ng/ml)	
Median (range)	6.24 (2.2, 16.4)
Risk group	
Low	5 (8.3%)
Favorable intermediate	21 (35%)
Unfavorable intermediate	34 (56.7%)
Prostate volume (cc)	
Median (range)	36 (17, 55)
DIL volume (cc)	
Median (range)	3.1 (0.7, 8.9)
IPSS score at baseline	
Median (range)	4 (0, 15)
DIL location	
Anterior medial	10 (16.7%)
Anterior lateral	8 (13.3%)
Posterior medial	22 (36.7%)
Posterior lateral	20 (33.3%)
Dosimetric variables	
Prostate median V100% (range)	96.9% (93.8, 99.7)
Prostate median V150% (range)	35.2% (28.3, 46.1)
Prostate median V200% (range)	12% (7, 18.8)
Urethra median lDmax (range)	123% (82.9, 136.7)
Urethral median D10cc (range)	116.5% (61.3, 117.7)
Rectal median Dmax (range)	4 (0, 15)
Rectal median V80% (range)	0.03 cc (0, 0.47)
DIL median D90% (range)	27.2 Gy (20.9, 35.7)

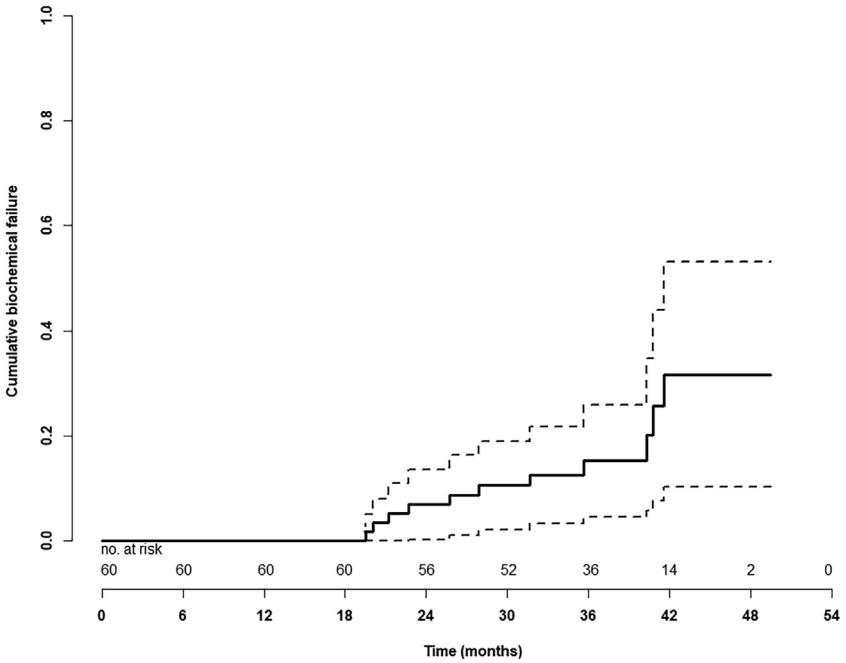

Fig. 1. Nelson-Aalen cumulative biochemical failure probability curve with 95% confidence intervals.

salvage EBRT. The median PSA nadir was 0.79 ng/ml, with a median time to nadir of 32 months (Fig. 2). No patient died from any cause or developed metastatic disease.

No acute or late grade ≥3 bowel or urinary toxicity was observed. The rate of acute grade 2 urinary toxicity was 21.7%, with one patient requiring a urinary catheter for retention. The cumulative worst toxicity rates are listed in Table 2. The median IPSS increased from a baseline of 4 up to 8 at 3 months, then decreased to 5 at 1 year and was stable thereafter. The mean EPIC QOL change from baseline (average score during the late period – baseline score) was −1.0 for the bowel domain, −2.1 for the urinary domain, and −8.8 for the sexual domain (Fig. 3). The proportion of patients with MCIC was 32.2% for the urinary domain, 22.4% for the bowel domain, and 30.9% for the sexual domain.

Discussion

There is increasing interest in single-fraction HDR monotherapy for the treatment of localized PCa. A few studies in the literature reported the outcomes of single-fraction HDR monotherapy using a dose of 19 to 20.5 Gy with mixed results [13–17]. Given the rising concern that 19 Gy in a single fraction is suboptimal for local con-

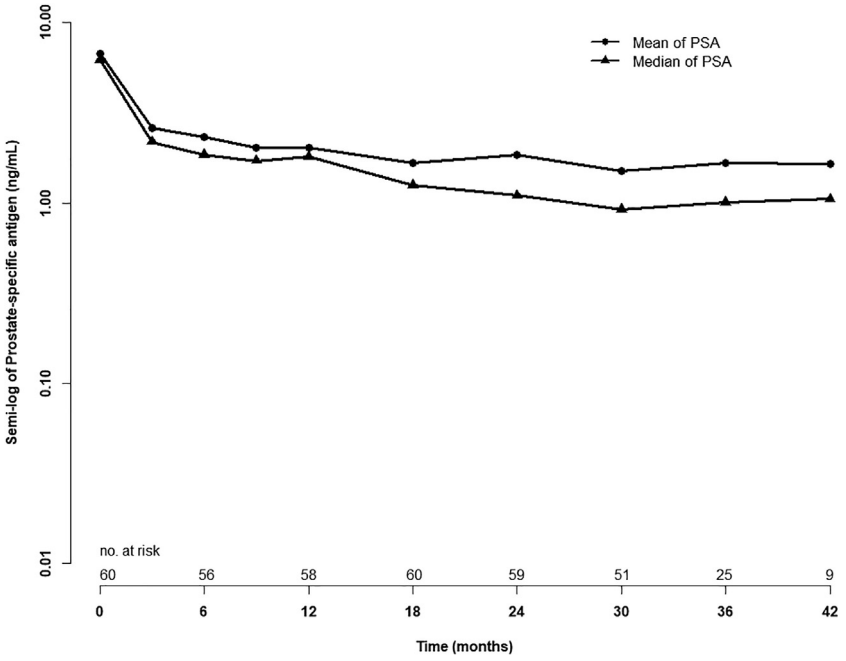

Fig. 2. Mean and median PSA over time.

Table 2
Cumulative worst acute and late CTCAE toxicities.

	CTCAE toxicity grade			
Cumulative worst toxicity	0	1	2	3
Acute period (N = 60)				
GI	51 (85%)	9 (15%)	0 (0%)	0 (0%)
GU	4 (6.6%)	17 (28.3%)	13 (21.7%)	0 (0%)
Sexual	42 (70%)	16 (26.6%)	2 (3.3%)	0 (0%)
Late period (N = 60)				
GI	52 (86.6%)	7 (11.6%)	1 (1.6%)	0 (0%)
GU	18 (30%)	33 (55%)	9 (15%)	0 (0%)
Sexual	18 (30%)	20 (33.3%)	20 (33.3%)	2 (3.3%)

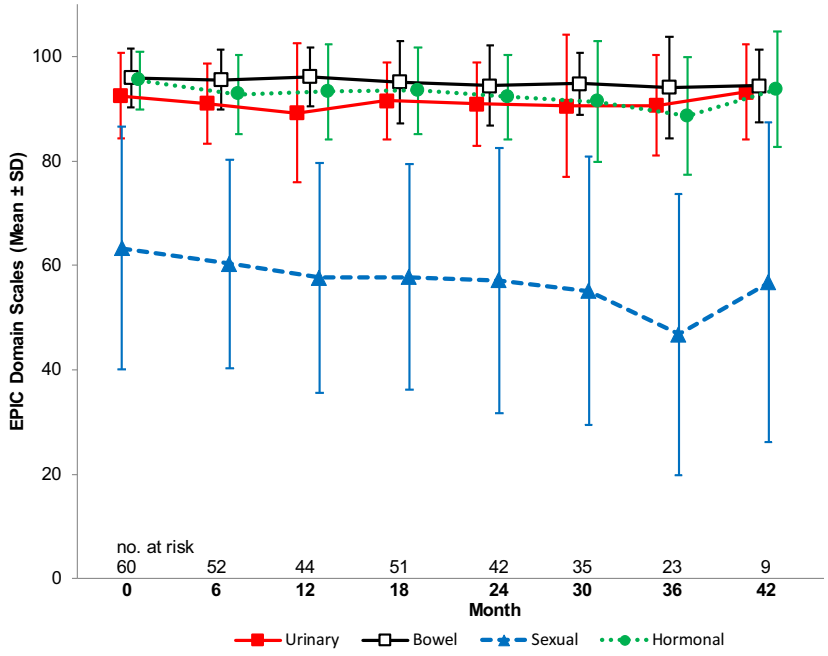

Fig. 3. EPIC QOL change from baseline in the urinary, bowel, sexual and hormonal domains.

trol, we hypothesized that adding a simultaneous boost to the DIL would improve the outcome with minimal toxicity. Here we reported the results of a phase II prospective trial of single-fraction 19 Gy HDR monotherapy with MRI-guided simultaneous DIL boost. With a median follow up under 4 years, our patients experienced a local failure rate that was higher than expected with the majority failing at the site of original DIL despite significant dose-escalation. The treatment was well tolerated, with no grade ≥3 toxicity and a minimal change in QOL.

Several groups published the results of single fraction HDR monotherapy for localized PCa, with doses ranging from 19 to 20.5 Gy to the whole gland. Five series were identified that had a follow up of ≥3 years. Of the 5 series, 3 reported suboptimal disease control. Prada et al. published outcomes of 60 patients with low- and intermediate-risk disease treated with a single-fraction of 19 Gy [14]. The biochemical control at 5 years was 66% for low-risk patients and 60% for patients with Gleason 7 disease. One criticism was that the implant dosimetry was inadequate, and their following dose-escalated series of 60 patients (63% with Gleason 6) showed a better biochemical control of 82% at 6 years using a dose of 20.5 Gy [15]. Morton et al. recently presented their updated results of a randomized trial comparing a single 19 Gy fraction to 27 Gy in 2 fractions [28]. 170 patients with low and intermediate-risk PCa were randomized, 72% of which had Gleason 7 disease. After a median follow-up of 51 months, the 5-year biochemical control rate was significantly worse for the single fraction arm at 74.5% compared to 97.3% for 2 fractions. The majority of failures in the single fraction arm were local, and were almost always at the site of original disease. Siddiqui et al. also reported a suboptimal 5-year estimated biochemical control of 77.2% in 68 patients treated with 19 Gy in one fraction [17]. Hoskin et al. reported the most favorable outcomes to date with single fraction HDR monotherapy [13]. 49 patients were treated with 19 Gy or 20 Gy in one fraction, with a 4-year biochemical relapse free survival of 94%. However, 74% of patients received a median of 6.9 months of ADT, and only 4 patients were at risk at 5 years. Longer follow-up will shed further light on whether the superior outcomes reported by Hoskin et al. would persist.

In conclusion, our report showed that a focal boost to the MRI-specified gross tumor did not adequately improve local control after 19 Gy single-fraction HDR monotherapy. To our knowledge, this is the first study that reported the impact of a simultaneous focal boost on outcomes in patients treated with HDR monotherapy. This report solidifies the available evidence that single-

fraction HDR monotherapy for prostate cancer provides suboptimal local control, and should not be offered outside of clinical trials.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized. Controlled Trials. Int J Radiat Oncol 2009;74:1405–18. https://doi.org/10.1016/j.ijrobp.2008.10.091.

[2] 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 2008;71:1028–33. https://doi.org/10.1016/j.ijrobp.2007.11.066.

[3] Chin J, Rumble RB, Kollmeier M, Heath E, Efstathiou J, Dorff T, et al. Brachytherapy for patients with prostate cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update. J Clin Oncol 2017;35:1737–43. https://doi.org/10.1200/JCO.2016.72.0466.

[4] Rogers CL, Alder SC, Rogers RL, Hopkins SA, Platt ML, Childs LC, et al. High dose brachytherapy as monotherapy for intermediate risk prostate cancer. J Urol 2012;187:109–16. https://doi.org/10.1016/j.juro.2011.09.050.

[5] Hoskin P, Rojas A, Lowe G, Bryant L, Ostler P, Hughes R, et al. High-dose-rate brachytherapy alone for localized prostate cancer in patients at moderate or high risk of biochemical recurrence. Int J Radiat Oncol 2012;82:1376–84. https://doi.org/10.1016/j.ijrobp.2011.04.031.

[6] Yoshioka Y, Suzuki O, Isohashi F, Seo Y, Okubo H, Yamaguchi H, et al. High-dose-rate brachytherapy as monotherapy for intermediate- and high-risk prostate cancer: clinical results for a median 8-year follow-up. Int J Radiat Oncol 2016;94:675–82. https://doi.org/10.1016/j.ijrobp.2015.05.044.

[7] Zamboglou N, Tselis N, Baltas D, Buhleier T, Martin T, Milickovic N, et al. High-dose-rate interstitial brachytherapy as monotherapy for clinically localized prostate cancer: treatment evolution and mature results. Int J Radiat Oncol 2013;85:672–8. https://doi.org/10.1016/j.ijrobp.2012.07.004.

[8] Hauswald H, Kamrava MR, Fallon JM, Wang P-C, Park S-J, Van T, et al. High-dose-rate monotherapy for localized prostate cancer: 10-year results. Int J Radiat Oncol 2016;94:667–74. https://doi.org/10.1016/j.ijrobp.2015.07.2290.

[9] Demanes DJ, Martinez AA, Ghilezan M, Hill DR, Schour L, Brandt D, et al. High-dose-rate monotherapy: safe and effective brachytherapy for patients with localized prostate cancer. Int J Radiat Oncol 2011;81:1286–92. https://doi.org/10.1016/j.ijrobp.2010.10.015.

[10] Martinez AA, Demanes J, Vargas C, Schour L, Ghilezan M, Gustafson GS. High-dose-rate prostate brachytherapy: an excellent accelerated-hypofractionated treatment for favorable prostate cancer. Am J Clin Oncol 2010;33:481–8. https://doi.org/10.1097/COC.0b013e3181b9cd2f.

[11] Mark RJ, Anderson PJ, Akins RS, Nair M. Interstitial high-dose-rate brachytherapy as monotherapy for early stage prostate cancer: median 8-year results in 301 patients. Brachytherapy 2010;9:S76. https://doi.org/10.1016/j.brachy.2010.02.127.

[12] Jawad MS, Dilworth JT, Gustafson GS, Ye H, Wallace M, Martinez A, et al. Outcomes associated with 3 treatment schedules of high-dose-rate brachytherapy monotherapy for favorable-risk prostate cancer. Int J Radiat Oncol 2016;94:657–66. https://doi.org/10.1016/j.ijrobp.2015.10.011.

[13] Hoskin P, Rojas A, Ostler P, Hughes R, Alonzi R, Lowe G. Single-dose high-dose-rate brachytherapy compared to two and three fractions for locally advanced prostate cancer. Radiother Oncol 2017;124:56–60. https://doi.org/10.1016/j.radonc.2017.06.014.

[14] Prada PJ, Cardenal J, Blanco AG, Anchuelo J, Ferri M, Fernández G, et al. High-dose-rate interstitial brachytherapy as monotherapy in one fraction for the treatment of favorable stage prostate cancer: toxicity and long-term biochemical results. Radiother Oncol 2016;119:411–6. https://doi.org/10.1016/j.radonc.2016.04.006.

[15] Prada PJ, Ferri M, Cardenal J, Blanco AG, Anchuelo J, Díaz de Cerio I, et al. High-dose-rate interstitial brachytherapy as monotherapy in one fraction of 20.5 Gy for the treatment of localized prostate cancer: toxicity and 6-year biochemical results. Brachytherapy 2018;17:845–51. https://doi.org/10.1016/j.brachy.2018.06.002.

[16] Xu MJ, Chen KS, Chang AJ, Lazar A, Shinohara K, Cunha JAM, et al. Single-fraction brachytherapy as monotherapy for early-stage prostate cancer: the UCSF experience. Brachytherapy 2019. https://doi.org/10.1016/j.brachy.2019.03.002.

[17] Siddiqui ZA, Gustafson GS, Ye H, Martinez AA, Mitchell B, Sebastian E, et al. Five-year outcomes of a single-institution prospective trial of 19-Gy single-fraction high-dose-rate brachytherapy for low- and intermediate-risk prostate cancer. Int J Radiat Oncol 2019. https://doi.org/10.1016/j.ijrobp.2019.02.010.

[18] Morton G, Chung HT, McGuffin M, Helou J, D'Alimonte L, Ravi A, et al. Prostate high dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: early toxicity and quality-of life results from a randomized phase II clinical trial of one fraction of 19 Gy or two fractions of 13.5 Gy. Radiother Oncol 2017;122:87–92. https://doi.org/10.1016/j.radonc.2016.10.019.

[19] Groenendaal G, Borren A, Moman MR, Monninkhof E, van Diest PJ, Philippens MEP, et al. Pathologic validation of a model based on diffusion-weighted imaging and dynamic contrast-enhanced magnetic resonance imaging for tumor delineation in the prostate peripheral zone. Int J Radiat Oncol 2012;82:e537–44. https://doi.org/10.1016/j.ijrobp.2011.07.021.

[20] Da Rosa MR, Milot L, Sugar L, Vesprini D, Chung H, Loblaw A, et al. A prospective comparison of MRI-US fused targeted biopsy versus systematic ultrasound-guided biopsy for detecting clinically significant prostate cancer in patients on active surveillance: MRI-Ultrasound Targeted Prostate Biopsy. J Magn Reson Imaging 2015;41:220–5. https://doi.org/10.1002/jmri.24710.

[21] Ravizzini G, Turkbey B, Kurdziel K, Choyke PL. New horizons in prostate cancer imaging. Eur J Radiol 2009;70:212–26. https://doi.org/10.1016/j.ejrad.2008.09.019.

[22] Bonekamp D, Jacobs MA, El-Khouli R, Stoianovici D, Macura KJ. Advancements in MR imaging of the prostate: from diagnosis to interventions. RadioGraphics 2011;31:677–703. https://doi.org/10.1148/rg.313105139.

[23] Shaaer A, Davidson M, Semple M, Nicolae A, Mendez LC, Chung H, et al. Clinical evaluation of an MRI-to-ultrasound deformable image registration algorithm for prostate brachytherapy. Brachytherapy 2019;18:95–102. https://doi.org/10.1016/j.brachy.2018.08.006.

[24] Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology 2000;56:899–905. https://doi.org/10.1016/S0090-4295(00)00858-X.

[25] Trotti A, Colevas A, Setser A, Rusch V, Jaques D, Budach V, et al. CTCAE v3. 0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 2003;13:176–81. https://doi.org/10.1016/S1053-4296(03)00031-6.

[26] Roach M, Hanks G, Thames H, 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 2006;65:965–74. https://doi.org/10.1016/j.ijrobp.2006.04.029.

[27] Zumsteg ZS, Spratt DE, Pei I, Zhang Z, Yamada Y, Kollmeier M, et al. A new risk classification system for therapeutic decision making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. Eur Urol 2013;64:895–902. https://doi.org/10.1016/j.eururo.2013.03.033.

[28] Morton G, Loblaw A, Chung HT, McGuffin M, Tseng E, Mendez L, et al. Efficacy results of a randomized trial of prostate HDR Monotherapy in either one or two fractions for low and intermediate risk disease. Brachytherapy 2019;18:s52.