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Scientific Article

Ten-Year Results From a Phase II Study on Image Guided, Intensity Modulated Radiation Therapy With Simultaneous Integrated Boost in High-Risk Prostate Cancer

Christian Ekanger, MD,[a,*] Svein Inge Helle, MD, PhD,[a] Daniel Heinrich, MD,[a,1] Dag Clement Johannessen, MD,[a] Åsa Karlsdóttir, MD, PhD,[a] Yngve Nygård, MD, PhD,[b] Ole Johan Halvorsen, MD, PhD,[c,d] Lars Reisæter, MD,[e,f] Rune Kvåle, MD, PhD,[a] Liv Bolstad Hysing, M.Sc., PhD,[g,h] and Olav Dahl, MD, PhD[a,i]

Departments of [a]Oncology and Institute of Clinical Science and [b]Urology, Haukeland University Hospital, Bergen, Norway; [c]Centre for Cancer Biomarkers CCBIO, Department of Clinical Medicine, University of Bergen, Norway; Departments of [d]Patohology and [e]Radiology, Haukeland University Hospital, Bergen, Norway; [f]Department of Clinical Medicine and [g]Institute of Physics and Technology, University of Bergen, Bergen, Norway; [h]Department of Oncology and Medical Physics, Haukeland University Hospital, Bergen, Norway; and [i]Department of Clinical Science Faculty of Medicine, University of Bergen, Norway

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Abstract

Purpose: There is no consensus on how to treat high-risk prostate cancer, and long-term results from hypofractionated radiation therapy are lacking. We report 10-year results after image guided, intensity modulated radiation therapy with hypofractionated simultaneous integrated boost and elective pelvic field.

Methods and Materials: Between 2007 and 2009, 97 consecutive patients with high-risk prostate cancer were included, treated with 2.7 to 2.0 Gy × 25 Gy to the prostate, seminal vesicles, and elective pelvic field. Toxicity was scored according to Radiation Therapy Oncology Group criteria and biochemical disease-free survival (BFS) defined by the Phoenix definition. Patients were subsequently divided into 3 groups: high risk (HR; n = 32), very high risk (VHR; n = 50), and N+/s−prostate-specific antigen (PSA) ≥100 (n = 15). Differences in outcomes were examined using Kaplan-Meier analyses.

Results: BFS in the patients at HR and VHR was 64%, metastasis-free survival 80%, prostate cancer-specific survival 90%, and overall survival (OS) 72%. VHR versus HR subgroups demonstrated significantly different BFS, 54% versus 79% ($P = .01$). Metastasis-free survival and prostate cancer-specific survival in the VHR group versus HR group were 76% versus 87% ($P = .108$) and 74% versus

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* Corresponding author: Christian Ekanger; E-mail: christian.ekanger@helse-bergen.no

[1] Current affiliation: Department of Oncology, Akershus University Hospital, Lørenskog, Norway.

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100% ($P = .157$). Patients reaching nadir PSA <0.1 (n = 80) had significantly better outcomes than the rest (n = 17), with BFS 70% versus 7% ($P < .001$). Acute grade 2 gastrointestinal tract (GI) and genitourinary tract (GU) toxicity occurred in 27% and 40%, grade 3 GI and GU toxicity in 1% and 3%. Late GI and GU grade 2 toxicity occurred in 1% and 8%.

Conclusions: High-risk prostate cancer patients obtained favorable 10-year outcomes with low toxicity. There were significantly better results in the HR versus the VHR group, both better than the N+/PSA ≥100 group. A nadir PSA value < 0.1 predicted good prognosis.

Introduction

Prostate cancer is the most common malignancy and the second leading cause of cancer mortality in Norwegian men. Although beneficial results are obtained when treating low- and intermediate-risk tumors by most treatment modalities, high-risk disease still represents a major challenge.[1] There are no randomized controlled trials comparing radiation therapy versus prostatectomy, and there is no consensus regarding optimal management. According to guidelines, standard treatment is intensity modulated radiation therapy (IMRT) combined with long-term androgen deprivation therapy (ADT) or prostatectomy with extended pelvic lymph node dissection.[1]

Dose-escalation improves relapse-free survival in prostate cancer,[2,3] and in intermediate- or high-risk disease, there is also evidence of an overall survival benefit.[4] Because the α/β ratio for prostate cancer is considered to be low, in the range of 1.1 to 1.7 Gy,[5,6] hypofractionation may improve local control. With the publication of 4 large phase III studies on moderate hypofractionation, it is now considered safe and effective,[7-12] and guidelines from the American Society for Radiation Oncology (ASTRO), American Society of Clinical Oncology (ASCO), and American Urological Association (AUA) state that moderate hypofractionation should be offered to low-risk, intermediate-risk, and high-risk localized prostate cancer candidates for external beam radiotherapy (EBRT).[13]

However, with the exception of a subset of patients in the Fox Chase trial,[14] none of the studies referred to by the guidelines included radiation of an elective pelvic nodal field, and long-term efficacy data beyond 5 years are still lacking.

The role of whole pelvic radiation therapy (WPRT) is controversial. It has been advocated for in patients with high estimated probability of spread to the regional nodes based on pre-treatment nomograms, but no randomized trial has shown a clear advantage compared with radiation to the prostate only. Hence, the question of WPRT still remains unresolved.[15]

There is great disease heterogeneity within the high-risk group,[16] and studies using surgery have shown differences in outcome. Patients who meet very high-risk (VHR) criteria (primary Gleason pattern 5 present on biopsy, ≥5 cores with Gleason sum 8 to10, or ≥2 high-risk factors) have particularly poor oncologic outcomes.[17-19] It is not clear whether these criteria also apply to men treated with EBRT.[20,21]

Our department has a long tradition of dose-escalation and WPRT.[22] In the present study, we report 10-year results from a prospective phase II protocol of pelvic radiation therapy using image guided IMRT with WPRT and hypofractionated simultaneous integrated boost (SIB) to the prostate in high-risk prostate cancer.

Methods and Materials

From June 2007 to February 2009, we included 97 consecutive patients with adenocarcinoma of the prostate referred to Haukeland University Hospital for EBRT. Patients with T3-4 tumors, risk of lymph node metastasis >15% according to Roach equation,[23] or positive lymph nodes detected by surgical staging were considered eligible. Lymph node sampling was not mandatory and performed in 18 patients. T-staging was mainly done by digital rectal examination. Bone scan (scintigraphy or skeletal magnetic resonance imaging [MRI]) was obtained in patients with s–prostate-specific antigen (PSA) >10 ng/mL or Gleason score >7, and a diagnostic abdominal and pelvic computed tomographic (CT) scan was performed in patients with s-PSA >50 ng/mL. All patients had 3 fiducial markers implanted in the prostate at least 1 week before radiation therapy. The study protocol was approved by the Regional Ethical Committee (REK 2006/15727), and a written informed consent was obtained from each patient before enrollment.

Patient characteristics are presented in Table 1. All patients had high-risk cancers defined as clinical stage ≥T3, Gleason score ≥8, or s-PSA >20 ng/mL. Median age was 66 years (range, 46-79 years) and median s-PSA was 20 (range, 5-128; mean, 30). Median follow-up was 121 months (range, 15-148) for all patients and 124 months (range, 113-148) for surviving patients. Clinical stage was ≥T3a in 79 patients, and Gleason score was ≥8 in 37 patients. Patients were subsequently divided into 3 different groups. Based on the 2015 National Comprehensive Cancer Network (NCCN) VHR criteria and results from studies on surgery and EBRT,[17-21,24] we formed a VHR group consisting of patients with primary Gleason pattern 5 present on biopsy, ≥5 cores with

Table 1 Patient characteristics by risk group

Characteristic	Regular high-risk N = 32	Very high-risk N = 50	N+/PSA ≥100 N = 15	Total N = 97
Age, median (range), y	67 (55-76)	65 (47-79)	62 (46-71)	66 (46-79)
Clinical T-stage				
T1	0	1	0	1
T2	6	7	4	17
T3	25	41	11	77
T4	1	1	0	2
Grade group (Gleason pattern)				
Grade group 1 (3 + 3)	2	4	1	7
Grade group 2 (3 + 4)	17	7	1	25
Grade group 3 (4 + 3)	12	11	5	28
Grade group 4 (4 + 4)	0	16	5	21
Grade group 5 (score 9-10)	1	12	3	16
Pretreatment s-PSA, ng/mL				
<10	8	4	1	13
10-19	19	9	3	31
20-39	3	25	3	31
40-99	2	12	3	17
≥100	0	0	5	5

Abbreviation: PSA = prostate-specific antigen.

Gleason score 8 to 10, or ≥2 high-risk factors (n = 50). The second group consisted of high-risk patients (HR) without VHR characteristics (n = 32). Patients with metastases to pelvic lymph nodes (N+; n = 11) or pretreatment s-PSA ≥100 (n = 5) were allocated to the third group (n = 15). Ten of the N+ patients had positive lymph nodes detected by lymph node sampling, and one had pathologically enlarged pelvic lymph nodes on MRI before initiation of ADT. Patients with suspicious but not enlarged lymph nodes were considered as lymph node negative.

The treatment procedure has been presented in detail elsewhere,[25] but will be briefly described. Three clinical target volumes (CTV) were defined receiving different dose levels, with the higher dose levels administered as SIB.

1. CTV67.5: prostate. Dose 2.7 Gy × 25 = 67.5 Gy (equivalent to 81.2 Gy in 2 Gy fractions).
2. CTV60: prostate and seminal vesicles. Dose: 2.4 Gy × 25 = 60 Gy (equivalent to 67.5 Gy in 2 Gy fractions).
3. CTV50: prostate and seminal vesicles and pelvic lymph nodes. Dose: 2 Gy × 25 = 50 Gy.

Radiation therapy was administered according to the plan in 96 patients. One patient stopped after 23 fractions owing to acute grade 3 GI toxicity. No additional boost to lymph nodes was given to the N+ patients as there were no enlarged lymph nodes at CT for dose planning. All patients received luteinizing hormone-releasing hormone analogs 3 months before initiation of radiation therapy with an intended total duration of 2 years, and with the addition of an antiandrogen the first 4 weeks to prevent a tumor flare.

The primary endpoints were BFS, metastasis free survival (MFS), and prostate cancer-specific survival (PCSS). Secondary endpoints were peak Radiation Therapy Oncology Group (RTOG) acute and late genitourinary tract (GU) and gastrointestinal tract (GI) a toxicity.[26] Additionally, we evaluated whether a detectable nadir PSA (nPSA), defined as the lowest PSA level after treatment that was ≥0.1 ng/mL, could predict an increased risk of recurrence. Follow-up assessments were performed 2 to 3 times during radiation therapy, and acute toxicity was scored using RTOG criteria during the last week of radiation therapy and at 3 months. Follow-up assessments were thereafter performed every third month up to 2 years after radiation therapy, later every sixth month up to 5 years. After 5 years, patients were followed once a year. Biochemical recurrence was defined according to Phoenix criteria (nPSA + 2 ng/mL).[27] Local recurrence was defined as biopsy confirmed local recurrence after radiation therapy, or radiologic findings on MRI.[28]

Statistical analyses were performed using SPSS statistics (IBM Corp, Armonk, NY, version 25). To assess survival outcomes for BFS, MFS, PCSS, and OS, Kaplan-Meier estimates were calculated, and differences were assessed by the log-rank test.

Results

At median follow-up of 10.1 years, Kaplan-Meier estimate of BFS for the entire cohort was 59% (95% confidence interval, 48%-70%), and MFS was 74% (95% CI,

65%-83%; Table 2). The most frequent location of distant disease was to bone (n = 18). No metastases to lymph nodes in the irradiated area were observed. All clinical recurrences followed a biochemical recurrence. Ten-year PCSS and OS was 87% (95% CI, 80%-94%) and 70% (95% CI, 61%-79%), respectively. Causes of death other than prostate cancer were other cancers (n = 6); infections (n = 2); cardiovascular (n = 3); Parkinson disease, Alzheimer disease, or dementia (n = 4); liver failure (n = 1); and unknown (n = 1). Local recurrence was observed in 11 patients (Table 2). Two of them later developed distant metastasis. Five patients had biochemical recurrence only (Table 2).

Median time to biochemical recurrence was 50 months (range, 9-106) among those with recurrence. The systemic recurrences occurred at median 39 months (range, 9-81), and the local recurrences occurred later, at median 73 months (range, 40-106).

In the 82 HR+VHR patients 10- year BFS was 64% (95% CI, 53%-75%), MFS 80% (95% CI, 71%-89%), PCSS 90% (95% CI, 83%-97%), and OS 72% (95% CI, 62%-82%).

We observed a significant difference in BFS across the risk groups (Fig 1). BFS was 79%, 54%, and 29% in the HR, VHR, and N+/PSA ≥100 groups, respectively ($P < .001$). There was a nonsignificantly different MFS and PCSS in the patients at HR compared with the patients at VHR, 87% versus 76% ($P = .1$) and 100% versus 84% ($P = .16$), respectively. The patients in the N+/PSA ≥100 group had significantly worse MFS and PCSS than the patients at VHR/HR, 39% versus 80% ($P < .001$) and 71% versus 90% ($P = .04$). There was no difference in OS in the respective groups; 75% in HR, 70% in VHR, and 60% in N+/PSA ≥100 patients ($P = .591$). PCSS and OS for the 3 groups are shown in Figure E1 (available online at https://doi.org/10.1016/j.adro.2019.11.007).

Of the 11 patients with lymph node positive disease, 7 had recurrence, all with metastases. Three patients were alive without any signs of recurrence after 10 years, and one died while still in remission (Table 2). Four out of 5 patients with pretreatment s-PSA ≥100 were still alive at 10-year follow-up, and 1 died of other causes. All 4 had a biochemical recurrence, but none were in a castration refractory phase at the last follow-up.

The rate of patients reaching a nPSA <0.1 was equal in the HR and VHR groups (88%), in the N+/PSA ≥100 group the rate was 53%. Outcomes were significantly better in patients reaching nPSA <0.1 (n = 80) compared with the rest (n = 17). Ten-year BFS was 70% versus 7% ($P < .001$), MFS 86% versus 15% ($P < .001$), PCSS 89% versus 61% ($P = .001$), and OS 72% versus 43% ($P = .005$), respectively. BFS stratified by nPSA in the entire cohort of 97 patients is shown in Fig 2.

BFS according to the new International Society of Urological Pathology grade group system[29] is shown in Fig E2 (available online at https://doi.org/10.1016/j.adro.2019.11.007). The 5-year BFS probabilities were 100%, 96%, 64%, 76%, and 40%, and 10-year BFS probabilities were 100%, 77%, 48%, 61%, and 20%. Notably, there was a significant difference between grade group 2 and grade group 3 ($P = .03$). The effect on BFS by the different levels of pretreatment s-PSA is shown in Fig E3 (available online at https://doi.org/10.1016/j.adro.2019.11.007).

Data on acute toxicity was complete in all patients; 3 patients missed data on late toxicity. The peak RTOG acute GI and GU score was grade 2 in 27% and 40%, respectively, and acute grade 3 GI and GU toxicity was observed in 1% and 3% (Table 3).

A peak late RTOG GI and GU grade 2 occurred in 1% and 8%, and only one patient experienced late grade 3 GU toxicity.

The scheduled 24 months of ADT was completed in 54%. More patients completed ADT in the N+/PSA ≥100 group (82%) compared with the regular HR and VHR group (47% and 50%). The reason for terminating ADT was in all cases intolerable side effects. We found no association between early termination of ADT and BFS (data not shown).

Discussion

To date there are limited published outcomes beyond 5 years for moderate hypofractionation in prostate cancer, and biochemical measures of cancer control predominate in studies. The present prospective study shows favorable long-term oncologic outcomes of importance such as

Table 2 Recurrence and cause of death by risk group (%)

	Regular high-risk N = 32 (%)	Very high-risk N = 50 (%)	N+/PSA ≥100 N = 15 (%)	Total N = 97 (%)
Biochemical recurrence only	1 (3)	3 (6)	1 (7)	5 (5)
Local recurrence	2 (6)	7 (14)	2 (13)	11 (11)
Metastasis	3 (9)	11 (22)	8 (53)	22 (23)
Death from prostate cancer	1 (3)	7 (14)	4 (27)	12 (12)
Death from other causes	8 (25)	8 (16)	2 (13)	18 (19)

Abbreviation: PSA = prostate-specific antigen.

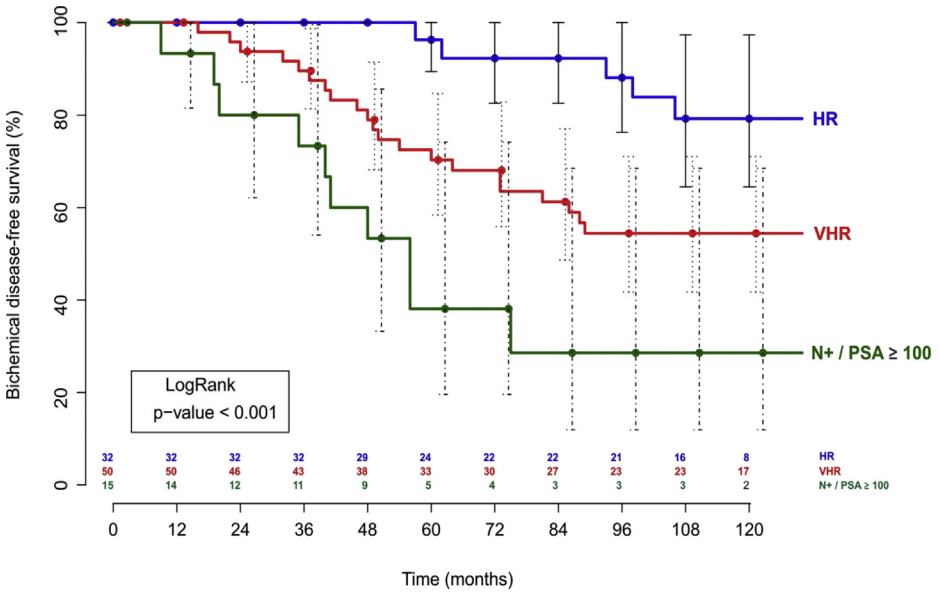

Figure 1 Biochemical disease-free survival by the different risk groups. *Abbreviation*: PSA = prostate-specific antigen.

MFS, PCSS, and OS, and it demonstrates significant heterogeneity within the high-risk population. The results compare favorably with other trials on surgery or EBRT combined with ADT. In the study from Johns Hopkins radical prostatectomy database, which used the same VHR definition as in our study, 10-year BFS was 21%, MFS 37%, and PCSS 62% in the VHR population compared with 41%, 78%, and 90% in other high-risk men.[17] A study on radiation therapy demonstrated 10-year BFS 46%, MFS 65%, and PCSS 82% in the VHR group compared with 65%, 87%, and 94% in other high-risk men.[20] A recent published study on moderately hypofractionated radiation therapy demonstrated 10-year BFS of 42% in the general high-risk population.[30] In the present study, 10-year BFS was 54%, MFS 76%, and PCSS 84% in the VHR population compared with 79%, 87%, and 100% in the HR group.

The proportion of VHR and N+/PSA ≥100 patients was large in the present study: 52% and 15%, respectively. This reflects the unselected population of patients treated with EBRT in our institution. The proportion is larger compared with studies on radical prostatectomy; in the Johns Hopkins radical prostatectomy database, the proportion of VHR patients was 15.1%,[17] and in the study from Lee et al, 56.5% had only one high-risk factor.[19] Heterogeneity in risk factors and comorbidities within

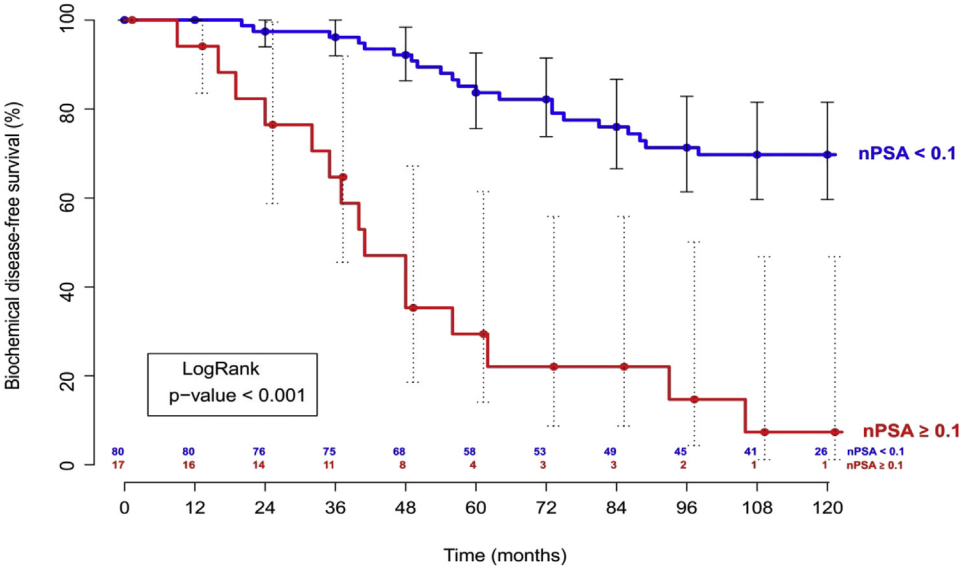

Figure 2 Biochemical disease-free survival by nadir prostate-specific antigen in the entire cohort. *Abbreviation*: PSA = prostate-specific antigen.

Table 3 Acute and late toxicity

	GI toxicity		GU toxicity	
	Acute (%)	Late (%)	Acute (%)	Late (%)
Grade 0	15	69	9	42
Grade 1	55	27	47	45
Grade 2	26	1	40	8
Grade 3	1	-	3	1
Grade 4	-	-	-	-

Abbreviations: GI = gastrointestinal tract; GU = genitourinary tract.

the high-risk population make it difficult and unreliable to compare outcomes from different treatment modalities; a smaller amount of VHR patients will lead to better cancer related outcomes, and differences in comorbidities have a large effect on OS in older men.

Patients with s-PSA ≥100 are frequently excluded from studies on radical treatment because they are considered having a high probability of systemic disease.[31] Although 4 out of 5 patients with pretreatment s-PSA ≥100 in our study had recurrence, there were no deaths from prostate cancer at 10-year follow-up. It is not clear whether the combined EBRT and ADT contributed to a more favorable outcome compared with the alternative lifelong treatment with ADT. However, during the past years there has been a growing interest in local therapy to patients with advanced and metastatic disease, culminating with the STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) trial which demonstrated an overall survival benefit treating the primary tumor with EBRT in patients with newly diagnosed metastatic prostate cancer and a low metastatic burden.[32]

There are no randomized trials establishing the role of radical therapy in men with clinically evident lymph nodes, and there is uncertainty regarding optimal treatment. In the inclusion period, metastasis to pelvic lymph nodes (N+) was considered a systemic disease state,[33] and the American Joint Committee on Cancer still classifies patients with N+ as having stage IV disease. The 11 N+ patients in our cohort did have the poorest outcomes. However, 4 patients had no signs of recurrence, and 3 patients were alive without signs of recurrence at 10 years. Patients with metastasis to pelvic lymph nodes should therefore not be omitted from radical treatment.

A low nPSA value is previously demonstrated to be a strong independent predictor of BFS after EBRT in intermediate and high-risk disease.[34] Our study demonstrates significantly better outcomes for all cancer related endpoints when nPSA <0.1 is reached after therapy. The nPSA level could therefore potentially be used in future selection of patients for a more frequent follow-up or inclusion in studies on adjuvant treatment.

Tolerance to treatment was excellent, and the frequencies of durable grade 2 and 3 GU and GI side effects were low and similar to the recent studies on hypofractionation and other studies using image guided radiation therapy to high dose.[7,10,12,35,36] Importantly, the addition of an elective pelvic field (to 50 Gy) did not increase long-term toxicity.

The main strengths of the study are the prospective study design and the long follow-up time. A follow-up time beyond 5 years is critical when analyzing long-term endpoints such as PCSM and local recurrence. Although patients were enrolled between 2007 and 2009, treatment technique with image guided IMRT, dose-escalation, hypofractionation, and simultaneous boost is up to date according to guidelines. Absence of a central pathology evaluation is a study limitation. Reports on tolerance were based on physician reports rather than from patient reported data. Hence, there was a risk of underreporting toxicity.

Patients with locally persistent prostate cancer are at greater risk for distant metastases.[37,38] Thus, the issue of local control is important. There were 11 patients with local recurrence in the total cohort. The low toxicity reported suggests a chance of dose escalation to even higher doses to achieve better local control, especially in patients with VHR where local recurrence occurred in 14% (n = 7) in our study. Further dose-escalation to intraprostatic lesions by the use of MRI- guided boost is the topic of an ongoing clinical trial in our department.

Conclusions

High-risk prostate cancer patients achieve favorable long-term outcomes with low toxicity when treated with pelvic image-guided IMRT with hypofractionated simultaneous integrated boost. Stratification of high-risk patients into HR and VHR subgroups demonstrated significant effect on BFS and can be used in the decision of which patients who may benefit from further dose-escalation or multimodal treatment. A low nadir s-PSA <0.1 was a strong predictor of better outcomes in the high-risk population. The long time for recurrences to appear demonstrates the importance of a long follow-up in studies on combined radiation therapy and ADT.

Supplementary data

Supplementary material for this article can be found at https://doi.org/10.1016/j.adro.2019.11.007.

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