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ORIGINAL ARTICLE

Treatment outcomes of prostate cancer patients with Gleason score 8–10 treated with definitive radiotherapy

TROD 09-001 multi-institutional study

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Abstract

Purpose To validate the clinical outcomes and prognostic factors in prostate cancer (PCa) patients with Gleason score (GS) 8–10 disease treated with external beam radiotherapy (EBRT) + androgen deprivation therapy (ADT) in the modern era.

Methods Institutional databases of biopsy proven 641 patients with GS 8–10 PCa treated between 2000 and 2015 were collected from 11 institutions. In this multi-institutional Turkish Radiation Oncology Group study, a standard database sheet was sent to each institution for patient enrollment. The inclusion criteria were, T1–T3N0M0 disease according to AJCC (American Joint Committee on Cancer) 2010 Staging System, no prior diagnosis of malignancy, at least 70 Gy total irradiation dose to prostate ± seminal vesicles delivered with either three-dimensional conformal RT or intensity-modulated RT and patients receiving ADT.

Results The median follow-up time was 5.9 years (range 0.4–18.2 years); 5-year overall survival (OS), biochemical relapse-free survival (BRFS) and distant metastases-free survival (DMFS) rates were 88%, 78%, and 79%, respectively. Higher RT doses (≥78 Gy) and longer ADT duration (≥2 years) were significant predictors for improved DMFS, whereas advanced stage was a negative prognosticator for DMFS in patients with GS 9–10.

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Conclusions Our results validated the fact that oncologic outcomes after radical EBRT significantly differ in men with GS 8 versus those with GS 9–10 prostate cancer. We found that EBRT dose was important predictive factor regardless of ADT period. Patients receiving 'non-optimal treatment' (RT doses <78 Gy and ADT period <2 years) had the worst treatment outcomes.

Keywords Pelvic radiotherapy · Grading system · Intensity modulated radiation therapy · Hormonal treatment · Androgen deprivation therapy

Behandlungsergebnisse von mit definitiver Strahlentherapie behandelten Prostatakrebspatienten mit einem Gleason-Score von 8–10

TROD 09-001 Multizenterstudie

Zusammenfassung

Ziel Beurteilung der klinischen Ergebnisse und prognostischen Faktoren bei Patienten mit Prostatakrebs (PCa) mit Gleason-Score (GS) 8–10, die mit externer Strahlentherapie (EBRT) und einer Androgendeprivationstherapie (ADT) behandelt wurden.

Methoden Zwischen 2000 und 2015 wurden insgesamt 641 mittels Biopsie diagnostizierte PCa-Patienten mit GS 8–10 von 11 Instituten in die Studie einbezogen. In dieser multizentrischen Studie der Turkish Radiation Oncology Group wurde ein Standard-Datenbankformular zur Patientenaufnahme an jedes Zentrum geschickt. Die Einschlusskriterien waren: keine vorherige Diagnose von Malignitäten, T1–T3 N0 M0 gemäß der TNM-Klassifikation des AJCC (American Joint Committee on Cancer) von 2010 und eine RT von Prostata und Samenblasen mindestens bis 70 Gy entweder mit dreidimensionaler oder mit intensitätsmodulierter RT zusammen mit einer ADT.

Ergebnisse Die mediane Nachbeobachtungszeit betrug 5,9 Jahre (Spanne 0,4–18,2 Jahre). Das 5-Jahres-Gesamtüberleben (OS), die biochemische Rezidivrate (BCR) und das fernmetastasenfreie Überleben (FÜ) der Patienten mit einer Nachbeobachtungszeit von 5 Jahren betrug jeweils 88%, 78% und 79%. Höhere Dosis der RT (≥78 Gy) und langfristige ADT waren signifikante Prädiktoren für ein verbessertes FÜ. Fortgeschrittenes Stadium bei Patienten mit GS 9–10 wurde als negativer Prognosefaktor für das FÜ identifiziert.

Schlussfolgerung Unsere Ergebnisse zeigen, dass sich die onkologischen Ergebnisse zwischen GS 8 und GS 9–10 bei Patienten mit PCa, die mit EBRT behandelt wurden, unterscheiden. Die EBRT-Dosis erwies sich als wichtiger prädiktiver Faktor unabhängig von ADT. Patienten, die keine optimale Behandlung erhielten (RT mit Dosen <78 Gy und ADT-Zeit <2 Jahre), hatten die schlechtesten Behandlungsergebnisse.

Schlüsselwörter Beckenstrahlentherapie · Bewertungssystem · Intensitätsmodulierte Strahlentherapie · Hormonelle Behandlung · Androgendeprivationstherapie

Introduction

The incidence of high-risk disease in prostate cancer patients, defined as clinical T3 disease, prostate specific antigen (PSA) level >20 ng/mL, or Gleason score (GS) 8–10, is approximately 15% [1]. Although conflicting results have been reported in previous series comparing different treatment strategies, the treatment options in high-risk patients include radical prostatectomy (RP), external beam radiation therapy (EBRT) with androgen deprivation therapy (ADT), and EBRT with a brachytherapy boost (EBRT + BT) and ADT in current practice [2–5].

GS is the most important predictive factor for outcome in prostate cancer patients, and increasing evidence has suggested that GS 8–10 disease defines a more aggressive natural history [6–9]. Although different risk classification systems stratified patients according to GS < 6, 7, and 8–10, several reports indicated that this was not sufficient to predict prognosis [9–11]. However, high-risk prostate cancer disease constitutes a heterogeneous group, including both GS 8 and GS 9–10 disease [12]. The new International Society of Urological Pathology (ISUP) grading system identifies GS 9–10 as a different entity with worse outcomes compared to GS 8 [8, 9]. Previous studies demonstrated that patients with GS 9–10 disease had higher incidence of biochemical failure and prostate-cancer specific mortality rates compared to patients with GS 8 disease after RP [13, 14]. Thus, high-risk disease was divided into GS 8 and GS 9–10 in the new five-tiered prostate cancer grading system (PCGS) [9].

A recent multi-institutional validation study for this new PCGS was performed by including different multimodal

therapeutic approaches [9, 13]. These studies evaluated the efficacy of RP or EBRT + BT in high-risk prostate cancer patients [14, 15]. Additionally, some studies assessed the outcomes of patients treated with EBRT and ADT [2, 4]. However, the studies assessing the efficacy of EBRT and ADT have limited patient numbers with inadequate RT data or ADT usage. Thus, these studies might inadvertently include biases against patients receiving EBRT by including patients not receiving the current standard of care. Furthermore, previous retrospective studies comparing the efficacy of RP and EBRT in high-risk prostate cancer included patients treated with lower EBRT doses or insufficient ADT [16–18]. On the other hand, recent studies demonstrated a clear benefit of dose escalation and long-term ADT on survival for patients with high-risk prostate cancer [16, 18–21].

Based on these findings, the aim of this study is to validate the clinical outcomes in prostate cancer patients with GS 8–10 disease treated with EBRT + ADT in the modern era. In addition, the prognostic factors effecting the survival were analyzed in the entire cohort and in patients with GS 8 and GS 9–10 disease separately.

Materials and methods

Patient selection

Clinical data of 641 biopsy proven patients with GS 8–10 prostate cancer treated between 2000 and 2015 were collected from 11 institutions. In this multi-institutional Turkish Radiation Oncology Group study, a standard database sheet was sent to each institution for patient enrollment. The inclusion criteria were T1–T3N0M0 disease according to American Joint Committee on Cancer (AJCC) 2010 Staging System, no prior diagnosis of malignancy, at least 70 Gy total irradiation dose to prostate ± seminal vesicles delivered with either three-dimensional conformal RT (3D-CRT) or intensity-modulated RT (IMRT), and patients receiving ADT. Patients with clinical and radiological evidence of lymph node metastasis or distant metastasis and patients receiving hypofractionated RT were excluded from the study. Additionally, patients treated for postoperative adjuvant or salvage RT were also excluded.

Treatment protocol

All patients were treated according to their institutional protocols; thus, the duration of ADT and RT treatment fields and doses showed variations. The ADT consisted of luteinizing hormone-releasing hormone analogue with or without anti-androgen therapy. Neoadjuvant ADT was delivered in 596 patients (93.0%), and the median duration was 3 months (range 1–12 months). Median duration of total ADT time was 24 months (range 2–72 months).

All patients were treated with either 3D-CRT (288 patients, 44.9%) or IMRT (353 patients, 55.1%). The decision of pelvic irradiation was based on institutional treatment protocols. Local RT to the primary tumor and pelvic lymphatics was administered to 311 patients (48.5%), and 330 patients (51.5%) did not receive pelvic lymphatic irradiation. The median RT dose to prostate ± seminal vesicles was 75 Gy (range 70–86 Gy) and that of pelvic lymph nodes was 46 Gy (range 40–62 Gy).

Statistical analysis

All statistical analyses were performed using standard software (SPSS version 21; SPSS Inc. [IBM], Chicago, IL, USA). Biochemical failure was defined according to Phoenix criteria (nadir PSA + 2 ng/dl) [22]. The primary outcomes of interest were the overall survival (OS), biochemical relapse-free survival (BRFS) and distant metastasis-free survival (DMFS). Time to death or progression was calculated as the period from the date of diagnosis to the date of death or the first clinical or imaging evidence of disease recurrence. A chi-square (χ^2) test or Student's t test was used to analyze the differences in the clinical and pathological factors between patients with GS 8 and GS 9–10 disease. The evaluated factors were, age (<70 years vs. ≥70 years), PSA value at diagnosis (≤10 ng/mL vs. 10.1–19.9 ng/mL vs. ≥20 ng/mL), GS (8 vs. 9–10), clinical T stage (T2a–T2c vs. T3a–T3b), treatment period, total RT dose (≤72 Gy vs. 72–78 Gy vs ≥78 Gy), RT technique (3D-CRT vs. IMRT), pelvic field irradiation, duration of ADT (<2 years vs. ≥2 years). OS, BRFS, and DMFS rates were estimated using the Kaplan–Meier method. A univariate analysis was performed via the log-rank test. Multivariate analyses were performed using the Cox proportional hazards model, using covariates with a p value of less than 0.05 based on the univariate analysis. All p values of less than 0.05 were considered statistically significant.

Results

Patient outcomes

The clinical characteristics of patients are presented in Table 1. The median follow-up time was 5.9 years (range 0.4–18.2 years), and the median follow-up for alive patients was 6.2 years (range 0.7–18.2 years), respectively. At the final follow-up, 528 patients (82.4%) were alive, and 113 patients (17.6%) had died (51 [8.0%] of their disease; 62 [9.6%] of other causes). Of the 235 patients with relapse,

Table 1 Patient and tumor characteristics for entire cohort, and patients with GS = 8 or GS = 9–10

Characteristics	Entire cohort ($n = 641$)	GS = 8 ($n = 335$)	GS = 9–10 ($n = 306$)	p
Age (years, median, range)	68 (41–88)	69 (41–88)	68 (51–87)	0.79
PSA (ng/mL, median, IQR)	21.3 (10.6–42.0)	22.1 (10.6–38.6)	20.0 (10.4–45.0)	0.34
Clinical stage				
T2a	90 (14.6)	52 (15.5)	38 (12.4)	0.12
T2b	129 (20.1)	72 (21.5)	57 (18.6)	
T2c	158 (24.6)	84 (25.1)	74 (24.2)	
T3a	156 (24.3)	78 (23.3)	78 (25.5)	
T3b	108 (16.8)	49 (14.6)	59 (19.3)	
RT dose (Gy, median, range)	75.0 (70.0–86.0)	75.0 (70.0–86.0)	75.0 (70–86)	0.42
Primary RT dose				
≤72 Gy	110 (17.1)	55 (16.4)	55 (18.0)	0.19
72–78 Gy	410 (64.0)	201 (60.0)	209 (68.3)	
≥78 Gy	121 (18.9)	79 (23.6)	42 (13.7)	
RT technique				
3D-CRT	288 (44.9)	140 (41.8)	148 (48.4)	0.16
IMRT	353 (55.1)	195 (58.2)	158 (51.6)	
Treatment period				
2000–2005	123 (19.2)	60 (17.9)	63 (20.6)	0.15
2006–2010	178 (27.8)	85 (25.4)	93 (30.4)	
2011–2015	340 (53.0)	190 (56.7)	150 (49.0)	
Pelvic field RT				
Absent	330 (51.5)	182 (54.3)	148 (48.4)	0.13
Present	311 (48.5)	153 (45.7)	158 (51.6)	
ADT time				
<2 years	179 (27.9)	81 (24.2)	83 (27.1)	0.23
≥2 years	462 (72.1)	239 (75.8)	223 (72.9)	

GS Gleason score, *RT* radiotherapy, *Gy* gray, *3D-CRT* three dimensional conformal radiotherapy, *IMRT* intensity-modulated radiotherapy, *ADT* androgen deprivation therapy, *IQR* interquartile range

Table 2 Recurrence patterns in entire cohort, and in patients with GS 8 or GS 9–10 disease

Recurrence	Entire cohort *n* (%)	GS 8 *n* (%)	GS 9–10 *n* (%)
None	531 (82.8)	289 (86.3)	242 (79.1)
Local/locoregional	11 (1.7)	6 (1.8)	5 (1.6)
Distant metastasis	77 (12.0)	35 (10.4)	42 (13.7)
Local and distant recurrence	22 (3.4)	5 (1.5)	17 (5.6)

GS Gleason score

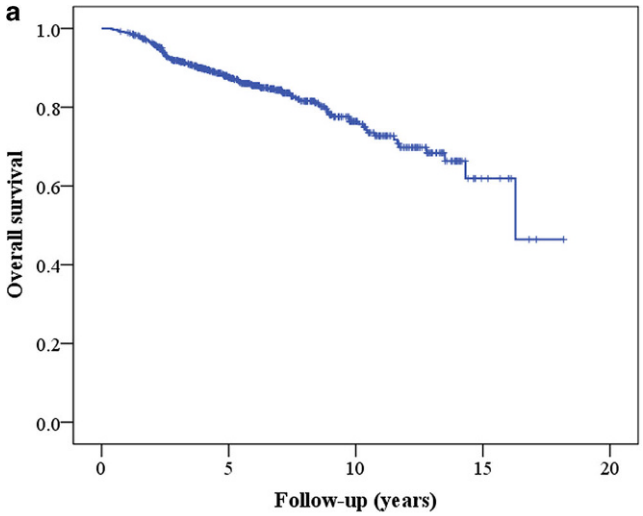
110 patients (17.1%) had local, locoregional, or distant relapse, 77 (12.0%) had distant metastases, 11 (1.7%) had local or locoregional recurrences, and 22 (3.4%) had both. The PSA relapse was observed in 60 patients (9.4%). The distant metastasis rates were significantly higher in patients with GS 9–10 compared to patients with GS 8 (19.3% vs. 11.9%; $p = 0.02$; Table 2).

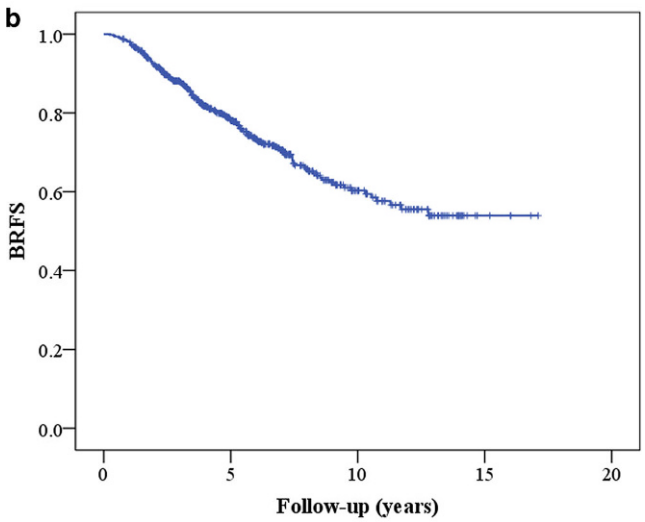
Prognostic factors

The 5-year OS, BRFS and DMFS rates were 88%, 78%, and 79%, respectively (Fig. 1). The tumor and patient characteristics were similarly distributed in patients with GS 8 group and GS 9–10 group (Table 1).

The 5-year OS rate in patients with GS 8 was significantly higher compared to patients with GS 9–10 (91% vs. 85%; $p = 0.003$; Fig. 2a). In univariate analysis, GS, AJCC stage, EBRT doses, and pelvic nodal irradiation were significant prognostic factors for OS (Table 3). In multivariate analysis, older age, GS 9–10, advanced clinical stage and low EBRT doses were significant negative predictors for OS (Table 4).

The 5-year BRFS rate was significantly higher in patients with GS 8 disease compared to that of GS 9–10 (82% vs. 73%; $p = 0.002$; Fig. 2b). The significant prognostic factors in univariate analysis were PSA value, GS, clinical stage, and total RT dose. In multivariate analysis, higher PSA value at diagnosis, GS 9–10, advanced clinical stage,





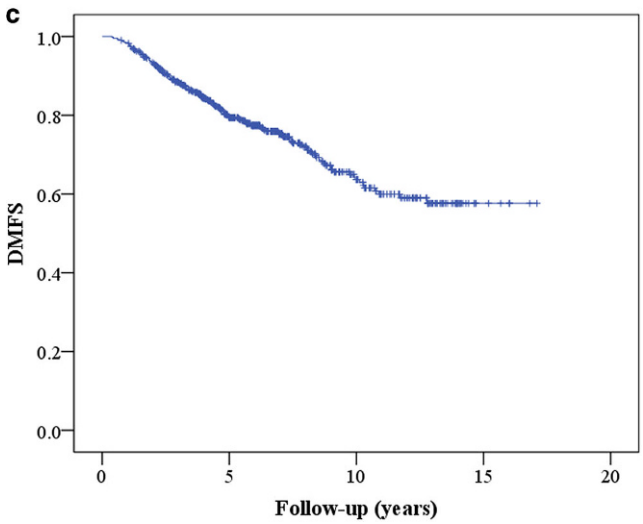
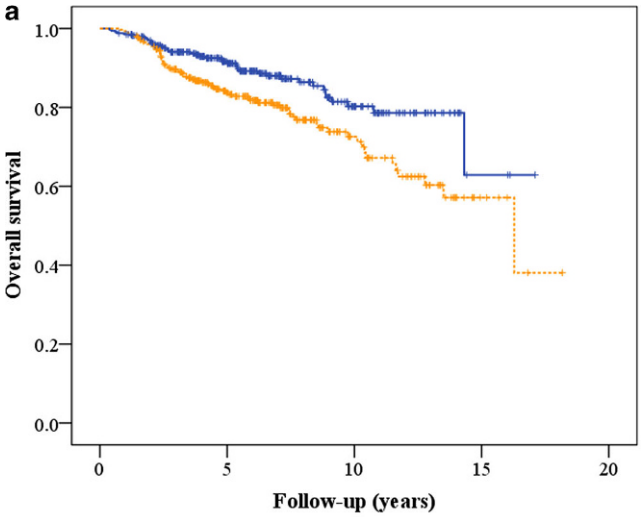
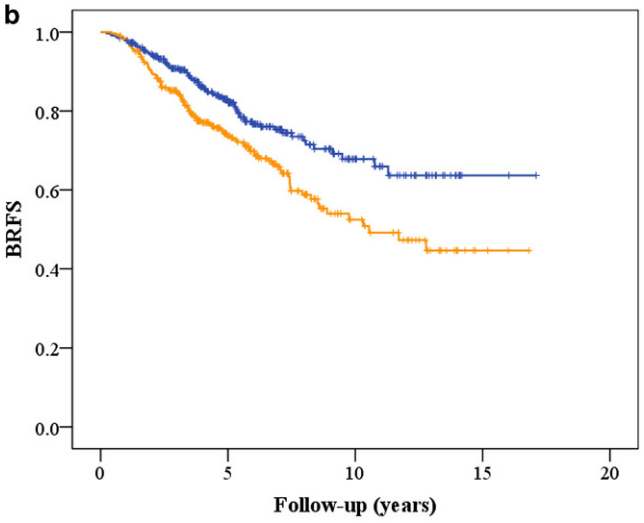


Fig. 1 The 5-year overall survival (OS), biochemical relapse-free survival (BRFS), and distant metastases-free survival (DMFS) rates for the whole cohort





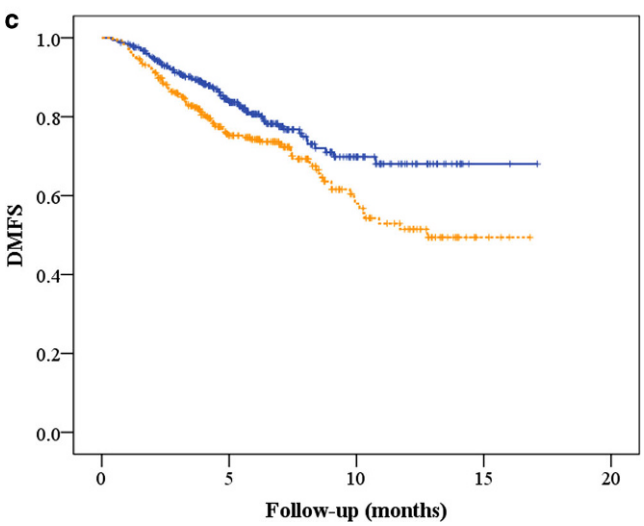


Fig. 2 Compared to patients with GS 9–10 disease patients with GS 8 disease had significantly better 5-year overall survival (OS, 91% vs. 85%; $p = 0.003$; **a**), biochemical relapse-free survival (BRFS; 82% vs. 73%; $p = 0.002$; **b**), and distant metastases-free survival (DMFS) rates (84% vs. 75%; $p = 0.008$; **c**). *Blue line* = GS 8 patient cohort, *yellow line* = GS 9–10 patient cohort

Table 3 Univariate analysis for overall survival (OS), biochemical relapse-free survival (BRFS), and distant metastasis-free survival (BRFS) for entire cohort

Covariate	Patient no	OS		BRFS		DMFS	
		HR (95%CI)	*p*	HR (95%CI)	*p*	HR (95%CI)	*p*
Age (years)							
<70	344	1	0.09	1	0.93	1	0.86
≥70	297	1.38 (0.96–2.01)		0.99 (0.73–1.33)		0.97 (0.71–1.32)	
PSA (ng/mL)							
≤10	155	1	0.31	1	0.04	1	0.09
10.1–19.9	148	0.73 (0.45–1.20)		1.50 (0.94–2.40)		0.70 (0.46–1.06)	
≥20	338	1.12 (0.72–1.73)		1.69 (1.13–2.54)		1.16 (0.81–1.66)	
Gleason score							
8	335	1	0.003	1	0.002	1	0.008
9–10	306	1.77 (1.21–2.59)		1.62 (1.20–2.20)		1.53 (1.12–2.09)	
Clinical stage							
T2a–T2c	377	1	0.003	1	0.002	1	<0.001
T3a–T3b	264	1.76 (1.21–2.54)		1.59 (1.18–2.14)		1.85 (1.36–2.52)	
Treatment period							
2000–2005	–	1	0.25	1	0.41	1	0.07
2006–2010	–	0.68 (0.40–1.16)		0.96 (0.65–1.43)		0.65 (0.42–1.01)	
2010–2015	–	0.70 (0.43–1.14)		0.79 (0.54–1.15)		0.67 (0.48–0.90)	
RT dose							
≤72 Gy	110	1	<0.001	1	<0.001	1	<0.001
72–78 Gy	410	0.87 (0.49–1.54)		1.22 (0.75–1.99)		0.82 (0.51–1.32)	
≥78 Gy	121	0.40 (0.24–0.66)		0.61 (0.40–0.95)		0.43 (0.28–0.65)	
RT technique							
3D-CRT	288	1	0.59	1	0.91	1	0.58
IMRT	353	1.11 (0.76–1.64)		1.02 (0.75–1.38)		1.10 (0.80–1.50)	
Pelvic field RT							
Absent	330	1	0.003	1	0.09	1	0.008
Present	331	0.57 (0.39–0.83)		0.77 (0.56–1.04)		0.66 (0.48–0.90)	
ADT duration							
<2 years	179	1	0.80	1	0.22	1	0.82
≥2 years	462	0.80 (0.71–1.56)		0.82 (0.60–1.13)		1.04 (0.75–1.45)	

GS Gleason score, *RT* radiotherapy, *Gy* gray, *3D-CRT* three-dimensional conformal radiotherapy, *IMRT* intensity-modulated radiotherapy, *ADT* androgen deprivation therapy, *HR* hazard ratio, *PSA* prostate-specific antigen

and lower total RT dose were negative predictors of BRFS (Table 4).

The DMFS rate was also significantly higher in patients with GS 8 disease, compared to patients with GS 9–10 (84% vs. 75%; $p = 0.008$; Fig. 2c). The significant prognostic factors for DMFS in univariate analysis were GS, clinical stage, total RT dose and pelvic lymphatic irradiation. In multivariate analysis, GS 9–10, clinical T3a–T3b disease, and ≤72 Gy EBRT dose had negative impact on DMFS.

Treatment outcomes of GS 8 and 9–10 disease

In univariate analysis, stage and total RT dose were significant predictors for OS, BRFS, and DMFS in patients with GS 8 (Fig. 3). Additionally PSA level was predictor for OS and DMFS, and ADT duration was significant prognosticator for BRFS and DMFS. In multivariate analysis, advanced stage and total RT dose ≥78 Gy were significant prognostic factors for OS, BRFS, and DMFS in GS 8. Moreover, PSA >20 ng/mL was significant predictor for OS and DMFS.

In patients with GS 9–10 disease, stage and total RT dose were significant prognostic factors for OS and DMFS in univariate analysis (Fig. 3). Another prognostic factor for OS was pelvic lymphatic irradiation. ADT duration was found to be significant factor for DMFS. However, we did not find any significant impact of any factor on BRFS for patients with GS 9–10 in univariate analysis. In multivariate analysis, only advanced stage was a negative predictor for OS in GS 9–10 disease. Higher total RT dose (≥78 Gy) and longer ADT duration (≥2 years) were significant predictors for improved DMFS, whereas advanced stage was a neg-

Table 4 Multivariate analysis for overall survival (OS), biochemical relapse-free survival (BRFS), and distant metastasis-free survival (BRFS) for entire cohort

	OS		BRFS		DMFS	
Covariate	HR (95%CI)	*p*	HR (95%CI)	*p*	HR (95%CI)	*p*
Age (years)	1.04 (1.02–1.07)	0.002	1.01 (0.99–1.03)	0.36	1.01 (0.99–1.04)	0.21
PSA (ng/mL)						
≤10	–	–	1	0.02	–	–
10.1–19.9	–	–	1.66 (1.04–2.67)		–	
≥20	–	–	1.71 (1.13–2.58)		–	
Gleason score						
8	1	0.01	1	0.004	1	0.02
9–10	1.65 (1.12–2.44)		1.57 (1.16–2.14)		1.45 (1.05–1.99)	
Clinical stage						
T2a–T2c	1	0.01	1	0.02	1	0.001
T3a–T3b	1.64 (1.12–2.41)		1.43 (1.05–1.95)		1.70 (1.24–2.34)	
RT dose						
≤72 Gy	1	0.003	1	0.02	1	0.001
72–78 Gy	0.78 (0.44–1.39)		1.15 (0.70–1.90)		0.82 (0.51–1.33)	
≥78 Gy	0.45 (0.26–0.7)		0.60 (0.39–0.94)		0.47 (0.30–0.73)	
Pelvic field RT						
Absent	1	0.22	–	–	1	0.54
Present	0.76 (0.50–1.16)		–		0.90 (0.63–1.28)	

PSA prostate-specific antigen, *RT* radiotherapy, *HR* hazard ratio, *95% CI* 95% confidence interval

ative prognosticator for DMFS in patients with GS 9–10 disease.

Association of total radiotherapy dose with outcomes

Patients receiving <78 Gy had a significantly lower OS (HR: 0.45 [0.26–0.7]; $p = 0.003$), BRFS (HR: 0.60 [0.39–0.94]; $p = 0.02$), and DMFS (HR: 0.47 [0.30–0.73]; $p = 0.001$) than those receiving ≥78 Gy. Another subset analysis demonstrated that patients receiving less than 78 Gy radiotherapy and ADT period less than 2 years had the worst OS, BRFS, and DMFS rates (Table 5). Regardless of ADT period, patients receiving ≥78 Gy had better outcomes compared to patients receiving less than 78 Gy.

Discussion

In this multi-institutional study, we found that GS 8–10 disease had worse outcomes, and should be subdivided into GS 8 and GS 9–10 on the basis of differences in OS, BRFS, and DMFS in prostate cancer patients treated with definitive EBRT. Besides GS, advanced stage and low EBRT doses were negative predictors of OS, BRFS, and DMFS. Additionally, advanced age was predictor for OS and higher PSA level at diagnosis was negative prognosticator for DMFS. The distant metastasis was significantly higher in GS 9–10 compared to GS 8 disease. Finally, we found that total EBRT dose was important predictive factor regardless of ADT period. Patients receiving 'non-optimal treatment' (RT doses <78 Gy and ADT period <2 years) had the worst treatment outcomes.

Current risk stratification system includes GS 8–10 disease in high-risk group; however, several studies demonstrated that oncological outcomes significantly differ in patients with GS 8 disease compared to those with GS 9–10 prostate cancer [7, 14, 23–27]. According to the current classification systems, some patients with high-risk prostate cancer fare quite well after local therapy, whereas others succumb despite multimodal treatment. Therefore, in order to better categorize high-risk prostate cancer patients, a novel five-tiered Gleason grade group was defined, and high-risk prostate cancer was further divided into group 4 (GS = 8) and group 5 (GS = 9–10) [11]. In this five-tiered staging system, GS 8 and GS 9–10 are not grouped together and 5-year BRFS after RP has been reported to be 48%, and 26% in a large cohort of patients with GS 8, and 9–10, respectively [9]. Tsao et al. [7] also showed that GS 9–10 disease is associated with worse outcomes compared to GS 8 disease in a cohort of men with GS 8–10 prostate cancer. In a validation study of new Gleason grading group conducted with 358 patients treated with RP, Djaladat et al. [23] demonstrated that GS 9–10 prostate cancer was associated with BRFS and clinical recurrence-free survival. However, no significant difference in OS was observed between GS 8

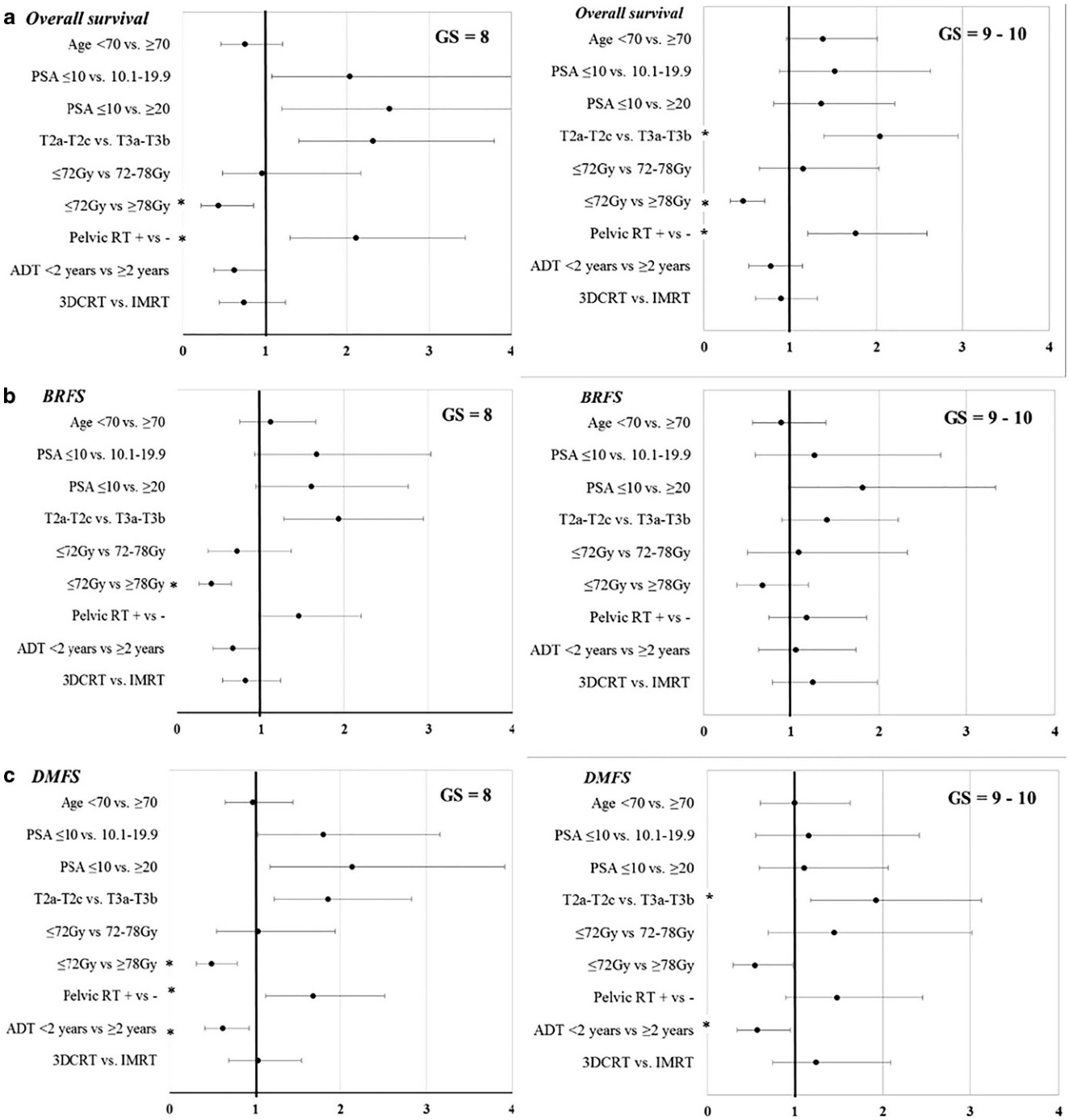


Fig. 3 Univariate analysis for factors affecting overall survival (OS, **a**), biochemical relapse-free survival (BRFS, **b**) and distant metastases-free survival (DMFS, **c**). *GS* Gleason score, *RT* radiotherapy, *PSA* prostate specific antigen, *3DCRT* 3-dimensional conformal radiotherapy, *IMRT* intensity modulated radiation therapy, *ADT* androgen deprivation therapy, *Gy* gray. *Factor is statistically significant

and GS 9–10 disease. Ham et al. [14] did also find that all-cause mortality and prostate-cancer specific mortality rates were significantly higher for patients with GS 9–10 prostate cancer compared to those with GS 8 disease. In a population-based validation study, Pompe et al. [24] found that prostate-cancer-specific mortality rates in RP, BT, EBRT and no local treatment arms different significantly among new Gleason grade groups. In another study with 331,320 prostate cancer patients that underwent RT, RP, or other treatments, He et al. [28] found that each Gleason grade group increase approximately doubled the prostate-cancer-specific mortality.

Besides these series conducted with RP or heterogeneous treatment strategies, a few studies with EBRT also validated

Table 5 Cox regression for overall survival, biochemical relapse-free survival, and distant metastasis-free survival according to radiotherapy doses and androgen deprivation treatment period

RT dose, ADT period	*n* (%)	Hazard ratio (95% CI)	*p*
Overall survival			
<78 Gy, <2 years	32 (5)	1	–
<78 Gy, ≥2 years	367 (57)	0.56 (0.26–1.19)	0.13
≥78 Gy, <2 years	148 (23)	0.30 (0.16–0.58)	<0.001
≥78 Gy, ≥2 years	95 (15)	0.30 (0.17–0.53)	<0.001
Biochemical relapse-free survival			
<78 Gy, <2 years	32 (5)	1	–
<78 Gy, ≥2 years	367 (57)	0.45 (0.22–0.90)	0.03
≥78 Gy, <2 years	148 (23)	0.41 (0.24–0.69)	0.001
≥78 Gy, ≥2 years	95 (15)	0.42 (0.24–0.76)	0.004
Distant metastasis-free survival			
<78 Gy, <2 years	32 (5)	1	–
<78 Gy, ≥2 years	367 (57)	0.58 (0.30–1.13)	0.11
≥78 Gy, <2 years	148 (23)	0.49 (0.28–0.86)	0.01
≥78 Gy, ≥2 years	95 (15)	0.32 (0.19–0.54)	<0.001

RT radiotherapy, *Gy* Gray, *ADT* androgen deprivation treatment

the new grading system [25–27]. Spratt et al. [26] analyzed 847 prostate cancer patients (95 patients with GS 8, 91 patients with GS 9–10 disease) treated with definitive EBRT between 1990 and 2013, and the authors demonstrated that higher Gleason grade, T stage and PSA levels were independent predictors for worse BRFS, DMFS, and prostate-cancer-specific survival. Berney et al. [27] found that higher Gleason grade and extensive stage were significant prognostic factors in 988 prostate cancer patients treated with conservative treatment strategies. In another 'National Cancer Database Study' (NCDB), Yang et al. [25] found that GS 9–10 disease derived less survival benefit from ADT, in contrast to significant survival benefit of ADT in GS 8 disease. In our study, we found that patients with GS 9–10 prostate cancer has significantly worse OS, BRFS, and DMFS compared to patients with GS 8 disease. Our findings supported the validity of the new Gleason grading system addressing high-risk disease should be subdivided into GS 8 and GS 9–10. Another tumor characteristic negatively impairs survival was extensive tumor stage, as it was previously demonstrated [26]. We also analyzed GS 8 disease and GS 9–10 disease separately. We found that extraprostatic disease and total EBRT dose ≥78 Gy were significant predictors for OS, BRFS, and DMFS, whereas PSA value at diagnosis ≥20 ng/mL was a negative prognostic factor for OS and DMFS. Since distant metastasis was significantly higher in GS 9–10 disease, extensive stage was associated with worse DMFS, while higher RT doses (≥78 Gy) and longer ADT usage (≥2 years) was related with better DMFS rates.

Emerging data have demonstrated a dose–response relationship for prostate cancer irradiation [29, 30]. Biochemical failure, clinical failure, and distant metastasis were all significantly lower and prostate-cancer-specific survival significantly improved at 10 years after treatment with 78 Gy as compared with 70 Gy in patients with pretreatment PSA >10 ng/mL or high-risk disease [19]. In a comparative effectiveness study of dose-escalated (≥75.6 to 90 Gy) vs standard-dose EBRT (from 68.4 to <75.6 Gy) for prostate cancer, Kalbasi et al. [16] demonstrated that dose-escalated EBRT was associated with improved survival in the intermediate-risk (HR, 0.84; 95%CI, 0.80–0.88; $p<0.001$) and high-risk groups (HR, 0.82; 95%CI, 0.78–0.85; $p<0.001$) but not for low-risk groups. The authors also stated a 7.8% and 6.3% reduction in the hazard of death for intermediate- and high-risk patients for every incremental increase of about 2 Gy in dose, respectively. In another NCDB study with 20,279 prostate cancer patients, including 12,617 at intermediate risk and 7662 at high risk, 71.3% received EBRT alone and 28.7% received EBRT plus brachytherapy, Amini et al. [31] found that EBRT + BT was associated with improved survival compared to EBRT alone (75.6 to 81 Gy; HR 0.75, $p<0.001$). This significance remained consistent for intermediate and high risk when analyzed separately (HR 0.73 and 0.76, respectively, each $p<0.001$). The authors also concluded that EBRT + BT or dose-escalated EBRT with doses of at least 79.2 Gy should be considered for intermediate- and high-risk prostate cancer. Recently, Kishan et al. [2] demonstrated that treatment with EBRT + BT (median equivalent dose 91.5 Gy) and ADT was associated with better prostate-cancer-specific mortality and longer time to DM compared to EBRT (median dose 73.4 Gy) and ADT or RP in 1809 prostate cancer patients with GS 9–10 disease. Similarly, our findings

supported the benefit of higher RT doses on treatment outcomes in GS 8–10 prostate cancer patients. Neither ADT duration nor pelvic field irradiation was associated with increased survival. Moreover, we demonstrated that total doses of ≥78 Gy was associated with better treatment outcomes regardless to ADT duration.

The role of pelvic elective nodal irradiation in the management of prostate cancer is controversial. To date, randomized studies have failed to demonstrate a survival benefit with the addition of pelvic nodal irradiation in N0 prostate cancer patients. RTOG 9413 examined the role of pelvic nodal irradiation in patients with ≥15% risk of lymph node involvement based on the Roach formula [32]. Although initial results demonstrated a significant improvement in PFS, favoring pelvic nodal irradiation updated results after a median follow-up of 6.6 years showed no statistically significant difference in either PFS or OS [33]. The French Genitourinary Study Group (GETUG)-01 study evaluated survival in 446 patients with T1b–T3, N0pNx, M0 prostate cancer who were randomly assigned to either pelvic lymph node or prostate or prostate-only radiation therapy. 'High-risk' group (T3 or Gleason score >6 or high PSA levels) received short-term 6-month neoadjuvant and concomitant hormonal therapy. The results showed that pelvic nodal irradiation did not statistically improve OS in the whole population [34]. A post hoc subgroup analysis showed a significant benefit of pelvic irradiation when the risk of lymph node involvement was <15% according to Roach formula. This benefit seemed to be limited to patients who did not receive hormonal therapy. Blanchard et al. evaluated the role of pelvic RT on the outcome in high-risk (Gleason score ≥8, stage T3 or T4 disease, serum PSA concentration >20 ng/mL or pN+) localized prostate cancer patients included in the GETUG 12 trial. Patients were assigned to receive 3 years of ADT or ADT plus 4 cycles of chemotherapy. In their study 358 patients were treated using primary RT and hormone therapy. There was no difference in OS between groups. Although univariate analysis showed worse BRFS with pelvic RT multivariate analyses failed to show this benefit even when the analysis was restricted to pN0 patients [35].

In the current study pelvic nodal irradiation did not affect BRFS. These findings are consistent with the current literature. However, the results of RTOG 0924 and the European PEACE 2 study will be important to make conclusions about using pelvic nodal irradiation in the modern RT era.

Current standard of care for high-risk patients treated with definitive RT is adding long-course ADT. Randomized studies demonstrated the efficacy of RT and ADT especially in high-risk patients, and at least 2–3 years of ADT was found to be more effective than short-term ADT [20, 21, 36]. However, Yang et al. [25] demonstrated that patients with GS 9–10 had smaller survival benefit from ADT compared to patients with GS 8 disease. However, this NCDB study provided only information on whether patients received ADT, but the duration and type of hormone therapy is not mentioned. Thus, still a subgroup of patients with GS 9–10 may benefit from ADT. In the present study, we could not identify any effect of ADT duration on survival, which might be due to homogeneity of ADT in entire cohort. Since most of the patients (72%) received more than 2 years of ADT, our study may not have a power to detect any possible effect of ADT duration.

This study possesses some limitations. First, it is a retrospective study that contains some biases in follow-up, treatment selection, the duration of ADT and patient comorbidities. Second, no central pathology review was conducted, and tertiary Gleason patterns were not routinely reported over the study period. Finally, we evaluated the GS detected from biopsy, not from prostatectomy specimens. However, our study had a large number of patients with long follow-up period, and a more homogeneous cohort treated with EBRT and ADT in the modern era.

Conclusion

Although all patients with GS 8–10 are considered as having high-risk prostate cancer, our results validated the fact that oncologic outcomes after radical radiotherapy significantly differ in men with GS 8 versus those with GS 9–10 prostate cancer. High-risk prostate cancer is biologically a heterogeneous disease. Our results showed that GS 8 prostate cancer was associated with significantly improved OS, BRFS, and DMFS compared to GS 9–10 disease. Together with GS, clinical stage and total RT dose were other important predictors for survival in patients with GS 8–10. Since patients with GS 9–10 have higher rates of distant metastasis compared to patients with GS 8, this group of patient had better DMFS rates with higher RT dose and longer ADT use. However, still more aggressive systemic treatments may be required to achieve better outcomes. This multi-institutional study validates the new five-tiered grading system classification for high-risk prostate cancer and the fact that it can be used for patient counselling and determining therapeutic strategies.

Conflict of interest G. Ozyigit, C. Onal, S. Igdem, Z.A. Alicikus, A. Iribas, M. Akin, D. Yalman, I. Cetin, M.G. Aksu, B. Atalar, F. Dincbas, P. Hurmuz, O.C. Guler, B. Aydin, F. Sert, C. Yildirim, I.B. Gorken, F.Y. Agaoglu, A.F. Korcum, D. Yuce, S. Ozkok, E. Darendeliler and F. Akyol declare that they have no competing interests.

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