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European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Matthew P. Deek, Ryan M. Phillips, Michael Haffner and Phuoc T. Tran on pp. 42–43 of this issue

Androgen Deprivation Therapy and Overall Survival for Gleason 8 Versus Gleason 9–10 Prostate Cancer

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Article info

Article history:
Accepted August 24, 2018

Associate Editor:
Giacomo Novara

Keywords:
Androgen deprivation therapy
Gleason score
High-grade
Prostate cancer
Prostate-specific antigen

Abstract

Background: While the addition of androgen deprivation therapy (ADT) to external beam radiation therapy (EBRT) is known to improve overall survival (OS) in Gleason 8–10 (Grade Group 4–5) prostate cancer (PCa), it has been hypothesized that Gleason 9–10 disease, which is less differentiated than Gleason 8 disease, may be less sensitive to ADT.
Objective: To examine the association between ADT and OS for Gleason 8 versus Gleason 9–10 PCa.
Design, setting, and participants: A retrospective cohort study of 20 139 men from the National Cancer Database with localized or locally advanced, Gleason 8–10 PCa who received EBRT. Data were collected from 2004 to 2012.
Intervention: ADT.
Outcome measurements and statistical analysis: Cox proportional hazards regression was used to examine the association between ADT and OS.
Results and limitations: Overall, 9509 (78%) of the 12 160 men with Gleason 8 disease and 6908 (87%) of the 7979 men with Gleason 9–10 disease received ADT. On multivariable analysis, ADT was associated with a significant improvement in OS for Gleason 8 patients (adjusted hazard ratio 0.78, 95% confidence interval 0.70–0.87, $p < 0.001$) but not for Gleason 9–10 patients (adjusted hazard ratio 0.96, 95% confidence interval 0.84–1.11, $p = 0.6$), with a significant interaction ($p_{\text{interaction}} = 0.020$). A higher Gleason score (8, 9, 10) correlated with an increased adjusted hazard ratio for the association between ADT and OS ($p_{\text{interaction}} = 0.042$). Our study may be limited by the relatively short follow-up (median of 4.0 yr).
Conclusions: In contrast to the significant survival advantage of ADT for Gleason 8 disease, our results suggest that Gleason 9–10 disease derives less survival benefit from ADT and that a higher Gleason score predicts lesser benefit. Consideration should be given to treatment intensification for Gleason 9–10 patients through enrollment in clinical trials or potentially adding novel antiandrogens or docetaxel, which have shown efficacy in both castration-resistant and castration-sensitive settings.
Patient summary: In this study, we examined the effect of androgen deprivation therapy (ADT) for Gleason 8 (Grade Group 4) versus Gleason 9–10 (Grade Group 5) prostate cancer. We found that Gleason 9–10 disease may derive a smaller survival benefit from ADT than Gleason 8 disease.

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https://doi.org/10.1016/j.eururo.2018.08.033
0302-2838/

1. Introduction

The addition of androgen deprivation therapy (ADT) to external beam radiation therapy (EBRT) is known to improve overall survival (OS) in men with high-risk prostate cancer (PCa) [1–3]. A Gleason score of 8–10 or Grade Groups (GGs) 4 and 5 is an established high-risk feature, and post hoc analysis of a randomized controlled trial suggests that the benefit of long-course ADT may be greatest for patients with Gleason 8–10 disease [4]. However, it has been hypothesized that Gleason pattern 5 disease, that is, predominantly tumors with a Gleason score of 9–10, may be less sensitive to ADT [5].

Determining whether Gleason 9–10 PCa has decreased sensitivity to ADT is critically important. It is generally assumed that ADT will substantially enhance survival for patients with Gleason 9–10 disease. If such is not the case, then there will be a dire need to utilize additional agents to optimize care for these patients. Phase 3 trials have shown an OS improvement from the use of novel antiandrogens [6–8] and docetaxel [9–11] in metastatic castration-resistant and castration-sensitive PCa, as well as a metastasis-free survival benefit from the use of novel antiandrogens in nonmetastatic castration-resistant disease [12,13]. Additional trials have suggested a possible benefit for these agents in the initial management of high-risk localized and locally advanced disease [14,15]. Should Gleason 9–10 PCa prove to be less sensitive to ADT, the use of novel antiandrogens and docetaxel may prove to be critical to its management.

Therefore, we investigated the association between ADT and OS for patients with Gleason 8 versus 9–10 PCa treated with EBRT.

2. Materials and methods

2.1. Study cohort

The National Cancer Database (NCDB) is a hospital-based tumor database created as a joint effort between the Commission on Cancer and the American Cancer Society [16]. It captures information regarding socio-demographic factors, tumor characteristics, first-course treatment details, including type of radiation therapy and receipt of hormone therapy, and OS from an estimated 70% of incident cancers in the USA.

We identified 20 139 men in the NCDB diagnosed with localized or locally advanced, Gleason 8–10 (GGs 4 and 5) PCa from 2004 to 2011 who were treated with EBRT as their only form of local therapy (Supplementary Fig. 1). Patients with nodal or metastatic disease were excluded. Additionally, patients with missing sociodemographic (age, race, insurance status, treatment facility type, and zip code-level income) or clinicopathologic (prostate-specific antigen [PSA], Gleason score, or clinical tumor stage) data of interest were also excluded. The NCDB captures OS but not disease-specific survival. To more accurately use OS to approximate disease-specific survival, we excluded patients with more than one documented malignancy or a Charlson-Deyo comorbidity score >0 as these patients have the highest risk of mortality from causes not related to PCa. Furthermore, patients with missing data on the use of ADT or those who began EBRT >365 d after PCa diagnosis or ADT >180 d before or after EBRT initiation were excluded as these patients may have received EBRT or ADT for palliative purposes. Follow-up was obtained from 2004 through 2012.

2.2. Statistical analysis

Baseline patient characteristics were compared using Pearson's χ^2 test for categorical variables and the Wilcoxon rank-sum test for ordinal or continuous variables. Cox proportional hazards regression was utilized to examine the association between ADT and OS. Included in models were natural log-transformed PSA (in ng/ml), clinical tumor stage (T1-T2a, T2b-T2c, T3a, T3x, T3b, T4), age (by year), race (white, black, other), treatment facility type (academic, comprehensive, community), and zip code-level income (by quartile). To investigate whether a significant interaction existed between receipt of ADT and Gleason score (8 vs 9–10), models included the use of ADT (yes, no), Gleason score (8, 9–10), and an ADT (yes, no) × Gleason score (8, 9–10) interaction term.

Furthermore, to investigate whether a higher Gleason score (8, 9, 10) correlated with an increased adjusted hazard ratio (AHR) for the association between ADT and OS, which would indicate that a higher Gleason score predicts lesser OS benefit from ADT, additional Cox regression models were constructed that included the use of ADT (yes, no), Gleason score (8, 9, 10) and ADT (yes, no) × Gleason score (8, 9, 10) interaction terms, in addition to the other variables listed above.

Sensitivity analyses were performed for the 16 830 men who were treated to 66.6–86.4 Gy and with known information on whether pelvic lymph nodes were also treated. In these regression models, information on treatment volume (whole-pelvis, prostate-only), use of dose escalation (no [<75.6 Gy], yes [≥75.6 Gy]), and the modality of radiotherapy (3D conformal radiation therapy, intensity-modulated radiation therapy, proton therapy, other) was also incorporated.

Adjusted Kaplan-Meier curves for OS were generated using the mean of covariates method based on the multivariable Cox regression model [17]. All statistical testing was two-sided with significance set at $p < 0.05$ and performed using Stata/SE version 14.2 (StataCorp, College Station, TX, USA). A waiver was obtained from the Dana-Farber/Harvard Cancer Center Institutional Review Board before undertaking this study.

2.3. Tumor grading convention

The 2014 International Society of Urological Pathology consensus conference noted the difference in outcomes between Gleason 8 (GG 4) and Gleason 9–10 (GG 5) disease and recommended the use of the GG system to describe PCa grading [18]. We agree with the importance of the GG system and have used it alongside the Gleason score when appropriate in this manuscript. Since a significant portion of our analyses concerns the difference in the survival benefit of ADT for Gleason 8 versus 9 versus 10 disease and the GG system does not capture potential differences between Gleason 9 and 10 disease, we chose to also use the Gleason score system to describe tumor grading.

3. Results

3.1. Baseline patient characteristics

Baseline patient characteristics are listed in Table 1. Median follow-up was 4.0 yr (interquartile range, 2.4–5.9 yr). Of the 20 139 men in the overall cohort, 12 160 (60%) had Gleason 8 disease, 7199 (36%) had Gleason 9 disease, and 780 (4%) had Gleason 10 disease. Furthermore, 9509 (78%) Gleason 8 patients and 6908 (87%) Gleason 9–10 patients received ADT.

3.2. OS benefit of ADT for Gleason 8 versus 9–10 disease

On multivariable analysis, receipt of ADT was associated with a significant improvement in OS for patients with

Table 1 – Baseline patient characteristics

Characteristics	No. of patients (%)					
	Gleason 8, *n* = 12 160 (60)			Gleason 9–10, *n* = 7979 (40)		
	No ADT 2651 (22)	ADT 9509 (78)	*p* value	No ADT 1071 (13)	ADT 6908 (87)	*p* value
Year of diagnosis			<0.001			0.8
2004–2006	771 (29)	3307 (35)		321 (30)	2091 (30)	
2007–2009	1072 (40)	3625 (38)		448 (42)	2813 (41)	
2010–2011	808 (31)	2577 (27)		302 (28)	2004 (29)	
Age (yr)			0.040			0.2
Median	72	72		72	72	
Interquartile range	66–77	66–77		66–77	65–77	
Race			0.3			0.003
White	2132 (80)	7747 (82)		863 (81)	5785 (84)	
Black	424 (16)	1467 (15)		183 (17)	922 (13)	
Other	95 (4)	295 (3)		25 (2)	201 (3)	
PSA (ng/ml)			<0.001			0.004
Median	7.9	9.2		9.1	9.9	
Interquartile range	5.3–12.9	5.8–18.0		5.7–17.5	6.0–20.3	
Clinical tumor stage			<0.001			<0.001
T1-T2a	1943 (73)	5804 (61)		665 (62)	3310 (48)	
T2b-T2c	588 (22)	2563 (27)		308 (29)	2239 (32)	
T3a	49 (2)	439 (5)		37 (4)	458 (7)	
T3x	36 (1)	335 (4)		33 (3)	397 (6)	
T3b	32 (1)	300 (3)		24 (2)	395 (6)	
T4	3 (0)	68 (1)		4 (0)	109 (2)	
Facility type			<0.001			0.003
Academic	976 (37)	3050 (32)		314 (29)	2205 (32)	
Comprehensive	1385 (52)	5458 (57)		595 (56)	3901 (56)	
Community	290 (11)	1001 (11)		162 (15)	802 (12)	
Zip code-level income			0.2			<0.001
Quartile 1 (lowest)	375 (14)	1218 (13)		183 (17)	936 (14)	
Quartile 2	460 (17)	1714 (18)		203 (19)	1247 (18)	
Quartile 3	757 (29)	2643 (28)		335 (31)	2012 (29)	
Quartile 4 (highest)	1059 (40)	3934 (41)		350 (33)	2713 (39)	

Percentages may not add to 100 due to rounding.
ADT = androgen deprivation therapy; PSA = prostate-specific antigen.

Gleason 8 disease (AHR = 0.78, 95% confidence interval [CI]: 0.70–0.87, $p < 0.001$; Fig. 1A). In contrast, use of ADT was not associated with a significant improvement in OS for patients with Gleason 9–10 disease (AHR = 0.96, 95% CI: 0.84–1.11, $p = 0.6$; Fig. 1B). A significant interaction between ADT and Gleason score was noted ($p_{interaction} = 0.020$), indicating that the association of ADT use with OS was different for Gleason 8 compared with Gleason 9–10 disease (Fig. 2). The 5-yr adjusted OS was 86% for Gleason 8 patients who received ADT versus 82% for those who did not receive ADT. The 5-yr adjusted OS was 80% for both Gleason 9–10 patients who received ADT as well as those who did not receive ADT.

As a sensitivity analysis, the study cohort was limited to the 16 830 men who were treated to 66.6–86.4 Gy and had information on the use of whole-pelvis versus prostate-only radiation. Use of ADT was again associated with a significant OS benefit for Gleason 8 patients (AHR = 0.75, 95% CI: 0.67–0.85, $p < 0.001$) but not for Gleason 9–10 patients (AHR = 0.94, 95% CI: 0.80–1.10, $p = 0.4$), with $p_{interaction} = 0.034$. The 5-yr adjusted OS was 86% Gleason 8 patients who received ADT versus 82% for those who did not receive ADT. The 5-yr adjusted OS was 81% for Gleason 9–10 patients who received ADT versus 80% for those who did not receive ADT.

3.3. *OS benefit of ADT for Gleason 8 versus 9 versus 10 disease*

To assess whether a higher Gleason score (8, 9, 10) correlated with an increased AHR for the association between the use of ADT and OS, which would indicate that a higher Gleason score predicts lesser OS benefit from ADT, Gleason 9–10 patients were considered separately as Gleason 9 and Gleason 10. On multivariable analysis, the AHR for the association between use of ADT and OS was 0.78 (95% CI: 0.70–0.87, $p < 0.001$) for Gleason 8 disease; 0.95 (95% CI: 0.81–1.10, $p = 0.5$) for Gleason 9 disease; and 1.13 (95% CI: 0.76–1.69, $p = 0.5$) for Gleason 10 disease, with $p_{interaction} = 0.042$ (Fig. 3). At 5 yr, adjusted OS for patients who received ADT versus who did not receive ADT was 86% versus 82% for Gleason 8, 81% versus 80% for Gleason 9, and 74% versus 77% for Gleason 10, respectively.

On sensitivity analysis of the 16 830 men who were treated to 66.6–86.4 Gy and had information on the use of whole-pelvis versus prostate-only radiation, the AHR for the association between use of ADT and OS was 0.75 (95% CI: 0.67–0.85, $p < 0.001$) for Gleason 8 patients; 0.91 (95% CI: 0.77–1.08, $p = 0.3$) for Gleason 9 patients; and 1.16 (95% CI: 0.72–1.87, $p = 0.6$) for Gleason 10 patients, with $p_{interaction} = 0.069$. At 5 yr, adjusted OS for patients who

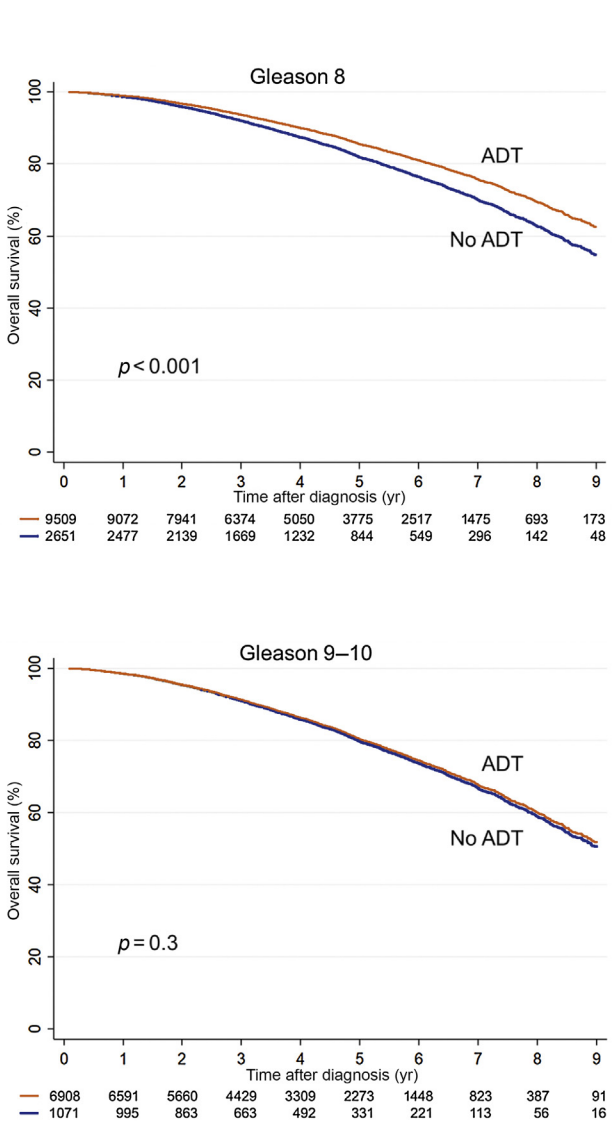

Fig. 1 – Adjusted Kaplan-Meier plots of overall survival: (A) Gleason 8, (B) Gleason 9–10. The *p* values were derived from the multivariable Cox regression model.
ADT = androgen deprivation therapy.

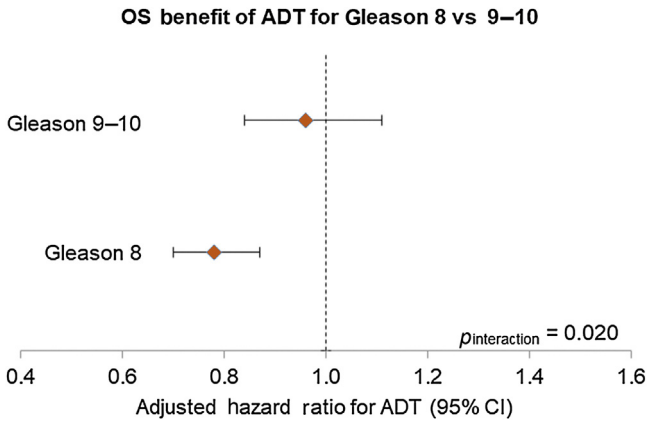

Fig. 2 – Forest plot of the overall survival benefit of ADT for Gleason 8 versus Gleason 9–10 disease.
ADT = androgen deprivation therapy; CI = confidence interval; OS = overall survival.

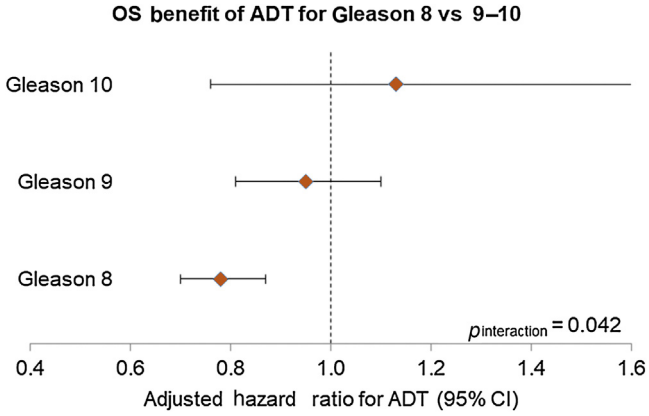

Fig. 3 – Forest plot of the overall survival benefit of ADT for Gleason 8 versus Gleason 9 versus Gleason 10 disease.
ADT = androgen deprivation therapy; CI = confidence interval; OS = overall survival.

received ADT versus who did not receive ADT was 86% versus 82% for Gleason 8, 82% versus 80% for Gleason 9, and 74% versus 77% for Gleason 10, respectively.

4. Discussion

We analyzed the association between receipt of ADT and OS in a contemporary, national cohort of over 20 000 patients with localized or locally advanced, Gleason 8–10 PCa treated with EBRT. Our results demonstrate that while ADT was associated with an approximately 20% decrease in all-cause mortality for patients with Gleason 8 disease, it was not associated with a significant survival advantage for patients with Gleason 9–10 disease. In addition, the AHRs for the association between use of ADT and OS increased with a higher Gleason score. Overall, these results suggest that compared with Gleason 8 PCa, Gleason 9–10 disease derives less survival benefit from ADT and that a higher Gleason score predicts lesser benefit.

Our findings potentially have major clinical implications. The current standard of care for patients with high-risk localized or locally advanced PCa managed with radiation therapy, including men with Gleason 8–10 disease, is the addition of long-course ADT, typically in the form of a luteinizing hormone-releasing hormone (LHRH) agonist with or without a first-generation antiandrogen [1–3]. Our study challenges the current paradigm of treating all patients with Gleason 8–10 disease similarly, as our results indicate that any survival advantage from the use of ADT is significantly weaker for Gleason 9–10 disease than for Gleason 8 disease.

Notably, our results do not contradict prospective evidence regarding the efficacy of ADT. The EORTC 22863, RTOG 8531, RTOG 8610, RTOG 9408, Dana-Farber Cancer Institute 95-096, and TROG 96.01 randomized controlled trials examined the benefit of adding ADT to radiation

therapy [1,3,19–22]. Additionally, EORTC 22961, RTOG 9202, GICOR DART 01/05, TROG 03.04, and PCS IV evaluated longer-course versus shorter-course ADT with radiation therapy [2,4,23–25]. To our knowledge, publications or presentations of these trials have not presented subgroup analyses of patients with Gleason 9–10 disease as patients with Gleason 8–10 disease have historically been grouped together. Furthermore, while it is known that 20% of the PCS IV cohort had Gleason 9–10 disease, the proportion of the other trial cohorts that harbored Gleason 9–10 disease is unknown. It may be that the survival advantage observed from the use of ADT is driven largely by patients with Gleason 8 or less PCa. A post hoc analysis of these trials may be helpful in further elucidating the survival benefit of ADT for Gleason 8–10 patients.

Importantly, our findings provide evidence that intensification of treatment is necessary for patients with Gleason 9–10 disease, both because of its worse prognosis and potentially decreased survival benefit from ADT compared with Gleason 8 disease. Gleason 9–10 PCa harbors Gleason pattern 5 disease, which is less differentiated and more aggressive than the Gleason pattern 4 disease found in most Gleason 8 tumors, and may have developed mechanisms to escape the traditional androgen dependence of lower-grade tumors. Specifically, mechanisms of castration resistance include androgen receptor (AR) amplification and overexpression; AR mutations and splice variants; modifications to AR coregulators; and AR activation secondary to intratumoral steroidogenesis [26]. Moreover, AR expression and activity are upregulated following radiotherapy and associated with disease progression, and the benefit of ADT in the adjuvant setting is thought to derive from suppressing radiotherapy-induced upregulation of the AR pathway [27]. It may be that AR expression and activity are elevated to a significantly greater degree in Gleason pattern 5 disease than in lower-grade tumors.

Novel antiandrogens, namely abiraterone [6], enzalutamide [7,13], and apalutamide [12], and docetaxel [9,10] have been shown to improve metastasis-free and OS in patients with castration-resistant PCa by circumventing some of these mechanisms of resistance [26]. In fitting with the hypothesis that Gleason pattern 5 disease has decreased sensitivity to ADT is our finding that Gleason 10 tumors, which have a greater component of Gleason pattern 5 disease than Gleason 9 tumors, derive a smaller OS benefit from the use of ADT compared with Gleason 9 PCa.

Recent prospective evidence has indicated a possible benefit from abiraterone and docetaxel in the upfront management of high-risk localized and locally advanced PCa. Planned subgroup analysis of locally advanced and node-positive patients from the STAMPEDE phase 3 trial found that the addition of abiraterone to long-course ADT improved failure-free survival (hazard ratio [HR] = 0.21, 95% CI: 0.15–0.31) and possibly also OS (HR = 0.75, 95% CI: 0.48–1.18), though the upper bound of the 95% CI was greater than 1.0 with median follow-up of only 3.3 yr [15]. Additionally, a meta-analysis of randomized controlled trials found that the addition of docetaxel to long-course ADT improved only failure-free survival (HR = 0.70, 95% CI: 0.61–0.81) but not OS (HR = 0.87, 95% CI: 0.69–1.09), although this result may become significant with further follow-up [14]. Because of these equivocal yet promising results, the oncology community has been rightfully reluctant to routinely adopt the use of either agent in addition to the standard of care, that is, long-course ADT in the initial management nonmetastatic Gleason 8–10 disease.

However, due to its clinical aggressiveness and decreased survival benefit from ADT compared with Gleason 8 disease, Gleason 9–10 disease may be the group which would benefit the most from docetaxel or abiraterone. Therefore, we encourage the serious consideration of either docetaxel or abiraterone in the management of Gleason 9–10 PCa as well as continued evaluation of novel antiandrogens and cytotoxic chemotherapy agents for these patients in an effort to improve outcomes, including through participation in clinical trials (eg, NCT02446444). Notably, clinical trials of high-risk patients have historically considered Gleason 8–10 patients as a homogenous entity, whereas future studies examining the differential benefit of a particular therapy for Gleason 9–10 compared with Gleason 8 disease will need to prospectively stratify.

Interestingly, the CIs of the AHR for Gleason 9 and particularly Gleason 10 patients were greater than those for Gleason 8 patients. This may be driven partially by the difference in the number of events, with the Gleason 10 groups experiencing only 211 deaths versus 1429 deaths for Gleason 9 and 1937 deaths for Gleason 8.

A few limitations of our study should be discussed. First, the follow-up was relatively short; however, the aggressive nature of high-grade disease allowed us to detect a robust OS difference within the short follow-up. Second, no central pathology review was conducted as patient samples were not available to the investigators. Third, the NCDB does not provide information on the type of metastatic workup that each patient received.

Fourth, the NCDB only provides information on whether a patient received hormone therapy but does not contain information on the type or duration of hormone therapy. Since National Comprehensive Cancer Network guidelines endorse the use of an LHRH agonist or antagonist but not antiandrogen alone as first-line ADT, the proportion of patients in the study cohort who received an LHRH agonist or antagonist should be high [28]. Furthermore, an analysis of the Surveillance, Epidemiology, and End Results-Medicare database found that an alarming 15% of high-risk men aged $\geq$65 yr in the USA did not receive any ADT, which is similar to the rates of ADT use found in our study cohort, and that the adherence to long-course ADT ($\geq$24 mo) is only 24% [29]. These rates may reflect provider and patient preference toward avoiding the many adverse effects of ADT, including a potential for increased cardiovascular morbidity and mortality [22] despite the well-documented survival benefit [1–3]. However, the duration of ADT was longer for patients with more aggressive disease, such as Gleason score of 9–10 compared with Gleason 8 [29]. Fifth, patients who received ADT likely had additional negative prognostic features not captured in the NCDB, such as higher PSA velocity.

These previous two points suggest that the observed AHR for OS associated with ADT use underestimates the true survival benefit of ADT for both Gleason 8 and 9–10 patients. However, our findings of significant interactions between ADT and Gleason score, which indicate that any survival advantage from the use of ADT is significantly weaker for Gleason 9–10 disease than Gleason 8 disease, should still stand. Lastly, our study is retrospective. The use of ADT was not randomized and may have been influenced by factors related to PCa (as discussed above), medical comorbidities not captured in the NCDB, and patient and provider preferences, which may have influenced survival outcomes. Specifically, patients with comorbidities may have been less likely to receive ADT given concerns about the lack of benefit from ADT in patients with comorbidities [22], while patients or providers who prefer using ADT may be more likely to pursue close post-treatment surveillance and aggressive therapies for recurrent disease. Since these covariates are not captured in the NCDB, they could not be adjusted for in multivariable models.

It is important to note that the AHR obtained from our analyses of the association between use of ADT and OS probably underestimates the true survival benefit from ADT for reasons described above. It may be that ADT still improves OS for certain Gleason 9–10 patients. However, we currently lack the tools necessary to predict which Gleason 9–10 patients have disease that would benefit from ADT and which patients harbor castration-resistant disease that requires novel antiandrogens or docetaxel. Genomics-based tools have shown promise in being able to predict response to ADT [30]; however, further development and validations of such tools are necessary before they can be incorporated into clinical practice.

5. Conclusions

In summary, in contrast to the significant survival advantage of ADT for Gleason 8 PCa, our results suggest that Gleason 9–10 disease derives less survival benefit from ADT and that a higher Gleason score predicts lesser benefit. Consideration should be given to intensification of therapy for Gleason 9–10 patients through enrollment in clinical trials or potentially adding novel antiandrogens or docetaxel, which have shown efficacy in both castration-resistant and castration-sensitive settings.

Author contributions: Paul Linh Nguyen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Yang, Nguyen.
Acquisition of data: Mahal, Muralidhar, Orio, Nguyen.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Yang, Nguyen.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Yang.
Obtaining funding: Nguyen.
Administrative, technical, or material support: Yang, Mahal, Muralidhar.
Supervision: Nguyen.
Other: None.

Financial disclosures: Paul Linh Nguyen certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following:
Paul L. Nguyen reports personal fees from Ferring, Astellas, GenomeDx Inc, Dendreon, Nanobiotix, Augmenix, Bayer, and Blue Earth, as well as research support for clinical trials from Astellas and Janssen, which goes towards his affiliated institution. These financial relationships are all outside this submitted work. Felix Y. Feng reports personal fees from Medivation/Astellas, Ferring, GenomeDx Inc, Sanofi, Dendreon, Janssen, and EMD Serono and is a founder of PFS Genomics; these financial relationships are outside this submitted work. Neil E. Martin has received financial compensation for being a committee chair of Via Oncology, outside this submitted work. Quoc-Dien Trinh has received personal fees from Bayer and Astellas, outside this submitted work. Peter F. Orio has consulted for Augmenix, outside this submitted work. All other authors have no relevant conflicts of interest to disclose.

Funding/Support and role of the sponsor: This work was supported by the Prostate Cancer Foundation, Wood Family Foundation, the Baker Family, the Freeman Family, Fitz's Cancer Warriors, David and Cynthia Chapin, the Frashure Family, Hugh Simons in honor of Frank and Anne Simons, the Campbell Family in honor of Joan Campbell, the Scott Forbes and Gina Ventre Fund, and a grant from an anonymous family foundation. The funders of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Acknowledgments: The National Cancer Database (NCDB) is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The Commission on Cancer's NCDB and the hospitals participating in the NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors. The authors would like to thank the Commission on Cancer and the American Cancer Society for the creation and maintenance of the NCDB.
We thank Anna Krasnova, MHS, of the Center for Surgery and Public Health at Brigham and Women's Hospital for her assistance in the revision of this manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2018.08.033.

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