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Original Article

# Gleason score and docetaxel response in advanced hormone-sensitive prostate cancer: The lower the better

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ABSTRACT

*Aim:* Recently, three randomized controlled trials evaluated the addition of docetaxel to ADT in advanced hormone-sensitive prostate cancer (aHSPC). Interestingly, all trials showed a trend towards improved OS in the subgroup of patients with Gleason <8 tumors. We herein performed a meta-analysis of these trials to assess the OS benefit of docetaxel in different Gleason score groups (<8 vs ≥8).

*Material and Method:* We searched the Pubmed and Medline databases and ASCO conference proceedings (through February 1st 2018) for relevant trials. For each study, median OS values and hazard ratios (HR) with 95% confidence intervals (CI) collected across different Gleason score groups. We combined the HRs from each of the three eligible trials in the meta-analysis using the random-effect model.

*Results:* Three eligible studies were included in the analyses (CHAARTED, GETUG-AFU-15, and STAMPEDE). In the meta-analysis of three studies, docetaxel-based chemotherapy plus ADT was associated with improved OS [HR: 0.74; 95% CI: 0.62-0.87; p<0.001]. Among patients with tumor Gleason score <8, addition of docetaxel to ADT significantly improved overall survival [HR: 0.66, 95% CI: 0.52–0.85, p=0.001]. Although there was a trend towards improved OS with docetaxel in patients with Gleason score of ≥8, the magnitude of risk reduction was lower and did not achieve statistical significance [HR: 0.81, 95% CI: 0.64–1.02, p=0.066].

*Conclusion:* In this meta-analysis, OS benefit with the addition of docetaxel to ADT was more prominent in Gleason score <8 tumors. We propose that Gleason score can be a useful criteria for treatment selection in patients with aHSPC.



## 1. Introduction

Prostate cancer is a global health problem which is 1st in incidence and 5th in mortality among cancers in men worldwide.[1] Watchful waiting may be an appropriate strategy in early stages but it's usually associated with substantial morbidity and morbidity in patients with advanced disease.[2] The proportion of patients presenting with locally advanced and metastatic disease at first diagnosis is around 15% percent with nearly one-third of this group having metastatic disease.[3] Also, a substantial portion of patients with early disease can develop metastases during the disease course.[4]

Prostate cancer is an androgen-dependent tumor, therefore androgen deprivation therapy (ADT) remains the mainstay of treatment in advanced prostate cancer.[5] However, androgen (ie, castration) resistance develops after 2nd year in most patients.[6] It is a heterogeneous disease with androgen-sensitive and resistant sub-clones thought to exist together from the disease onset.[7] A number of studies demonstrated that castration resistance is a dynamic process in which ADT causes a selective growth advantage to androgen insensitive clones rather than the development of androgen insensitivity in previously androgen sensitive clones.[8] These observations led to the idea of early use of docetaxel and abiraterone in addition to androgen supression in advanced hormone sensitive prostate cancer (aHSPC).[9,10] While the efficacy of both agents was confirmed by recent large-scale clinical trials that showed prolonged survival, head-to-head comparisons are lacking which makes patient selection complicated.[11]

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Recently, three randomized controlled trials evaluated the addition of docetaxel to ADT in aHSPC. The results of two trials (CHAARTED and STAMPEDE)[9,12] showed improved OS with the addition of docetaxel to ADT, while GETUG trial showed no benefit in terms of OS.[13] Interestingly, all three trials showed a trend towards improved OS in the subgroup of patients with Gleason <8 tumors (GETUG, CHAARTED, and STAMPEDE).[9,12,13] From this point, we hypothesized that Gleason score may aid in patient selection for the addition of docetaxel in aHSPC. We herein performed a meta-analysis of these trials to assess the OS benefit of docetaxel plus ADT compared with ADT alone in patients with Gleason <8 tumors.

## 2. Methods

### 2.1. Data sources

We have searched the Pubmed and Medline Databases (articles published through February 1st, 2018) for relevant studies on the addition of docetaxel to ADT in aHSPC. Search terms included 'docetaxel', 'hormone-sensitive' and 'metastatic prostate cancer' as well as combinations of this terms.

### 2.2. Study selection and data extraction

Randomized controlled trials (RCT) testing the addition of docetaxel to ADT in aHSPC were included. When more than one report of the same trial was available, the most recent information was considered in the analysis. Only studies written English were included and analysed. While STAMPEDE trial[9] was included in the meta-analysis due to enrollment of both metastatic and non-metastatic aCSPC patients, studies enrolling only non-metastatic patients were excluded (GETUG-12,[14] RTOG 0521[15]). Two reviewers (O.D. and D.G.) independently extracted data from the studies. Any disaggrement was resolved by discussion with an another author. Age, performance score, Gleason score, stage, docetaxel dose, overall survival and hazard ratio of overall survival were extracted from each study.

### 2.3. Statistics

For each study, median OS values and hazard ratios (HR) with 95% confidence intervals (CI) were collected across different Gleason score groups (<8 vs ≥ 8). The risk of bias in individual studies was assessed at the study level with the risk of bias tool version 2.[16] The principal summary measure used was the hazard ratios with 95% two-sided confidence intervals. The pre-specified subgroup analyses were performed separately for Gleason score groups combining the results using the random-effect method (due to the unlikely unique effect of docetaxel on different ADTs) variance within each subgroup, as well as across subgroups. For each subgroup Q-values and their statistical significance were evaluated and the heterogeneity within each subgroup is reported using the I-square statistics. The risk of bias across studies were analysed using funnel plots and the significance (1-sided) Egger's regression intercept. A sensitivity analyses was performed to investigate the possible effect of the risk of publication bias for the Gleason score subgroup of <8. The meta-analyses were performed using the Comprehensive Meta Analysis Software.

## 3. Results

Three eligible studies were included in the analyses (CHAARTED, GETUG-AFU-15, and STAMPEDE) (Fig. 1).[9,12,13] STAMPEDE trial had two docetaxel arms (docetaxel + ADT and docetaxel + zolendronic acid + ADT) in comparison with ADT alone, and both arms were included due to the lack of OS effect with the addition of zoledronic acid in this trial.[9] A total of 3544 patients were enrolled in the studies, with 1774 (49%) being in the docetaxel plus ADT arm and 1800 (51%) in the ADT arm. Basal characteristics of patients were evenly distributed in the trials (Table 1). Overall the risk of bias of the individual studies was low in according to risk of bias tool version 2.[16] The heterogeneity across studies was low and insignificant for the Gleason score <8 group (Q-value: 2.5, $p = 0.48$, $I^2 = \%0.0$), while it was statistically significantly higher in the Gleason score ≥8 group (Q-value: 8.8, $p = 0.032$, $I^2 = \%66.0$), confirming the non-unique additive treatment effect of docetaxel across studies (Fig. 2).

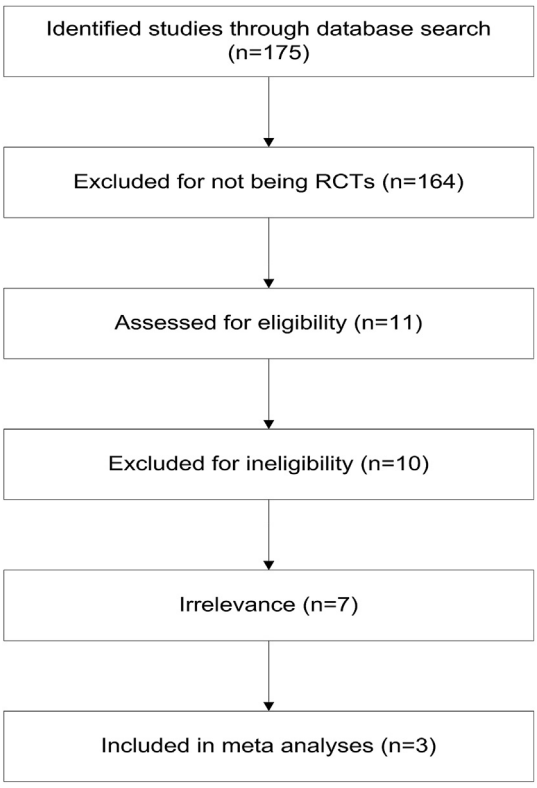


**Fig. 1.** Flowchart for study selection.

In the meta-analysis of three studies, docetaxel-based chemotherapy plus ADT was associated with improved OS [HR: 0.74; 95% CI: 0.62–0.87; $p < 0.001$]. Among patients with tumor Gleason score <8, addition of docetaxel to ADT significantly improved overall survival [HR: 0.66, 95% CI: 0.52–0.85, $p = 0.001$]. The sensitivity analyses excluding the study[9] with lowest HR but highest standard error to investigate the effect of a possible publication bias (Fig. 2), still resulted in a significant combined overall survival for this subgroup [HR: 0.72, 95% CI: 0.55–0.94, $p = 0.016$]. Although there was a trend towards improved overall survival with docetaxel in patients with Gleason score of ≥8, the magnitude of risk reduction was lower and did not achieve statistical significance [HR: 0.81, 95% CI: 0.64–1.02, $p = 0.066$] (see Fig. 3).

## 4. Discussion

This meta-analysis provides evidence that the addition of docetaxel to ADT improves survival in aHSPC and the benefit of docetaxel is particularly evident in patients with tumor Gleason score lower than 8.

Docetaxel is the first chemotherapeutic which showed a survival

**Table 1**
Summary of RCTs included in the analysis.

| | GETUG-AFU 15[13] | | CHAARTED[12] | | STAMPEDE[9] | | |
|---|---|---|---|---|---|---|---|
| | ADT | Docetaxel + ADT | ADT | Docetaxel + ADT | ADT | Docetaxel + ADT | Docetaxel + ZA + ADT |
| Age | 64 (58–70) | 63 (57–68) | 63 (39–91) | 64 (36–88) | 65 (41–82) | 65 (40–81) | 66 (42–84) |
| Performance Status | KFS ≥70 | KFS ≥70 | ECOG 0-2 | ECOG 0-2 | WHO 0-2 | WHO 0-2 | WHO 0-2 |
| Stage | M1 (100%) | M1 (100%) | M1 (100%) | M1 (100%) | M1 (61%) or N1 (14%) or 2 of 3 (25%): -T3/T4 -Gleason 8-10 -PSA≥40 ng/mL | M1 (62%) or N1 (15%) or 2 of 3 (23%): -T3/T4 -Gleason 8-10 -PSA≥40 ng/mL | M1 (62%) or N1 (13%) or 2 of 3 (25%): -T3/T4 -Gleason 8-10 -PSA≥40 ng/mL |
| Gleason Score <8 | 41% | 45% | 26.4% | 29.7% | 24% | 19% | 20% |
| Docetaxel Dose | NA | 75 mg/m$^2$ 9 cycles | NA | 75 mg/m$^2$ 6 cycles | NA | 75 mg/m$^2$ 6 cycles | 75 mg/m$^2$ 6 cycles |
| OS (months) | 54.2 | 58.9 | 44 | 57.6 | 71 | 81 | 76 |
| OS (HR, CI) | | HR: 1.01, 95% CI: 0.75–1.36 | | HR: 0.61, 95% CI:0.47–0.80 | | HR: 0.78, 95% CI: 0.66–0.93 | HR: 0.82, 95% CI: 0.69–0.97 |

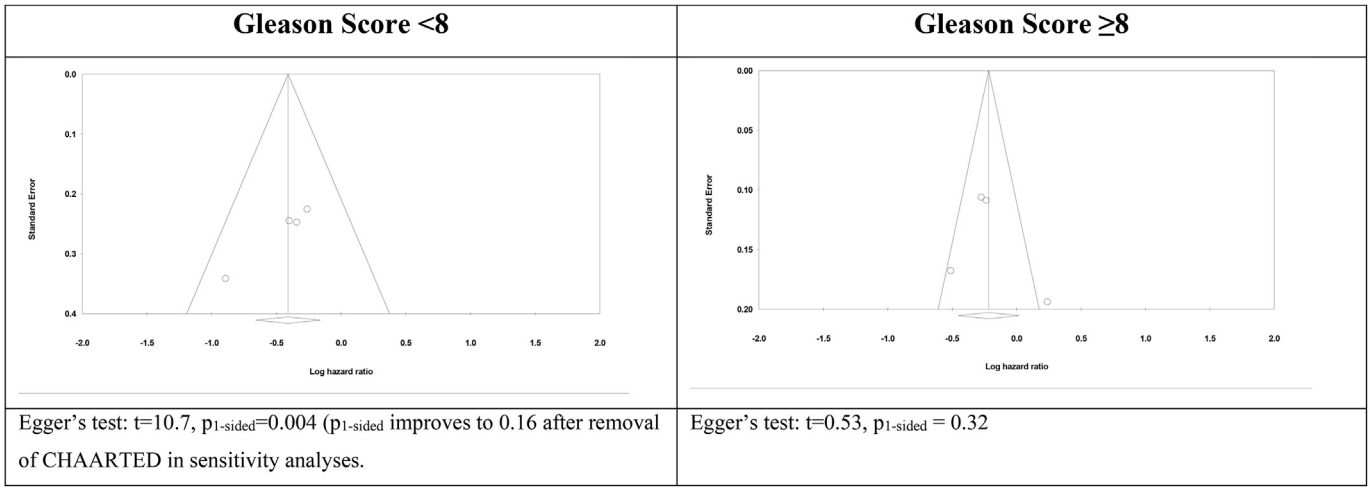


**Fig. 2.** Funnel plot analysis of publication bias and the associated statistics.

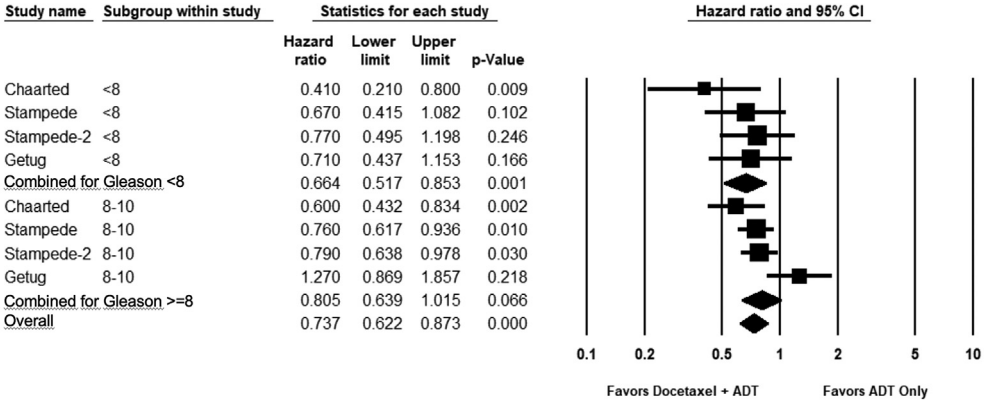


**Fig. 3.** Meta-analysis of trials according to Gleason score groups (<8 vs ≥ 8). (Stampede and Stampede-2 denotes to docetaxel and docetaxel + ZA arms, respectively.)

advantage in metastatic castration-resistant prostate cancer and approved for this indication after the findings in TAX327 and SWOG-9916 studies.[17,18] Recently it has entered the aHSPC stage after the positive results in the CHAARTED[12] and STAMPEDE[9] studies. CHAARTED study stratified patiently according to disease volume and showed a more a significant improvement in patients with high disease volume. The improvement in OS was seen both in GS < 8 and GS ≥ 8 tumors.[12] STAMPEDE study evaluated the addition of docetaxel, zolendronic acid or both to ADT in aHSPC. This study included both metastatic and non-metastatic high risk patients. Although docetaxel improved in the general population, survival advantage didn't reach the statistical significance in patients with GS < 8 tumors possibly due to low number of cases in this group.[9] GETUG-AFU-15 study was a negative study in regard to OS improvement, however there was a trend toward improved survival in patients with GS < 8 tumors[13] which was a contrasting finding to CHAARTED and STAMPEDE studies as both of them showed improvement in the patients with high GS tumors.[9,12]

The Gleason score is a well-established prognostic parameter which was developed more than 40 years ago.[19] It's calculated by

the sum of the grade patterns in the most predominant and second most common grade patterns and can range from 2 to 10.[20] It's stated to be the most important prognostic factor for survival in localized prostate cancer, while it's value was also showed in castration-sensitive and castration-resistant prostate cancer.[21] Studies in metastatic prostate cancer consistently demonstrated the better prognosis of <8 scores when compared Gleason score of ≥8.[22,23] However, it's value for patient selection in aHSPC treated with chemotherapy is rather an unanswered question due to lack of RCTs until recently.

In our meta-analysis, OS advantage of docetaxel was more prominent in patients with lower Gleason scores which suggested that more of the survival advantage of docetaxel resulted from the Gleason score <8 group. A similar trend was observed in the GETUG 12 trial which evaluated the comparison of docetaxel and estramustine plus ADT vs ADT in high risk localized prostate cancer. While patients with Gleason score <8 tumors conferred a progression-free survival (PFS) benefit with the addition of chemotherapy (HR: 0.54 CI:0.36–0.81), PFS with addition of docetaxel and estramustine in patients with Gleason score of ≥8 tumors was similar in both arms (HR: 1.02 CI: 0.68–1.54).[14] In contrast, the survival advantage of abiraterone acetate (AA) didn't seem to differ by various Gleason score groups in a meta-analysis of AA in aHSPC studies.[24]

Abiraterone acetate and docetaxel both improved OS in aHSPC but they have different toxicity profiles, cost and magnitude of OS advantage in different subgroups. All the included trials showed an increased rate of grade 3-5 adverse events with docetaxel, particularly myelotoxicity and neurotoxicity.,[9,12,13] and we think that it is rational to use docetaxel in patients who would derive the greatest benefit. Although head-to-head comparisons are lacking, Sydes et al. reported the direct comparison data from STAMPEDE multi-arm, multi-stage platform protocol comparing abiraterone vs docetaxel in addition to long-term hormone therapy for prostate cancer, which showed similar OS with docetaxel vs. abiraterone. However, no subgroup analysis based on Gleason score was reported in this study.[11] In a recent meta-analysis by Feyerabend et al., AA was at least effective as docetaxel in terms of OS and more effective in preventing disease progression and improving quality of life. Stratification according to different Gleason score groups was also lacking in this study.[25]

## 5. Conclusion

In this meta-analysis, we've demonstrated that OS benefit with the addition of docetaxel to ADT was more prominent in patients with Gleason score <8 tumors. We propose that Gleason score can be useful for tailoring treatment in patients with aHSPC. Further head to head comparison trials in different Gleason score groups can clarify the best upfront regimen in the treatment of aHSPC.

## Disclosure statement

The authors report no conflicts of interest.

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