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Original article

The prognostic significance of Gleason scores in metastatic prostate cancer

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Abstract

Purpose: Although the majority of metastatic prostate cancer (mPCa) will arise from tumors with Gleason scores (GS) of 8 to 10 existing tumor grade analyses for mPCa have been almost uniformly limited to comparisons of ≤ 7 vs. ≥ 8. In this analysis, we comprehensively evaluate the GS as a prognostic factor for mPCa in the era of the updated Gleason grading system.

Methods: The Surveillance, Epidemiology, and End Results (SEER) database was queried for patients with mPCa, GS 6 to 10, diagnosed from 2006 to 2008. GS and primary-secondary Gleason pattern variations were analyzed for overall survival and prostate cancer–specific survival (PCSS).

Results: A total of 4,654 patients were evaluable. At 4 years, the overall survival rates were 51%, 45%, 34%, 25%, and 15% and PCSS rates were 69%, 57%, 44%, 33%, and 21% for GS 6, 7, 8, 9, and 10, respectively. Survival differences for GS 7 vs. 8, 8 vs. 9, and 9 vs. 10 were highly significant on both univariate and multivariate analyses accounting for age, prostate-specific antigen level, and T stage (all $P < 0.001$). Gleason pattern 5 was an independent prognostic factor, both overall for patients with GS 6 to 10 and on primary-secondary Gleason pattern comparisons within the GS 8 ($4 + 4$ vs. $3 + 5$ and $5 + 3$) and GS 9 ($4 + 5$ vs. $5 + 4$) subgroups. No survival differences were observed between $3 + 4$ vs. $4 + 3$. Overall, lower prostate-specific antigen level, younger age, and lower GS were associated with improved survival, with GS being the strongest prognostic factor for PCSS.

Conclusions: In this large population-based cohort, stratified survival outcomes were observed for GS 6 to 10, with sequential comparisons of GS 7 to 10, and the presence and extent of Gleason pattern 5 representing independent prognostic factors in the metastatic setting.

Keywords: Prostate cancer; Metastasis; Gleason score; Histology; Prognosis

1. Introduction

The Gleason grading system is widely considered to be the most powerful prognostic factor for localized prostate cancer (PCa) [1]. Although Gleason scores (GS) of ≤ 6, 7, and 8 to 10 have traditionally been analyzed as homogenous risk categories, studies of localized PCa have demonstrated substantial prognostic heterogeneity within these groups based on overall GS and primary-secondary Gleason pattern (PSP) variations [1–4]. For metastatic PCa (mPCa), the GS is also a recognized prognostic factor for castrate-sensitive [5–7] and castrate-resistant disease [8–10], as well as an independent predictor for duration of hormone sensitivity [11]. However, while the majority of mPCa will arise from GS 8 to 10 disease [5,6], grade analyses in the metastatic setting have been almost uniformly limited to comparisons of GS ≤ 7 vs. ≥ 8.

As with localized PCa, a thorough characterization of GS stratifications relevant to survival outcomes in the metastatic setting would have important clinical implications, with the benefits of near-ubiquitous availability and ease of interpretation. In this analysis, we have used the Surveillance, Epidemiology, and End Results (SEER) database to comprehensively assess the survival outcomes based on GS stratifications in a large cohort of patients diagnosed in the era of the updated Gleason grading system [12].

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2. Methods

2.1. Data

Data were extracted from the National Cancer Institute–sponsored SEER database (18 Registries, Nov 2011 Sub [1973–2010]) using SEER*Stat v8.0.4. The search was confined to patients with microscopically confirmed PCa with known GS obtained on prostate biopsy, with American Joint Committee on Cancer staging system 7th edition defined M1 disease, diagnosed from 2006 to 2008 [13,14]. Individual GS were first made available in SEER in 2004. The year 2006 was selected as the first year in which all newly diagnosed cases of PCa were eligible for assessment using the updated 2005 International Society of Urologic Pathology (ISUP) consensus recommendations for Gleason grading [12].

Data regarding age, prostate-specific antigen (PSA) level, clinical T stage, overall survival (OS), and prostate cancer–specific survival (PCSS) were recorded for all cases. Total GS (2–10) was known for each case, and PSPs (1–5) were recorded in the subset of patients with available data. Data regarding tertiary Gleason patterns and systemic therapy administration, including androgen deprivation therapy and chemotherapy, were not available for analysis. Patient characteristic, staging, biopsy, and tumor grade information recorded in SEER are intended to represent disease characteristics at the time of initial cancer presentation and include "all information available within 4 months of the date of diagnosis" [13]. Cases of mPCa identifiable in SEER are, therefore, representative of synchronous or near-synchronous metastatic disease discovered within 4 months of initial presentation. Prostatectomy and external-beam radiotherapy were recorded as a component of initial management in 1.2% and 20.6%, respectively. However, due to the limited number of patients receiving prostatectomy and the lack of distinction between radiotherapy delivery to the prostate vs. sites of distant metastases, these data were not included as covariates in the primary survival analysis.

2.2. End points and analysis

The primary end point for this study was the comparative evaluation of OS and PCSS at 4 years in patients with GS 6 to 10. Twenty cases with GS ≤ 5 were identified during the study period and these cases were excluded from analysis. Secondary end points included a subset analysis of GS 6 to 10 for patients ≥ 70 years of age, an analysis of PSP variations within the subgroups of GS 7 (3 + 4 vs. 4 + 3), GS 8 with and without Gleason pattern 5 (GP5) (4 + 4 vs. 3 + 5 or 5 + 3), and GS 9 (4 + 5 vs. 5 + 4), comparisons of outcomes with and without GP5 for patients with GS 6 to 10 and known PSP, and an analysis of overall prognostic factors. Survival estimates were generated using the Kaplan-Meier method. Univariate analyses were performed using the log-rank test. Multivariate analyses accounting for age (<70 y, ≥ 70 y), T stage (1–4), and diagnostic PSA levels were performed using Cox proportional hazards regressions. SEER records diagnostic PSA values, representing the highest recorded value prior to diagnostic biopsy or the initiation of treatment, from 0.0 to 97.9 ng/ml and ≥ 98.0 ng/ml. Because approximately one-third of PSA levels were ≥ 98.0 ng/ml in this study cohort, PSA levels were divided into 3 groups for the purposes of analysis (0–49.9, 50–97.9, and ≥ 98.0 ng/ml) to allow proportional weighting in a multivariate model. Comparisons of characteristics between GS 6 to 10 were made using the chi-square test. Statistical significance was defined as $P < 0.05$ for all tests, and analyses were performed using SPSS version 22 (SPSS Inc, Chicago, IL).

3. Results

Our query returned 4,654 results. Patient characteristics are displayed in Table 1. GS groups included 272 (5.8%) patients with GS 6, 1,019 (21.9%) with GS 7, 1,128 (24.2%) with GS 8, 1,811 (38.9%) with GS 9, and 424 (9.1%) with GS 10. The median age was 71 years and age was well balanced by GS ($P = 0.200$). Higher PSA levels and T stage were observed with increasing GS (all $P < 0.001$).

3.1. Sequential Gleason sum comparisons (6 vs. 7, 7 vs. 8, 8 vs. 9, and 9 vs. 10)

Survival estimates for GS groupings are displayed in Fig. 1. The Kaplan-Meier 4-year OS rates were 50.9%, 45.3%, 33.6%, 25.4%, and 14.6% for patients with GS 6, 7, 8, 9, and 10, respectively. The 4-year PCSS rates were 68.7%, 57.4%, 43.9%, 33.2%, and 20.9% with GS 6, 7, 8, 9, and 10, respectively. Complete univariate and multivariate survival statistics for the primary analyses of GS 6 to 10 are shown in Table 2. Comparisons of GS 7 vs. 8, 8 vs. 9, and 9 vs. 10 were each highly significant on univariate and multivariate analyses (all $P < 0.001$). Comparisons of GS 6 vs. 7 demonstrated improved PCSS for patients with GS 6 on univariate analysis alone. However, GS 6 vs. 7 was not an independent prognostic factor for OS or PCSS on multivariate assessment accounting for age, PSA level, and T stage.

Subset analyses for patients ≥ 70 years of age demonstrated comparable patterns of significance overall, where GS 7 vs. 8, 8 vs. 9, and 9 vs. 10 were prognostic for OS and PCSS on univariate analyses (all $P < 0.001$). No significant differences were observed between GS 6 vs. 7 on univariate analyses of OS ($P = 0.614$) and PCSS ($P = 0.760$).

3.2. PSP comparisons

Survival estimates for PSP variations within GS 7, 8, and 9 are displayed in Fig. 2. Complete survival statistics are