Original Article

Incidence of metastasis and prostate-specific antigen levels at diagnosis in Gleason 3 + 4 versus 4 + 3 prostate cancer

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Abstract

Aims: The aim is to assess for a difference in the incidence of metastasis (IM) and prostate-specific antigen (PSA) levels at diagnosis in patients with Gleason score (GS) 3+4 versus 4+3 prostate cancer using a large veterans affairs database.

Subjects and Methods: A retrospective review of 1402 medical records from 5 VA hospitals was conducted. The study period was from 2009 to 2014. Primary endpoints were IM and PSA levels at diagnosis. A secondary endpoint was overall survival.

Statistical Analysis Used: Chi-square tests for categorical variables, Student's *t*-test for continuous, normally distributed variables, and rank sum tests for continuous nonnormally distributed variables.

Results: There were 1050 patients with GS3+4 and 352 with GS4+3. There were no differences in sociodemographic and clinical characteristics of the study population. PSA at the time of diagnosis was significantly higher in the GS4+3 patients compared to GS3+4 (18.0 vs. 11.4, respectively; $P < 0.001$). The IM at diagnosis was higher in the GS4+3 patients (10/352) compared to GS3+4 (9/1041) (2.8% vs. 0.9%; $P = 0.005$). In an adjusted model, GS4+3 was associated with higher PSA, higher IM at diagnosis. There was no difference in overall survival between the 2 groups though a 23% reduction in overall survival in the GS4+3 was noted ($P = 0.53$).

Conclusions: Our results indicate that patients with GS4+3 prostate cancers have higher PSA levels at diagnosis. GS4+3 is associated with 3-fold increased risk of IM at diagnosis than GS3+4 though the overall incidence is low. Further research is needed to assess whether GS4+3 patients need routine staging imaging investigations at the time of diagnosis similar to patients with higher Gleason scores (GS ≥8).

Keywords: Cancer, Gleason score, metastasis, prostate, prostate-specific antigen

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Received: 10.08.2017, **Accepted:** 08.10.2017

INTRODUCTION

Despite the recent rapid decline in prostate cancer diagnoses, prostate cancer remains the most common cancer diagnosis among males in the United States in the year 2016 (21% of all cancers) and the second most common cause of cancer deaths among men (8% of all cancers).[1] The diagnosis and management of prostate cancer have evolved over the years; however, prostate

Access this article online	
Quick Response Code:	Website: www.urologyannals.com
	DOI: 10.4103/UA.UA_124_17

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How to cite this article: Kamel MH, Khalil MI, Alobuia WM, Su J, Davis R. Incidence of metastasis and prostate-specific antigen levels at diagnosis in Gleason 3+4 versus 4+3 prostate cancer. Urol Ann 2018;10:203-8.

biopsy remains the mainstay of definitive diagnosis, and the management of the disease depends largely on histological grading.[2]

Conventionally, prostate cancer grading is done using the Gleason scoring (GS) system which offers both prognostic and risk data stratification based on score. The GS system characterizes prostate cancers based on a score between 2 and 10, with scores 2–6 representing well-differentiated tumors; and thus, a favorable prognosis, whereas a GS between 7–10 indicates a higher risk of disease severity and/or progression.[3]

A recent proposal at the 2014 International Society of Urological Pathology (ISUP) Consensus conference on Gleason Grading of Prostatic Carcinoma recommended a more meticulous system of classification, which allows for a more accurate prognostic and risk stratification.[4] In this model, GS 7 prostate cancers are more specifically reported as being either GS3+4 (with GS3 being more predominant with some GS4 pattern) or GS4+3 (with more predominant Gleason 4 and some GS 3 pattern). Therefore, GS4+3 cancers are thought to represent more severe disease when compared to GS 3+4 disease.

This recent dichotomization of Gleason 7 prostate cancers by the ISUP is based on various reports in the literature that have shown differences in prognosis and risk between GS3+4 and GS4+3 prostate cancers. Some studies describe an increased risk of adverse pathology at the time of radical prostatectomy as well as an increased risk of biochemical recurrence after prostatectomy in GS4+3 cancers compared to GS3+4 cancers.[5-7] However, little is known about the differences in the incidence of metastasis (IM) and prostate-specific antigen (PSA) levels at diagnosis between these 2 groups. Furthermore, most guidelines would recommend staging imaging investigations to newly diagnosed prostate cancer patients at diagnosis based on GS and PSA levels at the time of diagnosis.[8]

With the recent ISUP grading system, in which GS4+3 is assigned a higher risk category than GS3+4, we sought to investigate for differences in the IM and PSA levels at time of diagnosis between the two GS 7 prostate cancer groups. To achieve that we studied a large population of veterans presenting to 5 veterans affairs (VA) hospitals within the same region, with GS 7 prostate cancer. The United States VA health system is an equal access health-care system that maintains rigorous monitoring and recording of its data making its results reliable.

SUBJECTS AND METHODS

Data source

Five research collaborating VA hospitals in the same region pooled their data together. These hospitals were Biloxi, MS (BLX), Houston, TX (HOUSTON), Jacksonville, MS (JAX), Little Rock, AR (LR) and New Orleans, LA (NOLA).

Information on the Gleason grade in the database is recorded in the form of primary grade + secondary grade and the sum; GS. The VA database does not include information on tertiary grade patterns. Patients had their PSA recorded at the time of diagnosis of prostate cancer, as well as the presence or absence of metastasis. The VA database allows recording of up to 3 different sites of metastasis at the time of diagnosis. For the purpose of this study, patients were considered to be either positive/negative for metastasis at time of diagnosis regardless of how many anatomical sites were recorded. Other information available in the database include age, race, marital status, alcohol consumption/tobacco smoke, method of diagnosis of prostate cancer (needle biopsy/transurethral resection of prostate), digital rectal examination findings, treatment offered (surgery, radiation, hormones, or no treatment), the American Joint Committee on Cancer (AJCC) stage, presence or absence of lymphovascular invasion/lymph node status after radical prostatectomy, presence or absence of comorbidities, date of last follow-up, and survival status. Survival in the VA dataset is recorded as overall survival. Disease-specific mortality is unavailable.

Patient demographics

Between 2009 and 2014, 1402 veterans were diagnosed with Gleason 7 prostate cancer. This patient population comprised of 1050 patients with GS3+4 prostate adenocarcinoma and 352 patients with GS4+3 cancers. The mean age at diagnosis was 63.6 years for the GS3+4 patients and 65.4 years for patients with GS4+3 cancers. Differences in demographics between GS3+4 and 4+3 patients have been detailed in Table 1.

Clinical characteristics

Clinical characteristics assessed include vital status, PSA levels at diagnosis, digital rectal examination findings, AJCC stage, metastasis at diagnosis, and treatment administered. Clinical characteristics of the two study populations are shown in Table 2.

Statistical analysis

Sociodemographic and clinical characteristics between prostate cancer patients diagnosed with primary and

Table 1: Patient demographics

Characteristics	Characteristics		*P*
	3+4	4+3	
	Mean (STD)	Mean (STD)	
Age	63.6 (6.5)	65.4 (6.8)	0.25
	N (%)	*N* (%)	
Race			
American Indian, Aleutian, Eskimo/Asian Indian	6 (0.6%)	5 (1.4%)	0.24
Asian Pacific Islander	6 (0.6%)	2 (0.6%)	
Black	517 (49.4%)	186 (53.0%)	
White	518 (49.5%)	158 (45.0%)	
Facility*			
BLX	52 (5.0%)	13 (3.7%)	<0.001
Houston	395 (37.6%)	183 (52.0%)	
JAX	218 (20.8%)	50 (14.2%)	
LR	274 (26.1%)	72 (20.5%)	
NOLA	111 (10.6%)	34 (9.7%)	
Marital Status			
Divorced	336 (32.1%)	115 (32.8%)	0.45
Married	518 (49.4%)	175 (49.9%)	
Single	147 (14.0%)	40 (11.4%)	
Widowed	47 (4.5%)	21 (6.0%)	
Alcohol Use History			
Current	470 (48.6%)	155 (47.4%)	0.63
Never	351 (36.3%)	115 (35.2%)	
Previous	147 (15.2%)	57 (17.4%)	
Tobacco Use History			
Never	276 (27.7%)	85 (25.4%)	
Previous	323 (32.5%)	125 (37.3%)	
Current	351 (35.3%)	113 (33.7%)	
Combination use	3 (0.3%)	4 (1.2%)	0.12
Snuff	7 (0.7%)	2 (0.6%)	
Cigar	35 (3.5%)	6 (1.8%)	

*Note: BLX: Biloxi, MS, JAX: Jacksonville, MS, LR: Little Rock, AR, NOLA: New Orleans, LA

secondary GS3+4 versus 4+3 were examined using Chi-square tests for categorical variables, Student's *t*-test for continuous, normally distributed variables, and rank sum tests for continuous nonnormally distributed variables. Variables were then investigated as potential confounders in stratified analysis to compare the crude association between primary and secondary GSs and time to death with the stratified estimate. Variables were included in the multivariable model if they were significant at the alpha 0.05 level or if they changed the primary exposure beta estimate by more than 10%. The proportional hazards assumption was assessed by creating interaction terms for the covariates and time. Time-to-event analysis was performed using Kaplan–Meier and Cox proportional hazard methods with the primary endpoint mortality after cancer diagnosis. This study was conducted after granting an exemption from Institutional Review Board as no patient identifier was used.

RESULTS

The mean overall follow-up for patients (both alive and dead) was 1067.3 days (standard deviation [SD] =281.2 days). Mean follow-up for patients who died (n = 117) is 464.6 days (SD = 340.5 days) and for patients still alive (n = 1376) is 1118.5 days (SD = 206.1 days).

Patient demographics

There were no differences between the 2 groups regarding their demographics. Of note, the African American veterans were not at an increased risk of presenting with GS4+3 prostate cancer at the time of diagnosis.

Clinical characteristics

Average PSA levels were significantly higher in patients with GS4+3 prostate cancer compared to those presenting with GS3+4 cancer (18.0 vs. 11.4; $P < 0.001$; range 0.6–674.1 vs. 0.2–530.0, respectively). Digital rectal examination (DRE) performed at the time of diagnosis in 1,304 patients show no statistically significant correlation between clinically normal/abnormal prostate volume and Gleason score. Patients with clinically abnormal DRE at the time of diagnosis were not at higher risk of having GS4+3 prostate cancers. The incidence of distant metastasis at the time of diagnosis was higher in the GS4+3 (9/1041) (2.8%), compared to GS3+4 study group (10/352) (0.9%) ($P < 0.005$). Model to predict distant metastasis at diagnosis encompassing PSA level and DRE adjusting for age suggests that each increased unit (ng/mL) of PSA is associated with 3% increased chance of distant metastasis (odds ratio = 1.03, 95% confident interval = 1.01, 1.05), whereas clinically abnormal DRE is not associated with the likelihood of distant metastasis at diagnosis.

There was no preference in the treatment offered to patients with GS3+4 versus 4+3 in terms of surgery, radiation therapy, or androgen deprivation therapy. Of note, 19% of patients with GS3+4 and 15.6% of patients with GS4+3 did not receive treatment. The group of patients that did not receive treatment was older and with lower AJCC stage at diagnosis.

Using an adjusted model for age, PSA, tobacco use history, facility, race, incidence of distant metastasis, stage of disease at time of disease and treatment, we found that patients with GS4+3 prostate cancers were at a higher risk of having higher PSA levels at time of diagnosis, distant metastasis at diagnosis, and experienced a 23% reduction in overall survival when compared to those with GS3+4 prostate disease [Table 3].

DISCUSSION

Despite the reduction in prostate cancer-specific mortality, there has been an increase in the incidence and diagnosis of prostate cancer worldwide.[9]

Table 2: Clinical Characteristics of Study Patients

Characteristics	GLEASON		*P*
	3+4	4+3	
	Mean (STD)	Mean (STD)	
PSA Levels[1]	11.4 (23.3)	18.0 (54.7)	<0.001
Survival Days	1259.7 (534.2)	1265.7 (534.2)	0.85
	N (%)	*N* (%)	
Deceased			
Yes	63 (6.0%)	24 (6.8%)	0.58
DRE[2]			
Clinically abnormal	307 (29.4%)	106 (30.3%)	0.85
Clinically normal	668 (63.9%)	223 (63.7%)	
Not done/Not documented	71 (6.8%)	21 (6.0%)	
Stage[3]			0.06
II	8 (0.8%)	7 (2.0%)	
IIA	618 (59.5%)	182 (52.3%)	
IIB	256 (24.6%)	89 (25.6%)	
III	116 (11.2%)	51 (14.7%)	
IV	24 (2.3%)	13 (3.7%)	
Unknown	17 (1.6%)	6 (1.7%)	
Distant Metastasis			
No	1041 (99.1%)	342 (97.2%)	0.005
Yes	9 (0.9%)	10 (2.8%)	
Treatment			
NONE	199 (19.0%)	56 (15.9%)	0.08
XRT	398 (37.9%)	143 (40.6%)	
HORMONE	71 (6.8%)	36 (10.2%)	
SURGERY	382 (36.4%)	117 (33.2%)	

Note: 1. 9 GS3+4 and 5 GS4+3 PSA value was not available, 2. 4 GS3+4 and 2 GS4+3 DRE status was not available, 3. 11 GS3+4 and 4 GS4+3 clinical stage was not available

Table 3: Survival analyses comparing prostate cancer diagnosis with Gleason "3+4" (*n*=1,050) vs Gleason "4+3" (*n*=352) adjusting for confounders

Gleason Scores	Hazard Ratio	*P*
Crude model		
3+4	1.00	0.88
4+3	1.04 (0.64, 1.67)	
Age adjusted model		
3+4	1.00	0.97
4+3	0.99 (0.61, 1.61)	
Age	1.02 (0.99, 1.05)	0.26
Age and treatment adjusted model		
3+4	1.00	0.70
4+3	1.13 (0.61, 2.09)	
Age	1.00 (0.97, 1.04)	0.87
Treatment		
None	1.00	
Hormone	0.61 (0.25, 1.50)	0.28
Surgery	0.31 (0.12, 0.79)	0.01
XRT	0.38 (0.20, 0.74)	0.004
Fully adjusted model*		
3+4	1.00	0.53
4+3	1.23 (0.64, 2.41)	
Age	1.01 (0.97, 1.05)	0.82
Treatment		
None	1.00	
Surgery	0.32 (0.09, 1.12)	0.07
XRT	0.43 (0.21, 0.86)	0.02
Hormone	0.64 (0.23, 1.75)	0.38

* Model adjusted for age, PSA, tobacco use history, facility, race, distant metastasis, and stage at diagnosis

In 2014, The ISUP introduced a new grading system which includes five distinct Grade Groups, based on modified GSs; Grade Group 1 = GS ≤6, Grade Group 2 = GS3+4 = 7, Grade Group 3 = GS4+3 = 7, Grade Group 4 = GS4+4 = 8, and Grade Group 5 = GSs 9 and 10.[4] The classification of GS 7 prostate cancers into two distinct groups (GS3+4 and GS4+3) has further enhanced our understanding of Gleason 7 disease and the management of intermediate-risk prostate cancers.

There have been several reports in the literature describing higher risk prostate cancers and increased biochemical recurrence rates following treatment in prostate biopsy samples with predominant Gleason pattern 4.[5-7,10] The increased aggressiveness of GS4 disease has been discussed in the literature: Biopsy proven GS3+4 disease when compared to GS3+3 disease had an increased risk of adverse pathology being present at the time of surgery and men with elements of Gleason 4 prostate cancer who are initially treated with conservative management are at an increased risk of eventual metastasis.[11,12] To the best of our knowledge, our current report is the largest cohort, comparing GS4+3 and GS3+4 prostate adenocarcinoma patients (1402 patients). We focused on the IM and PSA levels at diagnosis, together with overall survival using a reliable, well-maintained database of an equal access health-care entity; the United States VA health care system. We first document the IM at diagnosis in patients with GS4+3 versus 3+4 as well.

The overall IM at diagnosis in GS4+3 and GS3+4 (2.8% vs. 0.9%, respectively) was low. Despite the low incidence of metastatic disease at time of diagnosis in GS7 patients, our findings indicate a 3-fold increased risk of distant metastasis for patients with GS4+3 disease compared to those with GS3+4 ($P < 0.005$). This low IM has been shown in the previous studies.[12,13] In a study of men with prostate cancer initially treated with surveillance, the incidence of metastasis was found to be 3.1% and the presence of Gleason pattern 4 on biopsy increased the risk of metastasis by threefold to fourfold.[12] A recent analysis of the Surveillance, Epidemiology, and End Results (SEER) database also found the incidence of metastasis in GS ≤6, GS7 and GS ≥8 prostate cancers to be 0.1%, 0.7%, and 12%, respectively.[13] Collectively, this suggests that cancers with predominantly grade 4 as GS4+3 cancers, increase the risk of distant metastasis. This also supports the idea that men with GS4+3 and GS8 prostate cancers may have similar pathologic characteristics and the recommendation that all men with GS ≥4+3 undergo lymphadenectomy at the time of radical prostatectomy regardless of clinical stage or serum PSA.[14]

Major North American and European guidelines recommend staging investigations at diagnosis for patients

with higher GS (≥8) and higher PSA levels.[15,16] Our findings that GS4+3 prostate cancers are likely to present with distant metastasis than GS3+4 may indicate the need for a more aggressive algorithm in the initial diagnosis and management of patients presenting with GS7. There have been reports of overuse of bone scans in patients with low and intermediate-risk prostate cancers (GS ≤7).[13] Our findings that incidence of metastasis at diagnosis in GS4+3 is higher than GS3+4 may help with solving this debate.

Our results show patients with GS4+3 presented with higher PSA at diagnosis than GS3+4 (18.0 vs. 11.4, respectively) ($P < 0.001$). Furthermore, in a model adjusted for age for every increase of 1 ng/ml in PSA level at diagnosis, the chance of developing distant metastasis increased by 3%.

Pre-operative PSA levels have been shown to correlate with aggressiveness and pathological stage of prostate cancer; patients with PSA levels >10 are more likely to have GS ≥7 prostate cancer, have positive margins, seminal vesicle involvement, and lowest 10-year progression-free survival rates.[17] However, it has also been reported that patients with high-risk prostate cancer (GS ≥8) may produce relatively little PSA due to the poorer differentiation of these tumors.[18,19] Nevertheless, a high-PSA level at the time of diagnosis will continue to be an indication of staging imaging investigations in both European and North American guidelines on prostate cancer.[15,16]

Regarding overall survival, there was no difference between GS4+3 versus 3+4 though in GS4+3 veterans, a 23% reduction in overall survival was observed. The previous studies have shown that a primary Gleason 4 pattern in GS7 prostate cancers is an independent risk factor for biochemical recurrence and lower recurrence-free survival, compared to tumors with primary Gleason 3 pattern at any time after radical prostatectomy.[7,10] Recent overall survival rates for GS 6, 7, 8, 9, and 10 have been reported as 51%, 45%, 34%, 25%, and 15%, respectively with significant survival differences between GS7 and GS8. However, no survival differences were observed between GS3+4 versus 4+3.[20] Compared to disease-specific mortality, a study of the 10-year prostate cancer-specific survival rates found no difference in disease-specific mortality between GS4+3 and GS8-10 prostate cancers, and patients with GS4+3 disease were at an increased risk for prostate cancer-specific mortality compared to those with GS3+4. The 10-year prostate cancer-specific survival rate for GS ≤6, 3+4, 4+3, and GS ≥8 was found to be 98.4%, 92.1%, 76.5%, and 69.9%, respectively.[21]

In our study, African-American men were not at increased risk of presenting with GS4+3 prostate cancer at diagnosis. This finding is similar to that reported by other studies performed using a VA health-care database.[22] The literature is rich with historical reports that African-American men are more likely to present with advanced prostate cancer disease, and therefore, have an increased risk of mortality.[23] However, more contemporary studies have shown an improvement in the racial disparities in lung and prostate cancers in men, indicating similar risks of mortality across races.[24] The results of our study support these recent trends as well as the hypothesis that the receipt of care within the VA health-care system reduces the disparities seen in prostate cancer. This may be attributed to the early, easy, and equal access to care afforded by the United States VA health-care system to all veterans.

In our study, there was no correlation between DRE findings and the risk of GS4+3 prostate cancer. Although a clinically abnormal DRE has been shown to be an independent predictor of GS ≥7 prostate cancer,[25] there is no data to suggest any such correlation between DRE findings and GS4+3 versus GS3+4-specific prostate cancers.

According to our results, it appears that Urologist's selection of treatment modality did not take into consideration, the subset/type of GS7 prostate cancer being treated (GS3+4 vs. GS4+3). As a whole group of GS7 patients, 41% were treated with external beam radiotherapy, 33% with surgery and 16% receiving no treatment at all. The no treatment at all group were older and having lower AJCC stage. This present study and results are comparable to other studies in the literature that have shown that tumors with Gleason grade 4 tend to pursue a more aggressive course than GS3+3 or GS3+4 prostate cancers.[26,27]

The current study has limitations. This includes the retrospective, nonrandomized approach to the review of medical information/data on patients with prostate cancer. In addition, the VA database did not analyze tertiary grades or specific numbers/percentages of positive cores in each prostate biopsy sample. Finally, disease-specific mortality is lacking which means that associated comorbidities in our patients may have contribute to the survival rates observed in our study.

CONCLUSIONS

We conducted a study of 1402 VA medical records to determine the incidence of metastasis and PSA levels at

diagnosis as well as overall survival among patients with GS3+4 versus GS4+3 prostate cancer. We found that patients with GS4+3 prostate cancer were more likely to present with higher incidence of distant metastasis at the time of diagnosis, had higher PSA levels and experienced a 23% reduction in overall survival, although the survival difference did not reach statistical significance. Whether this warrants consideration of a more aggressive initial management in the form of staging imaging investigations will require further research.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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