A comparative analysis of prostate cancer pre-treatment characteristics stratified by age

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Introduction: *To compare the pretreatment characteristics of prostate cancer, prostate-specific antigen (PSA), digital rectal examination (DRE) and Gleason sum score (GSS) by the American Urological Association (AUA) stratified age groups, < 55, 55-69 and ≥ 70 years old.*

Materials and methods: *A retrospective analysis of 402 sequential prostate cancer patients, who had transrectal ultrasound guided 12 core prostate biopsy for either elevated PSA (over 2.5 ng/mL) or positive DRE or both during a three period, 2010 to 2012. There were 36 patients < 55 years, 226 patients 55 to 69 years and 140 patients ≥ 70 years (range 44-78 years old). This study was conceptualized after the AUA released prostate cancer screening guidelines in which men ≥ 70 were deleted from screening.*

Results: *Overall, compared with patients < 70 years old, we found that in patients ≥ 70 years old:*
1) 60.7% had high GSS (7-10) (p = 0.0234); 2) 39.3% had low GSS (6) (p = 0.0234); 3) 31% had PSA level ≥ 10 ng/mL (p = 0.0010) and 4) 69.1% had high GSS (7-10) in the presence of a positive DRE (p = 0.0278).

Conclusion: *Patients ≥ 70 years old had a higher incidence of high GSS (7-10) compared to prostate cancer patients < 70 years old. Patients ≥ 70 years old who also had a positive DRE had the highest incidence of high GSS.*

Key Words: prostate cancer, age, Gleason sum score

Introduction

Prostate cancer is the second leading cause of cancer related death in American men. In 2014, the American Cancer Society estimated that there would be 233000 new cases of prostate cancer and 29480 deaths due to prostate cancer. One in six men will be diagnosed with prostate cancer during his lifetime. Nearly 66% of prostate cancer cases are diagnosed in men aged 65 years and older. If prostate cancer is diagnosed early and treated it has a 99% 5 year survival rate. Early diagnosis of prostate cancer by prostate-specific antigen (PSA) and digital rectal examination (DRE) has decreased the number of prostate cancer deaths by 40% in the last two decades.[1,2]

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The American Urological Association (AUA) has issued prostate cancer screening guidelines for the age groups, < 40, 40-54, 55-69, and ≥ 70 years old and recommended against screening in men < 40, 40-54, and ≥ 70 years old.[3] Loeb et al recently analyzed long term radical prostatectomy (RP) outcomes among participants from the European Randomized Study of Screening for Prostate Cancer. Four-hundred twenty of the screen detected prostate cancer patients and 54 of the non-screened patients underwent RP. Men from the screened arm had significantly higher progression-free survival, metastasis-free survival and cancer-specific survival.[4] Pathological analysis of radical prostatectomy specimens has shown that patients ≥ 70 years old have increased Gleason sum score (GSS) (8-10), positive surgical margins, extracapsular extension, seminal vesical invasion, and lymph node metastasis.[5]

Prostate cancer is stratified by risk category as originally defined by D'Amico et al.[6] The risk category is based on pre-treatment characteristics including

PSA, DRE, and Gleason sum score. In contradiction to the AUA guidelines, we hypothesize that patients ≥ 70 years old have more advanced pre-treatment characteristics of prostate cancer compared with younger patients and should be screened for prostate cancer. To test our hypothesis, we retrospectively reviewed 402 sequential men diagnosed with prostate cancer examining the role of pre-treatment characteristics (PSA, DRE and GSS) stratified by the AUA defined age groups, < 55, 55-69, and ≥ 70years old.

Materials and methods

We completed a retrospective analysis, focusing on PSA, DRE and GSS, in 402 sequential prostate cancer patients who had transrectal ultrasound guided 12 core prostate biopsy for either elevated PSA (over 2.5 ng/mL), positive DRE or both during a 3 year period, 2010 to 2012. The charts of consecutive patients from our practice were reviewed and the information was entered in a database. The data was analyzed to determine associations between the age groups and pre-treatment characteristics.

Our group of 12 board certified urologists performed DRE in all of the 402 sequential patients and performed biopsies under intravenous sedation. All patients were medically cleared for the procedure by their primary care doctors.

The Gleason pattern 4 component confers aggressive characteristics associated with tumor progression. We grouped all patients into two groups, Gleason sum scores of 7-10 (those containing Gleason pattern 4 or higher) and GSS 6 (Gleason pattern 3 only). This grouping was intended for comparison of high grade versus low grade tumors. Additionally, the grouping separates patients that are potential candidates for active surveillance versus patients that should receive treatment.

Chi-Squared or Fisher's Exact Tests were used to compare frequencies. A regression analysis for age, nodule and PSA predicting for Gleason score was performed (multivariable analysis). All analyses were conducted using the SAS software system.

The study was approved by the Western Institutional Review Board (study number 1087891).

Results

Patient characteristics

Four-hundred two patients were diagnosed with prostate cancer after referral to our urology group, by primary care physicians to rule out prostate cancer as they had either high PSA over 2.5 ng/mL, abnormal DRE or both. The mean age of the entire cohort was 66 years. One-hundred percent reported full independence in activities of daily living. Patients with moderate to severe comorbidity were not biopsied. Patients with a life expectancy less than 10 years were not biopsied. The median PSA value was 6.5 ng per milliliter (mean, 9.8). Sixty-two percent of men had stage T1c disease (not palpable, detected by means of PSA testing). Fifty-two percent had histologic scores of 7 or higher on the Gleason scale; 37% of the men had low risk, 36% intermediate risk, and 27% high risk prostate cancer. Sixty-three percent had tumors in the intermediate risk or high risk categories.

Age versus PSA

In the patients < 55 years old, 5 patients had a PSA under 4 (13.9%), 25 patients had a PSA between 4 and 10 (66.7%), and 6 patients had a PSA over 10 (19.4%). In the patients 55 to 69 years old, 23 patients had a PSA under 4 (10.2%), 150 patients had a PSA between 4 and 10 (64.6%), and 53 patients had a PSA over 10 (25.2%). In the patients ≥70 years old, 17 patients had a PSA under 4 (12.1%), 80 patients had a PSA between 4 and 10 (56.4%), 43 patients had a PSA over 10 (31.4%), (p = 0.0010), Table 1.

Age versus GSS

GSS of 7-10 were grouped together in order to compare high grade tumors to low grade tumors (GSS 6). In the patients < 55 years old, 18 patients had a GSS of 6 (50%), 16 patients had a GSS of 7 (44.4%), and 2 patients had a GSS of 8 (5.5%). This showed that 50% had a high GSS (7-10). In the patients 55 to 69 years old, 122 patients had a GSS of 6 (54%), 68 patients had a GSS of 7 (30%), 25 patients had a GSS of 8 (11%), 9 patients had a GSS of 9 (4%), and 2 patients had a GSS of 10 (1%). This showed that 46% had a high GSS (7-10). In the patients ≥ 70 years old, 55 patients had a GSS of

TABLE 1. **Age versus prostate-specific antigen (PSA)**

Total n = 402	**PSA < 4 ng/mL**	**PSA 4 ng/mL-9.9 ng/mL**	**PSA 10+ ng/mL**
Age < 55 (n = 36)	5 (13.9%)	25 (66.7%)	6 (19.4%)
Age 55-69 (n = 226)	23 (10.2%)	150 (64.6%)	53 (25.2%)
Age ≥ 70 (n = 140)	17 (12.1%)	80 (56.4%)	43 (31.4%)
p = 0.0010			

TABLE 2. **Age versus Gleason sum score (GSS)**

Total n = 402	**GSS 6**	**GSS 7-10**
Age < 55 (n = 36)	18 (50.0%)	9 (50.0%)
Age 55-69 (n = 226)	122 (54.0%)	104 (46.0%)
Age ≥ 70 (n = 140)	55 (39.3%)	85 (60.7%)
p = 0.0234		

6 (39%), 50 patients had a GSS of 7 (36%), 17 patients had a GSS of 8 (12%), 10 patients had a GSS of 9 (7%), and 8 patients had a GSS of 10 (6%). This showed that 60.7% had a high GSS (7-10), (p= 0.0234), Table 2.

Age and DRE versus GSS

In the patients < 55 years old, 27 patients had an positive DRE (75%), and 9 patients had a negative DRE (25%). In this group, 66.7% with positive DRE and 44.4% of the negative DRE had a low GSS of 6, while 33.3% of the positive group and 55.6% of the negative group had a high GSS of 7-10.

In the patients 55 to 69 years old, 139 patients had a positive DRE (61.5%), and 87 patients had a negative DRE (38.5%). In this group, 49.4% of the positive DRE and 56.8% of the negative DRE had a low GSS of 6, while 50.6% of the positive group and 43.2% of the negative group had a high GSS of 7-10.

In the patients ≥ 70 years old, 85 patients had a positive DRE (60.7%), and 55 patients had a negative DRE (39.3%). In this group, 30.9% of the positive group and 44.7% of the negative group had a low GSS of 6, while 69.1% of the positive group and 55.3% of the negative group had a high GSS of 7-10, (p = 0.0278).

A multivariable analysis was performed for age, DRE and PSA predicting for Gleason sum score. The multivariable analysis showed that age (p = 0.0003) and PSA (p = 0.0001) predicted for high grade GSS (7-10) independent of the other variables, Table 3.

Overall, compared with patients < 70 years old, we found that in patients ≥ 70 years old:

- 60.7% had high GSS (7-10) (p = 0.0234)
- 39.3% had low GSS (6) (p = 0.0234)
- 31% had PSA level ≥ 10 ng/mL (p = 0.0010)
- 69.1% had high GSS (7-10) in the presence of a positive DRE (p = 0.0278)

Discussion

The AUA issued guidelines recommending against screening men ≥ 70 years old for prostate cancer.[3] The prostate cancer literature has an abundance of data that indicates that older men suffer disproportionately with advanced prostate cancer disease. Scosyver et al analyzed 46498 patients who were diagnosed with prostate cancer from 1998 to 2007. They reported that the frequency of metastatic prostate cancer was 3% for the group below 75 years old versus 33% in the group over 75 years of age. The 5 year cumulative death from prostate cancer was 3% in those below 75 years versus 70% in patients over 75 years. Although patients aged 75 years and older represented 26% of all prostate cancer cases, they contributed 48% of metastatic cases and 53% of all prostate cancer deaths.[7]

Richstone et al reviewed patients who underwent radical prostatectomy (RP) for prostate cancer. The group included 258 men who were ≥ 70 years old, and 3777 men younger than 70 years. Comparison between these two groups showed that patients over 70 years old had higher stage disease, higher pathological GSS, and lower frequency of organ confined disease compared to their younger counterparts. In addition, upstaging was more frequent (40.2%) in patients older than 70 years compared with younger men (29.3%).[8]

Sun et al reported a study of 4561 men who underwent RP. They found that men over 70 years of age had a higher proportion of pathological tumors (stage 3 and 4), higher GSS (> 7), and larger tumor volume.[9]

TABLE 3. **Age and digital rectal examination (DRE) versus Gleason sum score (GSS)**

Total n = 402	**GSS 6**	**GSS 7-10**
Age < 55, positive DRE (n = 27)	18 (66.7%)	9 (33.3%)
Age < 55, negative DRE (n = 9)	4 (44.4%)	5 (55.6%)
Age 55-69, positive DRE (n = 139)	69 (49.4%)	70 (50.6%)
Age 55-69, negative DRE (n = 87)	49 (56.8%)	38 (43.2%)
Age 70+, positive DRE (n = 85)	26 (30.9%)	59 (69.1%)
Age 70+,negative DRE (n=55)	25 (44.7%)	30 (55.3%)
(p= 0.0278)		

Loeb et al found that in 8968 men who underwent RP, patients who were 70 years old or older had the highest frequency of GSS between 8 to 10, positive surgical margins, extracapsular extension, seminal vesical invasion, and lymph node metastasis. They concluded that men older than 70 years old were associated with poorer tumor histopathology and poorer survival rate.[5]

Adams et al reviewed 71 cases of newly diagnosed prostate cancer where the screening PSA level was ≥ 100. In these 71 men the median survival was 18 months and less than 10% lived beyond 3 years. Thirty-five percent of patients in this group were ≥ 71 years old.[10]

In addition to PSA, DRE has an important role in prostate cancer detection and prognostication. Meeks et al studying 1278 men who underwent radical retropubic prostatectomy (RRP) showed that of 77 men with PSA less than 2.5 ng/mL, 50 (66%) had an positive DRE, and the DRE was normal in 26 (34%).[11]

In the current study of 402 men biopsy diagnosed with prostate cancer, 61% of men ≥ 70 years old had a GSS 7-10 and of those with a positive DRE 69% had a GSS 7-10. These percentages are significantly higher compared to patients younger than age 70. Moreover, in the 55-69 year old group, 54% had GSS 6 and 46% had GSS 7-10 while in the ≥ 70 year old group, 39% had GSS 6 and 61% had GSS of 7-10. Both univariant and multivariant statistical analysis showed that higher age correlated to higher GSS.

To further confirm our results, we contacted the Miraco Life Sciences Laboratory (Irving, TX, USA), a national pathology facility. They reviewed their pathology data on biopsy positive prostate cancer. Thru personal communication, they reviewed 621 prostate cancer patients in regard to age versus GSS. For the age group 55-69 (n = 317), 48% had GSS 6, 52% had GSS 7-10. For the age group ≥ 70 (n = 251), 26% had GSS 6 and 74% had GSS 7-10. For GSS 8-10, ≥ 70 was 25% versus 55-69 was 3%.

Conclusion

Our study shows that 61%-69% of prostate cancer in men ≥ 70 years old is high grade with GSS 7-10. Our finding supports historical data that indicates that prostate cancer patients aged ≥70 years old have higher grade disease, higher incidence of metastasis and higher prostate cancer specific death compared with younger age men. Based on this evidence, we recommend that men ≥70 years old be screened for prostate cancer so as to decrease prostate cancer associated morbidity and mortality. □

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