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ORIGINAL ARTICLE

Prostate Cancer

Prostate cancer: a presentation of clinicopathologic prognosticators among Filipino and American men at radical prostatectomy

Mayen T Grageda¹, Bonnie Choy², Gladell P Paner², Jeffrey S So^{1,3}

Lower incidence and mortality rates from prostate cancer (PCa) have been shown in Asian men in general compared to Westerners. This is the first study detailing the clinicopathologic features of resected prostate cancer in Filipino men living in the Philippines (PH). This study investigated the supposed “lower risk” Filipino and “higher risk” American PCa patients from the PH and the United States of America (USA), respectively. We examined 348 (176 from PH, 172 from USA) radical prostatectomy cases. The clinicopathologic features of both groups (age at time of diagnosis, preoperative prostate-specific antigen [pre-op PSA] level, Gleason score [GS], Grade groups [GG], margin involvement, extraprostatic extension [EPE], seminal vesicle invasion [SVI], and regional lymph node [RLN] metastasis) were compared. Six of seven prognosticators examined were more strongly associated with Filipinos than with Americans. Filipinos were older at diagnosis (PH: 64.32 ± 6.56 years vs USA: 58.98 ± 8.08 years) and had higher pre-op PSA levels (PH: 21.39 ± 46.40 ng ml⁻¹ vs USA: 7.63 ± 9.19 ng ml⁻¹). Filipino men had more advanced grade, GG 2 with minor pattern 5 (PH: 6.2% vs USA: 2.9%) and GG 5 (PH: 14.8% vs USA: 3.5%). Likewise, other adverse pathological features in margin positivity (PH: 52.3% vs USA: 23.8%), focal EPE (PH: 14.2% vs USA: 2.3%), and SVI (PH: 17.1% vs USA: 5.8%) were more commonly observed in Filipinos. This study reveals the prognostic disadvantage of Filipinos versus Americans and highlights an important difference of Filipinos from other studied Asian ethnicities that have repeatedly been shown to have lower-risk PCa. This study, the first on Filipino PCa patients with RP, suggests the need to modify Western-based risk stratification when employed in other countries like the PH.

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INTRODUCTION

In the past decades, prostate cancer incidence and mortality have been repeatedly shown to be higher in American men, more specifically in African-American men, than in men from Asian countries and have been suggested to be due to multiple factors such as diet, lifestyle, socioeconomic status, hormonal status, race-specific genetic make-up such as transmembrane serine protease 2 and ETS-related gene (*TMPRSS2-ERG*) fusion, phosphatase and tensin homolog (*PTEN*) inactivation, germline alterations in breast cancer 1 (*BRCA1*) and breast cancer 2 (*BRCA2*) genes, and others.^{1–5} In men with prostate cancer, pathologic prognosticators such as preoperative (pre-op) prostate-specific antigen (PSA) level, Gleason score (GS), and radical prostatectomy Gleason score (RP-GS), and details of pathologic stage (margin status, extraprostatic extension [EPE], seminal vesicle invasion [SVI], and regional lymph node [RLN] metastasis) are important in predicting survival status.^{6,7} These factors are classified as category I by the College of American Pathologists (CAP), which is reported as standard practice in many nations outside the United States of America (USA) including the Philippines (PH).⁸ Although it is convenient to group patients from all countries that comprise the Asian continent under “Asians”, one must realize that each Asian geographic territory

is composed of different ethnicities with differences in genetics and probably in other prostate cancer-related factors. Some studies have recently suggested significantly higher incidence and mortality in specific Asian nations.⁹ However, only a few studies have actually looked into the histopathologic features of prostate cancer in a more specified regional Asian ethnicity and compare with that in Westerners. To date (based on a web-based search on PubMed), no study has been performed detailing the clinicopathologic features of resected prostate cancer in Filipino men living in the PH. In line with this, the current study takes particular interest in analyzing the histologic prognosticators of prostate cancer at radical prostatectomy (RP) among Filipino and American patients.

PATIENTS AND METHODS

Study population

The study subjects included patients who underwent RP in two tertiary hospitals, one located in Metro Manila (St. Luke’s Medical Center–Global City, Taguig, PH), and the other in University of Chicago Medical Center (Chicago, IL, USA) from 2012 to 2016. Of the 179 Filipino cases, three were excluded due to lack of definite histopathologic evidence of prostate cancer after RP. Ultimately, a

¹Institute of Pathology, St. Luke’s Medical Center–Global City, Taguig, Metro Manila 1634, Philippines; ²Department of Pathology, The University of Chicago, Chicago, IL 60637, USA; ³Institute of Pathology, St. Luke’s Medical Center–Quezon City, Metro Manila 1112, Philippines.

Correspondence: Dr. JS So (jeffreysomd@gmail.com)

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total of 348 (176 from PH, 172 from USA) cases were considered for this cross-sectional retrospective study. The study subjects in the PH cohort, to the best of our knowledge, are almost all of Filipino descent, with the corresponding USA cohort most of which are American citizens (subjects were from a patient cohort comprising Caucasian American [78.3%], African-American [12.4%], and other ethnicities [9.3%]). Both institutions utilized robotic-assisted RP specimens for majority of the cases included in this current study.

Data gathering

After obtaining the St. Luke's Medical Center Institutional Review Board (IRB) approval (ethical clearance number CT-18162) with the consent being waived by the Institutional Scientific Review Committee (ISRC) and Institutional Ethics Review Committee (IERC) because the research involves no more than minimal risk and does not adversely affect the rights and welfare of the subjects, the Filipino group used Healthcare System (HCS) to gather clinical information as well as final surgical reports of prostate cancer patients. The clinicopathologic data extracted included: age at time of diagnosis, pre-op PSA level, RP-GS, margin status, presence of EPE and SVI, and RLN metastasis. The Grade groups (GG) from both institutions were derived from the GS, as stated in the final surgical report. The American Joint Committee on Cancer (AJCC) stage was not considered in this study due to coding inconsistencies over time. Of the 176 surgical pathology reports from the Filipino group, only three were signed out by general pathologists, while the rest of cases were signed out by the institution's uropathology specialist. On the other hand, all RP cases in the American group were signed out by designated uropathologists.

Statistical analyses

Epi Info™ version 7.2.2.6 (Center of Disease Control, Atlanta, GA, USA) was used in the analysis of the data. Data from both institutions were encoded in an Excel spreadsheet. The descriptive statistics are presented as frequencies and tables, while numerical data are described using mean, standard deviation (s.d.), median, minimum, and maximum values. More specifically, an independent Student's *t* test was used to assess the mean age at diagnosis and pre-op PSA level. On the other hand, Chi-square test and Fisher's exact test were utilized for the association between qualitative variables such as RP-GS, RP-GG, margin involvement, EPE, SVI, and RLN metastasis.

RESULTS

The age at diagnosis and pre-op PSA levels of patients from the two groups are summarized in **Table 1**. At cancer diagnosis, Filipino patients were significantly older compared to USA patients (mean ± s.d.: 64.32 ± 6.56 years vs 58.98 ± 8.08 years, $P < 0.01$; median: 64 years vs 60 years) and had higher pre-op PSA levels (mean ± s.d.: 21.39 ± 46.40 ng ml⁻¹ vs 7.63 ± 9.19 ng ml⁻¹, $P < 0.01$). When GSs were translated to its corresponding prognostic GGs, Filipino men were categorized under more advanced grades, GG 2 with minor pattern 5 (PH: 6.3% vs USA: 2.9%, $P = 0.033$) and GG 5 (PH: 14.8% vs USA: 3.5%, $P < 0.01$) as shown in **Table 2**. By margin involvement, the Filipino group had considerably higher positive margins (PH: 52.3% vs USA: 23.8%, $P < 0.01$; **Table 3**). EPE is also significantly higher in the Filipino group compared to the USA group (47.7% vs 33.1%) and more notably in terms of focal EPE (14.2% vs 2.3%, $P < 0.01$), as shown in **Table 4**. Likewise, SVI is also significantly higher in Filipino compared to American men (17.1% vs 5.8%, $P < 0.01$; **Table 5**). There is no significant difference in the percentage of positive and negative RLN metastasis (**Table 6**) between PH and USA patients.

Table 1: Age at diagnosis and preoperative serum prostate-specific antigen level

Variable	Filipinos (total=46)	Americans (total=171)	P
Age at diagnosis (year)			
Mean±s.d.	64.32±6.56	58.98±8.08	0.000000*
Median	64	60	
Range	46–78	34–78	
Pre-op PSA (ng ml ⁻¹), mean±s.d.	21.39±46.40	7.63±9.19	0.0001*

* $P < 0.01$, statistically significant. Pre-op PSA: preoperative prostate-specific antigen; s.d.: standard deviation

Table 2: Radical prostatectomy-Gleason score and Grade groups

RP-GS and RP-GG	Patient, n (%)		P
	Filipinos (total=176)	Americans (total=172)	
GG 1	23 (13.1)	32 (18.6)	NA
2+3=5	1	0	
3+3=6	22	32	
GG 2	87 (49.4)	107 (62.2)	0.348
3+3=6 with tertiary pattern 4	18	0	
3+4=7	69	107	
GG 2 with minor pattern 5	11 (6.3)	5 (2.9)	0.033*
3+4=7 with tertiary pattern 5	11	5	
GG 3	16 (9.1)	13 (7.6)	0.128
4+3=7	16	13	
GG 3 with minor pattern 5	11 (6.3)	6 (3.5)	0.055
4+3=7 with tertiary pattern 5	11	6	
GG 4	2 (1.1)	3 (1.7)	0.659
4+4=8	2	3	
GG 5	26 (14.8)	6 (3.5)	0.000*
4+5=9 with <5% pattern 5	1	2	
4+5=9	19	4	
5+4=9	5	0	
5+5=10	1	0	

* $P < 0.01$, statistically significant. GG: Grade group; GS: Gleason score; RP-GG: radical prostatectomy-GG; RP-GS: radical prostatectomy-GS; NA: not analyzed

Table 3: Margin involvement

Margins	Filipinos (total=176), n (%)	Americans (total=172), n (%)	P
Negative	84 (47.7)	131 (76.2)	NA
Positive	92 (52.3)	41 (23.8)	0.000*

* $P < 0.01$, statistically significant. NA: not analyzed

Table 4: Extraprostatic extension

EPE	Filipinos (total=176), n (%)	Americans (total=172), n (%)	P
None	92 (52.3)	115 (66.9)	NA
Positive	84 (47.7)	57 (33.1)	0.0029*
Focal	25 (14.2)	4 (2.3)	0.000*
Nonfocal	59 (33.5)	53 (30.8)	0.081

* $P < 0.01$, statistically significant. EPE: extraprostatic extension; NA: not analyzed

DISCUSSION

Despite numerous reports that highlight the survival advantages of Asians compared to Westerners, this study supports the increasing evidence that this may not be uniformly true in all Asian ethnicities and that certain groups such as Filipinos actually pose more unfavorable outcomes. A study on the differences in cancer burden among Asian-



Table 5: Seminal vesicle invasion

SVI	Filipinos (total=170), n (%)	Americans (total=172), n (%)	P
Negative	141 (82.9)	162 (94.2)	NA
Positive	29 (17.1)	10 (5.8)	0.0005*

* $P < 0.01$, statistically significant. SVI: seminal vesicle invasion; NA: not analyzed

Table 6: Regional lymph node metastasis

RLN mets	Filipinos (total=88), n (%)	Americans (total=166), n (%)	P
Negative	86 (97.7)	154 (92.8)	NA
Positive	2 (2.3)	12 (7.2)	0.082

RLN mets: regional lymph node metastasis; NA: not analyzed

American ethnic groups in the USA suggested that Filipinos had higher incidence and death rate from prostate cancer.¹⁰ Another study by Lin *et al.*¹¹ proposed that among non-Hispanic whites and Asian subpopulations of Japanese, Chinese, and Filipinos living in the USA, Filipinos are more likely to be diagnosed with advanced-stage prostate cancer and likewise had the highest proportion of cancer deaths. The current study shows that Filipino men living in the PH tend to be older at cancer diagnosis and had significantly higher pre-op serum PSA levels compared to their American counterparts. There has been a conflicting significance of serum PSA as a screening biomarker for prostate cancer where several authors recommended its use only at the patients' preference. This recommendation was based on a thorough review of several randomized trials that did not exhibit any cancer-specific mortality benefit after a 10-year follow-up.^{12,13} However, in patients with histologically-confirmed prostate cancer, serum PSA level is valuable in risk stratification of patients with localized versus those with metastatic disease.¹⁴ Higher PSA level was shown to predict an increased risk for more advanced clinical stage, adverse pathologic features, and worse disease-specific survival.^{15,16} These findings are in keeping with our study where the Filipino group had a mean pre-op PSA level roughly three times that of the American group and was accompanied by more adverse pathologic features. Of these features, grade remains to be the most robust and well-studied parameter in prostate cancer where a direct association is seen between increasing GSs and biochemical failure with local and distant recurrence in both untreated and treated patients.^{17,18}

Several revisions have been made in the Gleason system since its inception nearly five decades ago. It has repeatedly been shown that the presence of even small amounts of higher grade patterns augments the biochemical recurrence risk.¹⁸⁻²⁰ In 2014, the International Society of Urological Pathology (ISUP) consensus modified the use of tertiary patterns in RPs recommending the term "tertiary grade" be replaced with "minor high-grade pattern" which emphasizes the minor or limited extent of the third pattern to 5% of the total tumor volume.²¹ A usual dilemma is encountered when pattern 4 comprises <5% of total tumor volume wherein some pathologists would grade this as GS 3 + 3 = 6 with tertiary pattern 4, while others would grade this as GS 3 + 4 = 7. In this study, a similar occurrence may be inferred with the results presented in **Table 2**, in which GS 3 + 3 = 6 with tertiary pattern 4 is reported in Filipino patients but is virtually nonexistent in the American group. Furthermore, the latter had a disproportionately greater percentage of tumors with GS 3 + 4 = 7. With the new recommendation, this ambiguity is addressed by a uniform grading rule among pathologists to grade such cases as GS 3 + 4 = 7 with <5% pattern 4.

A new grade grouping for prostate cancer was introduced recently by Epstein and the Johns Hopkins group.²² The authors proposed the

use of five prognostic GGs based on the modified GS system: GG 1 to 5 which corresponds to GSs ≤ 6 , $3 + 4 = 7$, $4 + 3 = 7$, $4 + 4 = 8$, and 9 to 10, respectively. The goal was to simplify and reaffirm that GSs of up to 6 conveyed an excellent prognosis that can be followed with active surveillance as these tumors tend to be indolent, while increasing GSs of 7 and above entailed worsening prognosis.^{18,22-26} Minor high-grade patterns, although significant, do not change the prognostic GGs and have yet to be formally incorporated under such categories. Hence, GSs with minor (tertiary) patterns are reported in separate categories as seen in **Table 2**. Nevertheless, after analyzing and translating the GSs to their respective GGs, results of this study show that Filipinos tend to have higher GGs (GG 2 with minor pattern 5 and GG 5) than their American counterparts. Although GS and consequently GGs are strong predictors of biochemical disease progression and metastatic potential, various studies have found that this alone may not reliably predict disease outcome, and hence, consideration of other histopathologic parameters is warranted to increase prognostic accuracy.²⁷⁻³⁴

Positive margin status, EPE, SVI, and RLN metastasis at RP have been recognized to increase the risk of biochemical recurrence and mortality from prostate cancer, and that presence of any or a combination of two or more variables would foster the need for adjuvant therapy.^{6,7,17,35-40} Studies recognized the interdependent nature of these factors to one another, and that a consistent trend in studies was the exponential association of worsening prognosis to increasing GSs and increasing number of concurrent adverse prognostic factors.^{6,41} Data, from the present study, suggest worse pathologic risk of Filipino prostate cancer patients after RP compared to their American counterparts by outnumbering the latter in almost all prognostic variables examined, except RLN metastasis as this did not yield a statistically significant result. This may be due to the unavailability or lack of RLNs submitted for histologic examination in half of the PH cases.

This study has several limitations. First, apart from the inherent degree of subjectivity in Gleason grading system, interobserver variability is inevitable in any retrospective study such as ours. This is especially true when considering that even between urologic pathology specialists, concordance is no more than 70%.⁴¹ Second, the technical skill of the surgeons and operative method (open, laparoscopic, and robotic) in these RP specimens were not considered, and these could impact the results significantly, particularly when pertaining to the margin status. Third, data on the time interval between the initial diagnosis of prostate cancer at needle biopsy and RP were not taken into account as this was not uniformly available in both groups. A longer time interval from biopsy to definitive surgery would logically lead to disease progression even in indolent tumors such as prostate cancer. Fourth, there were also no data on possible previous treatment as well as disease-free survival as these were also unavailable on both institutions' databases. Screening protocols for certain populations have been raised a possible issue in these types of studies, especially when comparing PH screening to USA protocols. However, we think we were able to compensate for this because the study population from the PH was from a large tertiary hospital having patients with the means to have early and consistent screening and monitoring comparable to their USA counterparts. Another limitation would be the availability of data on certain preoperative status of the patient such as testosterone levels, which may contribute to the prognosis of certain patients.

Finally, a selection bias is recognized due to the regional nature of the data (Metro Manila in PH and Chicago in the USA). In addition, the data analyzed came from only two institutions, one from each country. Nevertheless, to our knowledge, this is the first study that specifically looked into and compared the clinicopathologic characteristics of

Filipino and American prostate cancer patients, consequently generating much-needed region-specific data, especially in the former group.

CONCLUSIONS

Although often regarded as a geographic region having men with low prostate cancer burden, evidence of increasing incidence and mortality of prostate cancer in select Asian nations has been suggested in recent years.^{9–11,42–44} This study supports this notion and further emphasizes the prognostic disadvantage specifically of Filipino men living in the PH with prostate cancer when compared to its American counterparts. These region-specific data could be a valuable contribution to the need to modify western-based risk stratification strategies widely employed in Asia.

AUTHOR CONTRIBUTIONS

All authors contributed to the design and implementation of the study. MTG and BC collected and analyzed the data. All authors discussed the results and contributed to the final manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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