Original Article

Assessment of the American Joint Committee on Cancer 7th Edition Staging for Localised Prostate Cancer in Asia Treated with External Beam Radiotherapy

Meihua Wong, [1]*MBBS*, Connie Yip, [2]*MBChB, MRCP, FRCR*, Huihua Li, [3]*MS, PhD*, Terence Tan, [2]*FRCR*, Ravindran Kanesvaran, [1]*MD, MRCP(UK), FAMS*, Balram Chowbay, [4,5,6]*PhD*, Puay Hoon Tan, [7]*MBBS, FRCPA, MD*, Min-Han Tan, [1,8]*MBBS, MRCP, PhD*, Fuh Yong Wong, [2]*MBBS, FRCR*

Abstract

Introduction: Most international clinical practice guidelines for prostate cancer (PCa) are driven by data derived in a Western setting. However, tumour biology and clinical disease progression are likely to differ in the Asian population. We compare the performance of the revised American Joint Committee on Cancer (AJCC) prognostic groups with the commonly used D'Amico Risk Classification and conventional predictors for PCa, in a large cohort of Asian patients. Materials and Methods: We retrospectively reviewed data for 404 consecutive Singaporean patients receiving definitive radiotherapy at our centre between December 1996 and October 2006. The primary outcome was biochemical relapse-free survival (BRFS), defined using the Phoenix definition. The secondary outcome was overall survival (OS). Prognostic risk groups were defined using AJCC 7th edition (AJCC7) and 6th edition (AJCC6). Univariate analysis (UVA) and multivariate analysis (MVA) were performed for the following putative risk factors: age, Gleason score, prognostic grouping, tumour classification, radiation delivery technique, radiotherapy dose, hormonal therapy and initial PSA value. Results: For the cohort, median age was 69 years. Median follow-up was 66.3 months. Five-year BRFS rate was 84.3% with 71 biochemical relapses and 5-year OS rate was 89.1% with 54 deaths. The concordance-indices for BRFS prediction were 0.588, 0.550 and 0.567 for AJCC7, AJCC6 and D'Amico respectively. Initial PSA, T-stage and AJCC7 were prognostic for BRFS on UVA. Comparison of AJCC7 vs. D'Amico showed no statistical additional value of either classification system although D'Amico was superior when compared to AJCC6 in predicting BRFS. T-stage ≥3 and D'Amico were significant prognostic factors for BRFS on MVA. Conclusion: In our local, predominantly Chinese population, neither AJCC6 nor AJCC7 demonstrated a high predictive accuracy for BRFS although AJCC7 has a slightly better predictive ability than AJCC6.

Ann Acad Med Singapore 2014;43:484-91

Key words: D'amico, Intensity modulated radiotherapy, Prognosis, Risk stratification

Introduction

Prostate cancer (PCa) is the second most frequently diagnosed cancer in men, with a worldwide incidence of approximately 900,000 in 2008.[1] Internationally, there is marked variation in incidence, ranging from 104.2 per 100,000 in some Western populations, to 4.1 per 100,000 in South and Central Asia.[1] However, there has recently been a reported increase in incidence and mortality from PCa in various Asian countries.[2] In Singapore, the age-standardised incidence rates (ASIR) have risen from 8.3 per 100,000 (1983 to 1987) to 23.9 per 100,000 (2003 to 2007) in just 20 years. The ASIR in Singapore has reached 28.7 per 100,000, more than double that in Shanghai, China (ASIR of 11.3 per 100,000) or Mumbai, India (ASIR of 11.5 per 100,000).[3] This may be attributed in part to increased PSA screening, the availability of transrectal ultrasound and extended sextant biopsies for prostate cancer detection in the late 1990s, although there may be other still unknown contributing factors.[4]

[1]Department of Medical Oncology, National Cancer Centre Singapore, Singapore
[2]Department of Radiation Oncology, National Cancer Centre Singapore, Singapore
[3]Health Services Research, Singapore General Hospital, Singapore
[4]Laboratory of Clinical Pharmacology, Division of Medical Sciences, Humphrey Oei Institute of Cancer Research, National Cancer Centre Singapore, Singapore
[5]Singhealth Clinical Pharmacology Core, Discovery Tower, Academia, Singapore
[6]Clinical Sciences, Duke-NUS Graduate Medical School, Singapore
[7]Department of Pathology, Singapore General Hospital, Singapore
[8]Institute of Bioengineering and Nanotechnology, Singapore
Address for Correspondence: Dr Wong Fuh Yong, Department of Radiation Oncology, National Cancer Centre Singapore, 11 Hospital Drive, Singapore 169610.
Email: ntrwfy@nccs.com.sg

The majority of international clinical practice guidelines are largely driven by data derived in a Western setting. However, tumour biology and clinical disease progression may differ in the Asian population. Polymorphic variants in the region of 8q24 and 17q have been found to have a cumulative and significant association in prostate cancer.[5] There are differences in prostate cancer risk-allele frequencies in an Asian population from Singapore compared to the Caucasian and African cohorts, although the biological significance of these genetic variants has yet to be fully elucidated.[6] A study of prostate cancer incidence and survival in immigrants to Sweden found that the group of non-European immigrants of mainly Middle East, Asian, North African, and Chilean origin had the most favourable survival in the disease, and the calculated hazard ratio of mortality was 0.60 (range, 0.45 to 0.81).[7] It has yet to be determined conclusively that the adoption of these guidelines in the Asian clinical practice is appropriate, as there is limited data on long-term outcomes of definitive radiotherapy in Asia. The absence of such reported outcomes is of concern given the increasing incidence of prostate cancer in Asia.[2]

Additionally, the American Joint Committee on Cancer (AJCC) Cancer Staging Manual has recently been revised to its 7th edition. The new prognostic grouping for prostate cancer integrates both prostate specific antigen (PSA) and Gleason score (GS). Limited information on the extent of stage reclassification and the impact of this new approach on the estimation of clinical outcomes such as BRFS in a clinical setting is available. We thus seek to validate the performance of the revised AJCC groups, in comparison to the previous 6th edition and the commonly used D'Amico Risk Classification, in a large and uniform cohort receiving definitive radiotherapy with or without androgen-deprivation therapy in an Asian tertiary cancer centre. We also evaluated the performance of classical PCa prognostic factors derived from Western settings in this population, which is particularly salient given the paucity of such information in Asia.

Materials and Methods

Institutional Review Board approval was obtained for this retrospective study.

Clinical data were collected for 404 consecutive Singaporean patients with localised adenocarcinoma of the prostate (clinical stage T1-T4, NX/N0/N1, M0) who underwent definitive radiotherapy between December 1996 and October 2006 at the National Cancer Centre Singapore. Patients' characteristics are listed in Table 1.

Treatment

All patients received definitive radiotherapy up to a median total dose of 70 Gy (range, 66 to 80 Gy). Neoadjuvant

Table 1. Patient Characteristics

Characteristics				**Number (%) n = 404**
Age				
Median (range)				69 years (47 to 86)
Race				
Chinese				347 (85.9%)
Malay				23 (5.7%)
Indians				26 (6.4%)
Others				8 (2.0%)
Clinical classification stage				
T1				194 (48.0%)
T2				139 (34.4%)
T3				61 (15.1%)
T4				6 (1.5%)
No data available				4 (1.0%)
Initial PSA (ng/mL)				
<10.0				126 (31.2%)
10 to 20.0				102 (25.2%)
>20				170 (42.1%)
No data available				6 (1.5%)
Gleason score				
≤6				129 (39.1%)
7				173 (42.8%)
8 to 10				57 (14.1%)
No data available				16 (4.0)
Prognostic groups (AJCC, 7th edition)				
Group I	TNM	PSA	Gleason	62 (15.3%)
	T1a-c N0 M0	<10	≤6	
	T2a N0 M0	<10	≤6	
	T1-2a N0 M0	X	X	
Group IIA	TNM	PSA	Gleason	121 (30.0%)
	T1a-c N0 M0	<20	7	
	T1a-c N0 M0	≥10<20	≤6	
	T2a N0 M0	≥10<20	≤6	
	T2a N0 M0	<20	7	
	T2b N0 M0	<20	≤7	
	T2b N0 M0	X	X	
Group IIB	TNM	PSA	Gleason	151 (37.4%)
	T2c N0 M0	Any	Any	
	T1-2 N0 M0	≥20	Any	
	T1-2 N0 M0	Any	≥8	
Group III	TNM	PSA	Gleason	60 (14.9%)
	T3a-b N0 M0	Any	Any	

AJCC: American Joint Committee on Cancer
TNM: Tumour, Node, Metastasis
PSA: Prostate-specific antigen

Table 1. Patient Characteristics (Con't)

Characteristics				Number (%) n = 404
Prognostic groups (AJCC, 7th edition)				
Group IV	TNM	PSA	Gleason	9 (2.2%)
	T4 N0 M0	Any	Any	
	Any T N1 M0	≥20	Any	
	Any T Any N M1	Any	Any	
Unclassifiable *even if PSA is not available, grouping can still be determined by T stage and/or either PSA or Gleason as available				1 (0.2%)
Prognostic groups (AJCC, 6th edition)				
Group I	TNM	Grade		0 (0%)
	T1a N0 M0	1		
Group II	TNM	Grade		331 (81.9%)
	T1a N0 M0	2 – 4		
	T1b N0 M0	Any		
	T1c N0 M0	Any		
	T1 N0 M0	Any		
	T2 N0 M0	Any		
Group III	TNM	Grade		60 (14.9%)
	T3 N0 M0	Any		
Group IV	TNM	Grade		9 (2.2%)
	T4 N0 M0	Any		
	Any T N1 M0	Any		
	Any T Any N M1	Any		
Unclassifiable				4 (1.0%)
D'Amico				
Low risk				61 (15.1%)
Intermediate risk				119 (29.5%)
High risk				221 (54.7%)
Unclassifiable				3 (0.7%)

AJCC: American Joint Committee on Cancer
TNM: Tumour, Node, Metastasis
PSA: Prostate-specific antigen

hormonal therapy was given to 85 patients (21.0%) for a median duration of 2 months (range, 0.5 to 11.5 months). Treatment characteristics are reported in Table 2.

Patient Evaluation and Staging

All patients underwent a history and physical examination, initial serum PSA measurement and histologic confirmation of prostate adenocarcinoma. Tumour staging was performed according to the 6th and 7th edition of the AJCC Cancer Staging Manual (AJCC6 and AJCC7 respectively). In addition, patients were also classified according to the D'Amico Risk Classification.[8]

Table 2. Treatment Characteristics

Treatment	Number (%)
Hormonal therapy	89 (22%)
Neoadjuvant	
Only	17 (19.1%)
+ concurrent HT	14 (15.7%)
+ concurrent HT + adjuvant HT	54 (60.7%)
Concurrent + adjuvant HT	1 (1.1%)
Adjuvant only	3 (3.4%)
RT dose (Gy)	
60 ≤ RT dose <70	27 (6.7%)
≥70	377 (93.3%)
RT technique	
IMRT	57 (14.1%)
Conformal	257 (63.6%)
No data available	90 (22.3%)

HT: Hormonal therapy; RT: Radiation therapy; IMRT: Intensity modulated radiation therapy

Statistical Analysis

The primary outcome was BRFS, defined as the time from the end of radiotherapy to the date of biochemical relapse as per the 2005 Phoenix definition.[9] Patients were censored at the date of last clinical follow-up or death. Overall survival (OS), the secondary outcome, was defined from the diagnosis date to death date, or last follow-up date for censored cases. Both BRFS and OS were estimated by the Kaplan-Meier method. Univariate analysis (UVA) was performed for known prognostic factors: age, AJCC prognostic risk groupings, tumour classification, Gleason score, radiation delivery technique, radiation therapy (RT) dose, hormonal therapy, and PSA value at the time of first positive biopsy. Multivariate analysis (MVA) was performed by means of reduced model selection by including those prognostic factors with P <0.2 on UVA. Proportional hazards assumptions were verified systematically for all proposed models.

Likelihood ratio test of nested models were performed to compare AJCC7/AJCC6 to D'Amico. Harrell's c-index was calculated to evaluate the concordance between predicted and observed responses of individual subjects separately. The c-index is commonly used to measure the performance of prediction models; c = 1 indicates the model has perfect predictive accuracy and c = 0.5 implies no predictive ability (random concordance). The proportion of the variation explained by each constituent component against the full predictive model is quantified by the Adequacy Index.[10]

All analyses were done using R 3.0.2 (Available at: http://www.R-project.org) and STATA 11 (STATA Corporation, College Station, TX USA), and all tests were 2-sided with a significance level of 0.05.

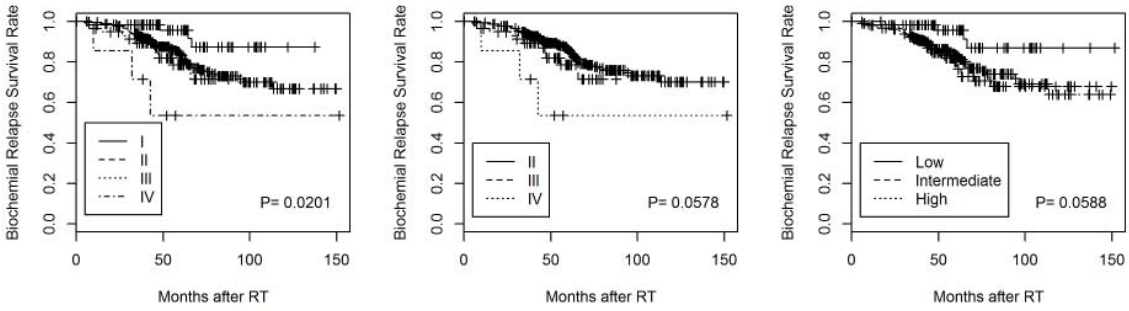

Fig. 1. Biochemical relapse free survival of patients in AJCC7, AJCC6 and D'Amico classification.

Results

Patient Characteristics

Median age for the entire cohort was 69 years (range, 47 to 86 years). Median PSA was 15.5 ng/mL (range, 1.0 to 290.0 ng/mL). See Table 1 for patient characteristics. Median follow-up was 66.3 months (range, 5.3 to 155.1 months). There were 71 biochemical relapses with 5-year BRFS of 84% (Fig. 1). Five-year overall survival rate was 89% with a total of 54 deaths in our study cohort. Eleven deaths (20.4%) were attributable to PCa.

AJCC Staging

There was a migration of stage II patients to stage I with AJCC7. The proportion of patients with stage II disease decreased from 81.9% to 67.4%, whilst patients with stage I disease increased from 0% to 15.3%. There were slightly more patients in the IIB subcategory (37.4%) than in the IIA subcategory (30.0%). There was no change to the proportion of patients with stage III and IV disease (14.9% and 2.2% respectively) (Table 1).

Predictive Accuracy

The results of the UVA and MVA for the various BRFS prognostic factors are summarised in Table 3. Initial PSA value (P = 0.0147), clinical T-stage (P = 0.0026), and AJCC7 (P = 0.0201) were significant prognostic factors on UVA. D'Amico intermediate/high risks group and T4 disease were the only significant prognostic factor following MVA (Table 3).

None of the risk stratification instruments prognosticated for BRFS well although AJCC7 performed marginally better compared to AJCC6 and D'Amico's in our cohort of patients, with c-indices of 0.588, 0.550 and 0.567 respectively (Fig. 1).

The results of likelihood ratio tests for AJCC7 and D'Amico against their nested models are shown in Table 4A. Neither AJCC7 nor D'Amico shows additional statistical value relative to each other for BRFS or OS; however, the addition of D'Amico to AJCC7 showed significant statistical improvement (P = 0.0378) for PCa specific survival (CSS). In contrast, D'Amico shows significantly better prognostic power for BRFS compared to AJCC6 (Adequacy index 96.9% vs. 59.3%, respectively, P = 0.0169) whereas AJCC6 shows better prognostic power for OS compared to D'Amico (Adequacy index 70.7% vs. 42.4%, respectively, P = 0.0395) (Table 4B). Taking their c-indices into consideration, these likelihood ratio tests suggested an additional contribution of AJCC7 over and above AJCC6 in prognosticating BRFS. AJCC6 cannot be compared directly to AJCC7 using likelihood ratio test because of their identical classification of stage III and IV patients.

In contrast to the poor predictive power of these staging instruments for BRFS, they were demonstrably better at prognosticating OS (Fig. 2). In UVA, both AJCC7 and AJCC6 were significant prognosticators of OS with c-indices of 0.612 and 0.570 respectively. Age (P = 0.0072) and T-stage (P = 0.0158) were also predictive of OS in UVA (Table 5). Notably, initial PSA value which was not useful in prognosticating OS (P = 0.491) was significantly prognostic for BRFS as well as being the sole prognosticator for CSS (P = 0.0012). In MVA, age, T-stage, hormonal therapy and D'Amico risk groups were predictive of OS (Table 5).

Discussion

Our study evaluated the clinical outcomes of patients with prostate cancer treated with definitive radiotherapy in a large tertiary cancer centre that serves approximately 70% of all cancer patients in this country. Patients were treated with standard departmental radiotherapy protocols with minimal protocol deviations.

In our local, predominantly Chinese population, neither

Table 3. Univariate and Multivariate Analysis of Prognostic Factors for BRFS

Prognostic factors	Univariate analysis	Multivariate analysis	
	P value	*P* value	HR (95% CI)
Initial PSA value (continuous variable)	0.0147	Not significant on MVA	
Prognostic risk groups (AJCC, 7th edition)	0.0201		
Prognostic risk groups (AJCC, 6th edition)	0.0578		
Prognostic risk groups (D'Amico)	0.0588		
Low risk			Reference
Intermediate risk		0.0449	2.99 (1.03, 8.71)
High risk		0.1930	2.05 (0.70, 6.03)
T-stage (continuous variable)	0.0026		
T1			Reference
T2		0.1437	1.50 (0.87, 2.60)
T3		0.0755	2.01 (0.93, 4.36)
T4		0.0032	9.54 (2.13, 42.65)
RT dose (60 to 70 Gy vs >70 Gy)	0.1057	Not significant on MVA	
HT (any vs none)	0.4129		
Gleason score (≤6 vs7 vs ≥8)	0.1403		
Age (continuous variable)	0.2471		
RT delivery technique (IMRT vs non-IMRT)	0.4261		

BRFS: Biochemical relapse-free survival; PSA: Prostate-specific antigen; AJCC: American Joint Committee on Cancer; RT: Radiation therapy; HT: Hormonal therapy; IMRT: Intensity modulated radiation therapy; MVA: Multivariate analysis

Table 4A. Comparison of AJCC7 and D'Amico as Predicators of BRFS, OS and CSS

	Likelihood		*P* value		Adequacy index	
Full model	AJCC7	D'Amico	AJCC7*	D'Amico†	AJCC7‡	D'Amico§
BRFS						
12.36	10.03	7.12	0.1555	0.3125	81.1%	57.6%
OS						
11.65	10.06	5.57	0.1081	0.4523	86.4%	47.8%
CSS						
9.02	2.47	7.63	0.7076	0.0378	27.4%	84.6%

AJCC: American Joint Committee on Cancer; BRFS: Biochemical relapse-free survival; OS: Overall survival; CSS: PCa specific survival
*The comparison of the model with the predictor of D'Amico only with the one with predicators of both AJCC7 and D'Amico.
†The comparison of the model with the predictor of AJCC7 only with the one with predicators of both AJCC7 and D'Amico.
‡The proportion of the variation explained by AJCC7 compared to that explained by both AJCC7 and D'Amico.
§The proportion of the variation explained by D'Amico compared to that explained by both AJCC7 and D'Amico.

Table 4B. Comparison of AJCC6 and D'Amico as Predicators of BRFS, OS and CSS

	Likelihood		*P* value		Adequacy index	
Full model	AJCC6	D'Amico	AJCC6*	D'Amico†	AJCC6‡	D'Amico§
BRFS						
12.38	4.22	6.90	0.0643	0.0169	34.1%	55.7%
OS						
11.21	7.93	4.75	0.0395	0.1942	70.7%	42.4%
CSS						
8.32	2.39	6.98	0.5115	0.0514	28.7%	83.9%

AJCC: American Joint Committee on Cancer; BRFS: Biochemical relapse-free survival; OS: Overall survival; CSS: PCa specific survival
*The comparison of the model with the predictor of D'Amico only with the one with predicators of both AJCC7 and D'Amico.
†The comparison of the model with the predictor of AJCC7 only with the one with predicators of both AJCC7 and D'Amico.
‡The proportion of the variation explained by AJCC7 compared to that explained by both AJCC7 and D'Amico.
§The proportion of the variation explained by D'Amico compared to that explained by both AJCC7 and D'Amico.

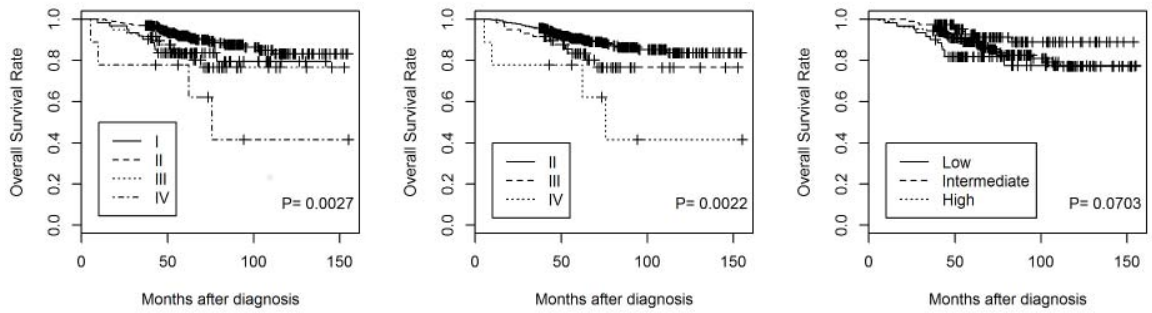

Fig. 2. Overall survival of patients in AJCC7, AJCC6 and D'Amico classification.

Table 5. Univariate and Multivariate Analysis of Prognostic Factors for OS

Prognostic factors	Univariate analysis	Multivariate analysis	
	P value	*P* value	HR (95% CI)
Age (continuous variable)	0.0072	0.0013	1.08 (1.03, 1.13)
Prognostic risk groups (AJCC, 7th edition)	0.0027	Not significant on MVA	
Prognostic risk groups (AJCC, 6th edition)	0.0022		
T-stage (continuous variable)	0.0158		
T1			Reference
T2		0.0100	2.55 (1.25, 5.21)
T3		0.0020	4.36 (1.72, 11.06)
T4		<0.0001	29.77 (5.78, 153.36)
Prognostic risk groups (D'Amico)	0.0703		
Low Risk			Reference
Intermediate Risk		0.0020	0.23 (0.09, 0.59)
High Risk		0.0072	0.32 (0.14, 0.74)
HT (any vs none)	0.0600	0.0167	0.31 (0.12, 0.81)
RT delivery technique (IMRT vs non-IMRT)	0.0483	Not significant on MVA	
Initial PSA value	0.4911		
RT dose (60 to 70 Gy vs. >70 Gy)	0.1201		
Gleason score (≤6 vs. 7 vs ≥8)	0.3542		

OS: Overall survival; AJCC: American Joint Committee on Cancer; HT: Hormonal therapy; RT: Radiation therapy; PSA: Prostate-specific antigen; MVA: Multivariate analysis

AJCC6 nor AJCC7 demonstrates a high predictive accuracy for BRFS although AJCC7 (c = 0.588) has a slightly better concordance with BRFS than AJCC6 (c = 0.550) or D'Amico (c = 0.567). Our results are consistent with the findings reported in a study by Zaorsky et al which compared the ability of AJCC6 and AJCC7 to predict biochemical failure as per the 2005 Phoenix definition, in 2469 men with locally advanced prostate who received definitive RT with or without adjuvant hormonal therapy.[11] In this study, the concordance probability estimate (CPE) for biochemical failure for AJCC6 was 0.51 ± 0.009, and the CPE for AJCC7 was 0.59 ± 0.02. The substratification of stage IIA and IIB was also not prognostic.

Interestingly, we noted that higher risks patients in the D'Amico risk classification were more likely to sustain a biochemical failure but were significantly less likely to die overall. While this non-intuitive observation may be due to chance, the protective effects of additional adjuvant hormonal treatment for the high-risk patients or other confounders may be contributory. PCa patients at higher risks of relapse or who have relapsed often undergo extended periods of hormonal therapy. The incidence of hormonal therapy in the low, intermediate and high risks D'Amico group was 8.2%, 18.5% and 28.1% ($P = 0.0016$) respectively and use of hormonal therapy was independently predictive of improved survival ($P = 0.0167$, 95% CI, 0.12 to 0.81) on MVA.

The AJCC7 prognostic groups incorporate 3 well

acknowledged prognostic factors, PSA, Gleason score and T-stage. However, only initial PSA value, T-stage and AJCC7 were found to be significant predictors for BRFS in our local population on UVA; no significant association was found for Gleason score. There are several possibilities to explain our findings if there is indeed a true relationship between Gleason score and biochemical relapse. First, the true biological effect of poor tumour differentiation could be confounded by treatment bias as more patients with high Gleason scores could be treated with hormonal therapy that delayed biochemical failure. Besides that, not all of our pathological specimens were centrally reviewed and hence, inter-observer variability which could affect concurrence, consistency and reproducibility of Gleason score, as delineated in several studies, could be another potential confounding factor.[12,13] Our study also spanned over a decade when progressive modifications in the Gleason scoring system have occurred.[14,15] Overall, the subtle differences in grading could have biased the effect towards null. Finally, the major prognostic impact for tumour differentiation may be related to higher Gleason scores of 9 to 10, which were present in only a small proportion (7.4%) of our patients.

In contrast to our study, Gleason score has been validated as a significant predictor of BRFS, together with PSA and T-stage in a Japanese retrospective study with 679 patients.[16] However, it is difficult to compare the 2 studies because different definitions of biochemical relapse are used. The 2005 Phoenix definition of PSA nadir plus 2 ng/mL for biochemical failure is used in this study instead of the 1996 ASTRO definition which was used in the Japanese study, because it has been assessed and found to have better concordance with clinical outcome in an Asian population.[17] This would undoubtedly affect the interpretation of these results as PSA definition is integral to the identification of patients with biochemical relapse and could account for the difference in the 5-year BRFS between that reported in the Japanese study (71.9%) and ours (84%). For the same reason, it is difficult to compare our results to previous studies which validated Gleason score as a significant prognostic factor for BRFS using the ASTRO definition for biochemical relapse. Moreover, our study is not the first to report a negative finding for Gleason score as a predictor for biochemical failure. Pellizzon et al[18] evaluated several prognostic factors for biochemical failure in 209 patients with locally advanced prostate cancer treated with external beam radiotherapy and high dose rate brachytherapy. The authors found that Gleason score was a significant prognostic factor on UVA but not on MVA.

Conclusion

In conclusion, the AJCC7 prognostic grouping performed marginally better than AJCC6 or D'Amico Risk Classification in prognosticating BRFS. Additionally, our findings suggest that clinical T-stage is the most significant prognostic factor for disease control and survival in our population and the commonly used D'Amico Risk Classification continued to be of relevance in prognosticating outcomes and guide treatment of the Asian prostate cancer patient.

Acknowledgments

This paper was submitted in abstract form to the American Society of Clinical Oncology Genitourinary Cancers Symposium in 2011. We thank Hou Xuan from Clinical Trials Epidemiological Sciences, National Cancer Centre Singapore, for assistance in analysing the data. The National Cancer Centre Research Fund provided funding for this study.

REFERENCES

1. Ferlay J, Shin H, Bray F, Forman D, Mathers C, Parkin D. Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. France: International Agency for Research on Cancer, 2010. Available at: http://globocan.iarc.fr. Accessed 8 March 2013.
2. Sim HG, Cheng CW. Changing demography of prostate cancer in Asia. Eur J Cancer 2005;41:834-45.
3. Chia SE, Tan CS, Lim GH, Sim X, Lau W, Chia KS. Incidence, mortality and five-year relative survival ratio of prostate cancer among Chinese residents in Singapore from 1968 to 2002 by metastatic staging. Ann Acad Med Singapore 2010;39:466-71.
4. Chia SE, Tan CS, Lim GH, Sim X, Pawitan Y, Reilly M, et al. Incidence, mortality and survival patterns of prostate cancer among residents in Singapore from 1968 to 2002. BMC Cancer 2008;8:368.
5. Zheng SL, Sun J, Wiklund F, Smith S, Stattin P, Li G, et al. Cumulative association of five genetic variants with prostate cancer. New Engl J Med 2008;358:910-9.
6. Chan JY, Li H, Singh O, Mahajan A, Ramasamy S, Subramaniyan K, et al. 8q24 and 17q prostate cancer susceptibility loci in a multiethnic Asian cohort. Urol Oncol 2013;31:1553-60.
7. Hemminki K, Ankerst DP, Sundquist J, Mousavi SM. Prostate cancer incidence and survival in immigrants to Sweden. World J Urol 2013;31:1483-8.
8. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998;280:969-74.
9. Roach M 3rd, Hanks G, Thames H Jr, Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006;65:965-74.
10. Harrell FE. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. New York: Springer, 2001.
11. Zaorsky NG, Li T, Devarajan K, Horwitz EM, Buyyounouski MK. Assessment of the American Joint Committee on Cancer staging (sixth and seventh editions) for clinically localized prostate cancer treated with external beam radiotherapy and comparison with the National Comprehensive Cancer Network risk-stratification method. Cancer 2012 15;118:5535-43.

12. Burchardt M, Engers R, Muller M, Burchardt T, Willers R, Epstein J. Interobserver reproducibility of Gleason grading: evaluation using prostate cancer tissue microarrays. J Cancer Res Clin Oncol 2008;134:1071-8.
13. Brimo F, Schultz L, Epstein JI. The value of mandatory second opinion pathology review of prostate needle biopsy interpretation before radical prostatectomy. J Urol 2010;184:126-30.
14. Billis A, Guimaraes MS, Freitas LL, Meirelles L, Magna LA, Ferreira U. The impact of the 2005 international society of urological pathology consensus conference on standard Gleason grading of prostatic carcinoma in needle biopsies. J Urol 2008;180:548-52.
15. Epstein JI, Allsbrook WC Jr, Amin MB, Egevad LL; ISUP Grading Committee. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol 2005;29:1228-42.
16. Nakamura K, Mizowaki T, Imada H, Karasawa K, Uno T, Onishi H, et al. External-beam radiotherapy for localized or locally advanced prostate cancer in Japan: a multi-institutional outcome analysis. Jpn J Clin Oncol 2008;38:200-4.
17. Ramalingam M, Lau W, Tan T, Fook S, Ngoi F, Cheng C. Asians with localized prostate cancer treated with 3-dimensional conformal radiation therapy and adjuvant hormonal therapy: comparing Phoenix and American Society of Therapeutic Radiology and Oncology (ASTRO) definitions in an Asian population. Urology 2008;71:506-10.
18. Pellizzon AC, Salvajoli J, Novaes P, Maia M, Fogaroli R, Gides D, et al. The relationship between the biochemical control outcomes and the quality of planning of high-dose rate brachytherapy as a boost to external beam radiotherapy for locally and locally advanced prostate cancer using the RTOG-ASTRO Phoenix definition. Int J Med Sci 2008;5:113-20.