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ORIGINAL ARTICLE

Prostate Cancer

Refining the American Urological Association and American Society for Radiation Oncology guideline for adjuvant radiotherapy after radical prostatectomy using the pathologic Gleason score

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Recently, it has been suggested that the guideline for adjuvant radiotherapy (ART) following radical prostatectomy (RP) sponsored by the American Urological Association and American Society for Radiation Oncology (AUA/ASTRO) may result in a significant overtreatment. Thus, the objective of the present study was to refine the AUA/ASTRO guideline for ART in patients at risk for biochemical recurrence (BCR) after RP. To this end, we reviewed our prospectively maintained database and selected 193 patients who met the AUA/ASTRO ART criteria. With a median follow-up of 24.0 months, BCR rate was 17.6% (34/193). When stratified by the Gleason score, BCR rate in men with Gleason score 6 was 6.8%. There was no significant association between BCR-free survival and surgical margin ($P = 0.690$) and pathologic stage ($P = 0.353$) in patients with the Gleason score 6. However, in patients with positive surgical margins (PSMs)/pathologic stage ≥T3, there was a significant difference in BCR-free survival according to Gleason score (≤7 *vs* 8–10, $P = 0.047$). Multivariate Cox regression analysis demonstrated that pathologic stage ≥T3 (HR = 2.106; $P = 0.018$), PSMs (HR = 2.411; $P = 0.003$), and pathologic Gleason score 8–10 (HR = 4.715; $P < 0.001$) were independent predictors of BCR after RP. Therefore, in addition to pathologic stage ≥T3 and PSMs, Gleason score 8–10 predicts BCR after RP. In patients with Gleason score 6, observation rather than ART may be more appropriate regardless of stage and surgical margin status.
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INTRODUCTION

Radical prostatectomy (RP) is one of the most effective curative treatment options for patients with localized prostate cancer (PCa).[1,2] However, it is estimated that approximately 30% of patients experience biochemical recurrence (BCR) after RP within 10 years.[3,4] Moreover, the rate of BCR increased to 40%–60% in men with adverse pathologic findings defined as positive surgical margin (PSM), extracapsular extension (ECE), seminal vesicle invasion (SVI), or lymph node invasion (LNI).[5,6] Without additional treatment, most patients with BCR are likely to develop distant metastasis and cancer-related death.

Because BCR predicts clinical disease progression, the American Urological Association (AUA) and American Society for Radiation Oncology (ASTRO) jointly released a guideline for adjuvant radiotherapy (ART) to decrease the risk of BCR in high-risk patients. The AUA/ASTRO guideline recommended that "*patients with adverse pathologic findings including SVI, PSM, and extraprostatic extension (EPE) should be informed that ART, compared to RP only, reduces the risk of BCR, local recurrence, and clinical progression of cancer.*"[7] These recommendations are mainly based on three prospective, randomized trials that suggested that ART may have a favorable impact on BCR and local recurrence for patients with pathologically nonorgan confined PCa and/or PSMs.[8–10]

However, there is a controversy on the impact of ART on metastasis-free survival and overall survival though European Organization for Research and Treatment of Cancer (EORTC) trial demonstrated that clinical progression-free survival was improved with ART. Indeed, the AUA/ASTRO guideline on ART acknowledges that the "*impact of ART on subsequent metastases and overall survival is less clear.*"[7] Consistent with this uncertainty concerning the effect of ART on survival outcome, a matched case-control study demonstrated that ART did not improve rates of overall and cancer-specific survival.[11] Thus, the universal adoption of ART in patients with adverse pathologic findings likely represents overtreatment in many men.

Disregarding the potential clinical benefit of ART, there is a concern among urologists regarding the toxicity of radiotherapy. Specifically, ART after RP showed twice as many grade III toxicities as RP alone.[8,9] Thus, it is not surprising that a recent study on the pattern of care analysis revealed that <20% of patients with adverse pathologic findings received ART.[12]

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Given this controversy, it is important to analyze the AUA/ASTRO guideline for ART to further clarify the role of ART and to reduce excessive treatment. In this framework, our group is focused on further refining the inclusion criteria of ART. We have previously reported that the AUA/ASTRO guideline on ART after RP is overly broad as only 16.6% of the patients who met the inclusion criteria for ART developed BCR.[13] In this study, we assessed the risk of BCR after incorporating the pathologic Gleason score into the current AUA/ASTRO guideline.

MATERIALS AND METHODS

Patients

This study was approved by the Institutional Review Board of Rutgers, The State University of New Jersey (IRB No: 0220080225). To date, more than 1300 cases of robot-assisted radical prostatectomy (RARP) have been performed at the Rutgers Cancer Institute of New Jersey, New Brunswick, NJ using the daVinci Surgical System (Intuitive Surgical, Sunnyvale, CA, USA) from 2006. We retrospectively reviewed the prospectively maintained database of the first 702 patients who underwent RARP between January 2006 and July 2011. Of 702 patients, 30 patients were excluded due to missing pathologic information (8), loss of follow-up (5), and not achieving prostate specific antigen (PSA) nadir to undetectable levels defined as serum PSA level <0.1 ng ml^{-1} on the first follow-up visit after RP (17). None of the remaining 672 patients had received neoadjuvant or adjuvant treatment. High-risk pathologic risk features were determined using the AUA/ASTRO guideline for ART.

Baseline characteristics including age and preoperative PSA, pathologic stage, surgical margin status, and Gleason score were analyzed. Patients were stratified into subgroups based on adverse pathologic findings and Gleason score. BCR was defined as two consecutive rises in PSA with the last PSA ≥0.2 ng ml^{-1}.

Surgery

All surgical procedures were conducted via the transperitoneal approach. Pelvic lymph node dissection was performed according to the National Comprehensive Cancer Network (NCCN) guideline at the time of the surgery.[14,15] Surgical drains were not routinely used. Patients were monitored every 3 months for the first year, every 6 months for the second year, and yearly thereafter with a physical examination and serum PSA level.

Statistical analysis

Independent sample *t*-test was used to compare the continuous variables. Surgical margin status, pathologic stage, and Gleason score were analyzed using the Pearson's Chi-square test. Kaplan–Meier survival analysis was used to assess BCR-free survival, and the log-rank test was applied to compare survival rates of subgroups. Univariate and multivariate Cox proportional hazard models were utilized to identify factors predicting BCR. All statistical analyses were performed with the IBM SPSS version 20.0 (IBM Corp. Armonk, NY, USA) and a two-sided *P* < 0.05 was considered statistically significant.

RESULTS

Patient demographics

Descriptive statistics of the 672 patients included in this study are summarized in **Table 1**. The median follow-up was 24 months. The mean age was 59.1 years and mean preoperative PSA was 6.0 ng ml^{-1}. The clinicopathological characteristics associated with BCR were age, preoperative PSA, surgical margin status, pathologic stage, and

Table 1: Clinicopathologic characteristics of 672 patients who underwent robot assisted radical prostatectomy

Variables	Total (n=672) (%)	BCR^d (%)		P
		Negative (n=615)	Positive (n=57)	
Age, years				
Mean±s.d.^{e}	59.1±6.8	58.9±6.9	61.2±6.1	0.014^a
Range	36.0–77.0	36.0–77.0	43.0–77.0	
Preoperative PSA^c (ng ml^{-1})				
Mean±s.d.^{e}	6.0±4.3	5.8±4.1	7.6±5.8	0.029^a
Range	0.2–55.4	0.2–55.4	1.4–35.6	
Pathologic Gleason score				
6	304 (45.2)	291 (47.3)	13 (22.8)	<0.001^b
7	284 (42.3)	265 (43.1)	19 (33.3)	
8–10	84 (12.5)	59 (9.6)	25 (43.9)	
Pathologic stage				
≤T2	533 (79.3)	506 (82.3)	27 (47.4)	<0.001^b
T3a	120 (17.9)	95 (15.4)	25 (43.9)	
≥T3b	19 (2.8)	14 (2.3)	5 (8.7)	
Surgical margin				
Negative	568 (84.5)	532 (86.5)	36 (63.2)	<0.001^b
Positive	104 (15.5)	83 (13.5)	21 (36.8)	
Prostate volume (ml)				
Mean±s.d.^{e}	47.5±16.8	47.5±16.8	46.7±16.4	0.872^a
Range	18.0–151.0	18.0–151.0	19.0–112.0	

^{a}Independent sample *t*-test; ^{b}Pearson's Chi-square test. ^{c}PSA: prostate specific antigen; ^{d}BCR: biochemical recurrence; ^{e}s.d.: standard deviation

pathologic Gleason score (*P* < 0.05). Consequently, a higher rate of adverse pathologic findings and a greater percentage of Gleason score 8–10 were present in the BCR group.

Pathologic parameters associated with BCR-free survival

Of the 672 patients, 139 (20.7%) had pathologic stage ≥T3. The overall PSMs rate was 15.5% (104/672), and pathologic Gleason score 8–10 was found in 84 (12.5%) men. The overall BCR rate in this cohort was 8.5% (57/672). There were notable differences in BCR-free survival with respect to pathologic stage, surgical margin status, and pathologic Gleason score (≤T2 *vs* ≥T3, negative SM *vs* positive SM, and 6–7 *vs* 8–10, all *P* < 0.001, respectively). Based on the AUA/ASTRO ART inclusion criteria, adverse pathologic findings were found in 193 patients; of these patients, 34 (17.6%) developed BCR. Of the remaining 479 patients who had no adverse pathologic findings, only 23 (4.8%) patients showed BCR. When patients in this cohort were stratified by pathologic Gleason score, BCR rate in men with Gleason 6 was 4.3% (13/304) in the overall group and 6.8% (3/44) in the subgroup with adverse pathologic features.

Margin status stratified by pathologic stage and pathologic Gleason score

As an initial attempt to identify men who will likely benefit the most from ART, we reanalyzed the data after subgrouping patients based on the combination of surgical margin status, pathologic stage, and pathologic Gleason score. Kaplan–Meier analysis was again used to evaluate BCR-free survival rates among the subgroups.

In patients with PSMs, there were differences in BCR-free survival according to pathologic stage (*P* = 0.001) (**Figure 1a**, left panel) and Gleason score (*P* < 0.001) (**Figure 1a**, right panel). The 5-year BCR-free survival rate in patients with PSM/pathologic stage ≥T3 and PSM/Gleason score 8–10 was 34.2% and 22.2%, respectively. In the context of negative surgical margin, there were also differences

in BCR-free survival according to pathologic stage and Gleason score (**Figure 1b**).

Pathologic stage stratified by surgical margin status and pathologic Gleason score

In patients with pathologic stage T2, there was no difference in BCR-free survival with regard to surgical margin status ($P = 0.267$) (**Figure 1c**, left panel); however, there was a difference according to Gleason score ($P = 0.011$) (**Figure 1c**, right panel). In patients with pathologic stage ≥T3, there were differences in BCR-free survival with regard to surgical margin and Gleason score ($P = 0.003$ and $P < 0.001$, respectively) (**Figure 1d**). The 5-year estimated BCR-free survival rate in patients with pathologic stage ≥T3 and Gleason score 8–10 was 43.4%.
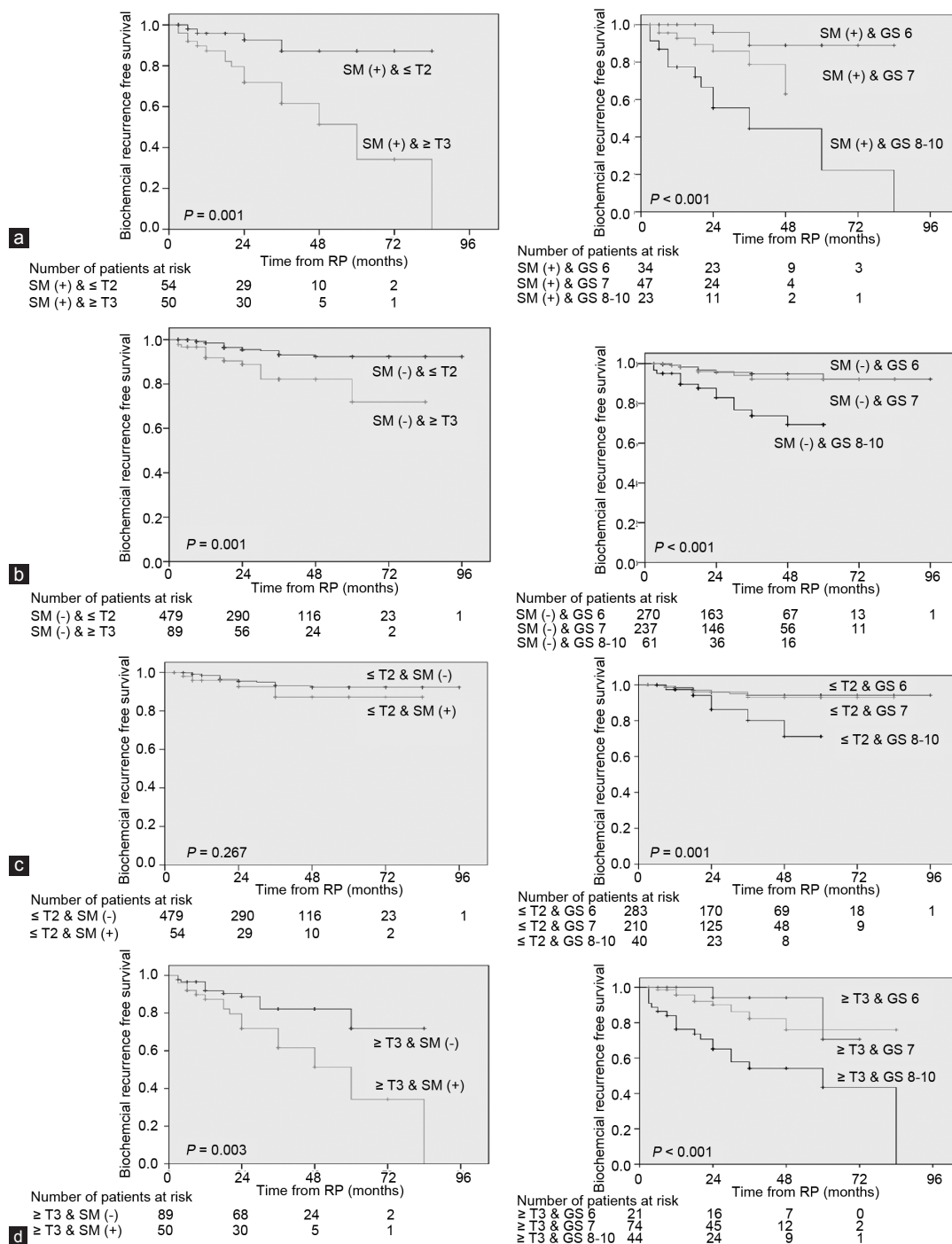

Figure 1: Kaplan–Meier curves depicting BCR-free survival in patients with (**a**) positive surgical margin stratified by pathologic stage (*Left*) and pathologic Gleason score (*Right*), (**b**) negative surgical margin stratified by pathologic stage (*Left*) and pathologic Gleason score (*Right*), and (**c**) pathologic stage T2 stratified by surgical margin status (*Left*) and pathologic Gleason score (*Right*) (**d**) pathologic stage ≥T3 stratified by surgical margin status (*Left*) and pathologic Gleason score (*Right*). The results demonstrate that incorporating pathologic Gleason score further stratifies patients with PSM or pathologic stage ≥T3. BCR: biochemical recurrence; PSM: positive surgical margin.

Pathologic Gleason score stratified by surgical margin and pathologic stage

Since pathologic Gleason score is not part of the AUA/ASTRO ART guideline criteria, we next studied the impact of surgical margin status and pathologic stage after stratifying patients based on pathologic Gleason score. In patients with Gleason score 6, there was no difference in BCR-free survival with regard to surgical margin ($P = 0.690$) and pathologic stage ($P = 0.353$) (**Figure 2a**). Furthermore, no difference was observed between Gleason 3 + 4 and 4 + 3 ($P = 0.40$). However, a notable difference in recurrence existed in men with Gleason scores 7 and 8–10 ($P < 0.05$ for both) (**Figure 2b** and **2c**). In summary, Gleason

6 disease, regardless of its high-risk group status as indicated by PSM or pathologic stage ≥T3, did not demonstrate aggressive oncologic features that justifies the use of ART.

Comparing various combinations of high-risk pathologic parameters

Interestingly, in patients with PSMs and Gleason score 8–10, there was no difference in BCR-free survival with regard to pathologic stage (≤T2 *vs* ≥T3, $P = 0.648$). Similarly, in men with pathologic stage ≥T3 and GS 8–10, there was no difference in BCR-free survival with regard to surgical margin status (negative *vs* positive, $P = 0.599$). However, in patients with PSMs and pathologic stage ≥T3, higher Gleason score was associated with a shorter BCR-free survival (≤7 *vs* 8–10, $P = 0.047$).
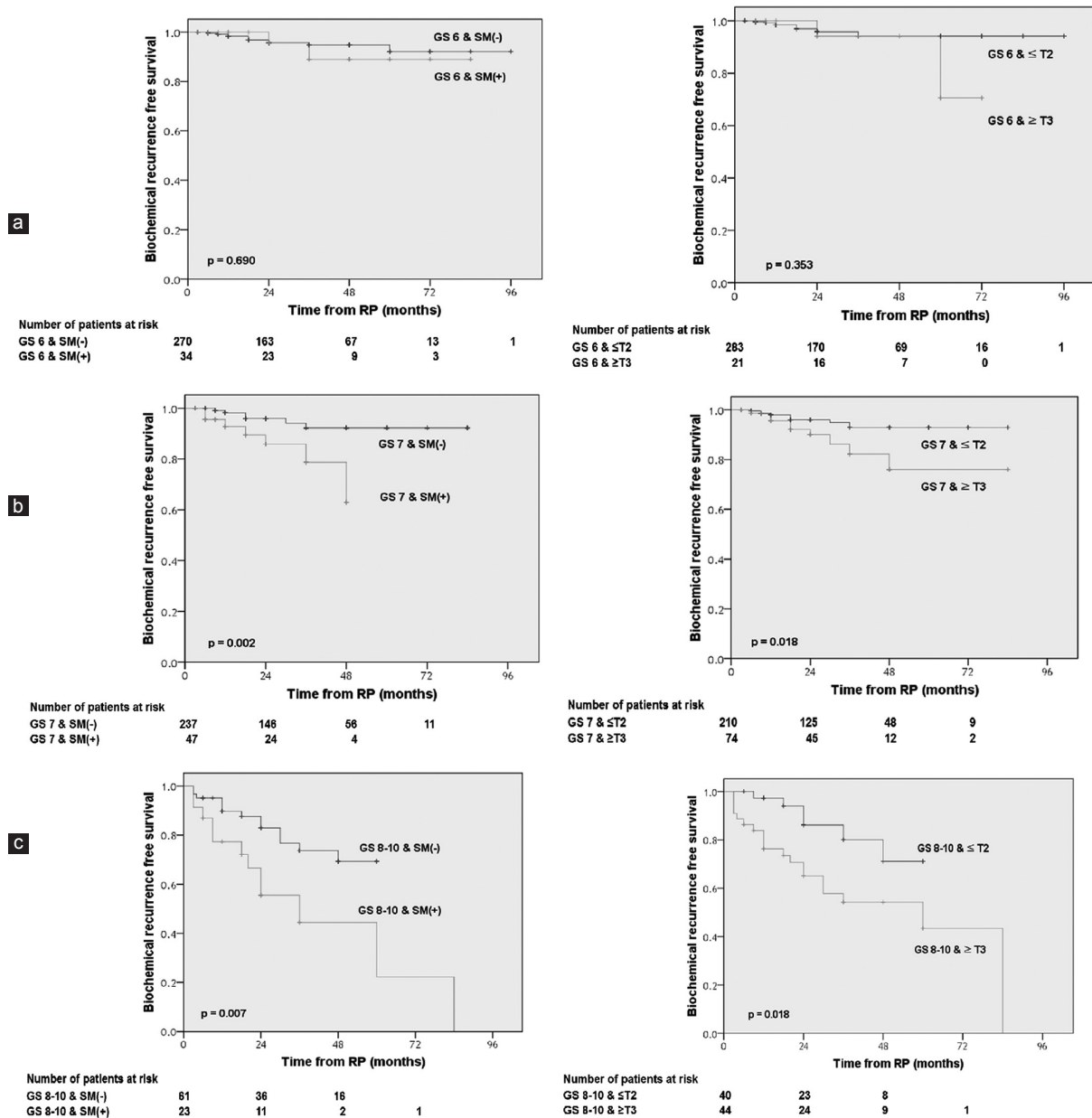

Figure 2: Kaplan–Meier curves depicting BCR-free survival in patients with a (**a**) pathologic Gleason score of 6 stratified by surgical margin status (*Left*) and pathologic staging (*Right*), (**b**) pathologic Gleason score of 7 stratified by surgical margin status (*Left*) and pathologic stage (*Right*) and (**c**) pathologic Gleason score of 8–10 stratified by surgical margin status (*Left*) and pathologic stage (*Right*). In men with pathologic Gleason score 6, PSM or pathologic stages did not increase risk of biochemical recurrence. BCR: biochemical recurrence; PSM: positive surgical margin.

Therefore, the subpopulation with Gleason 8–10 and either PSMs or pathologic stage ≥T3 had a clear indication for ART.

Cox proportional hazard regression analysis

Cox proportional hazard regression analysis was used to assess the prognostic factors for BCR after RP. On univariate analysis, age, preoperative PSA, pathologic stage, surgical margin status, and pathologic Gleason score were associated with increased risk of BCR ($P < 0.05$). On multivariate analysis, pathologic stage ≥T3 ($P = 0.018$, hazard ratio [HR] 2.106, 95% confidence interval [CI] 1.135–3.907), PSMs ($P = 0.003$, HR: 2.411, 95% CI: 1.338–4.343), and pathologic Gleason score 8–10 ($P < 0.001$, HR: 4.715, 95% CI: 2.200–10.103) were independent predictors of BCR after RP (**Table 2**).

DISCUSSION

In the present study, we have demonstrated that nonorgan confined disease and PSMs are associated with increased risk of BCR. However, the overall BCR rate in these high-risk men was only 17.6% after a median follow-up of 24 months. When Gleason score was analyzed, overall BCR rate in men with Gleason score 6 was 4.3%. More importantly, in men with Gleason score 6 and adverse pathologic features based on the AUA/ASTRO guideline, the BCR rate remained low at 6.8% (3/44). Subsequent analysis demonstrated that surgical margin status and pathologic stage did not predict BCR in patients with the pathologic Gleason score 6 ($P = 0.690$ and $P = 0.353$, respectively). However, in patients with PSMs and pathologic stage ≥T3, higher Gleason score was associated with shorter BCR-free survival (≤7 *vs* 8–10, $P = 0.047$). These findings collectively suggest that Gleason score 6 has a relatively benign clinical course, and observation should be considered regardless of stage and surgical margin status. In contrast, in men with Gleason score 8 or higher, ART is justified if either PSM or extraprostatic/SVI are present.

BCR after RP predicts progression to distant metastasis and cancer-specific mortality.[16] Since three randomized clinical trials have demonstrated the beneficial effect of ART on BCR, the AUA and ASTRO jointly recommended that patients with adverse pathologic findings following RP should be offered ART to reduce BCR. However, multiple investigators have reported that the BCR-free rate in men with high-risk features pathologically ranges 40%–57.5% over a 5-year period.[5,17,18] Accordingly, the uniform application of AUA/ASTRO's ART guideline is an overtreatment in approximately half of the patients.

Given that the salvage rate of radiation in men with BCR following surgery in 37%–64%,[19–21] the benefit of ART on BCR is likely small. In this context, only 17.6% (34/193) of the men who met the AUA/ASTRO ART inclusion criteria developed BCR in the current study. In comparison, BCR occurred in 4.8% (23/479) of patients with negative surgical margin and pathologic stage T2. Thus, high-risk pathologic features as defined by the AUA/ASTRO ART guideline are associated with an increased risk of BCR. Nevertheless, the overall recurrence rate does not justify the cost and the potential toxicity of ART.

Recently, several studies have analyzed predictive factors for BCR after RP.[22–25] These reports have demonstrated that preoperative PSA, pathologic stage such as ECE, SVI, PSMs, and LNI, and pathologic Gleason score are prognostic factors. Consistent with these published data, we have confirmed that pathologic stage, surgical margin status, and pathologic Gleason score are important prognostic factors of BCR. Similarly, nomograms predicting BCR or cancer-specific mortality require Gleason score.[3,22,26] Collectively, these results suggest that pathologic Gleason score should be considered in selecting the optimal candidates for ART. Nevertheless, Gleason score is currently not a part of the AUA/ASTRO guideline for ART.

If pathologic Gleason score was to be adopted as a factor in selecting patients for ART, high pathologic Gleason score should be considered as one of the inclusion criteria. Not surprisingly, multiple groups have demonstrated that the pathologic Gleason score 8–10 tightly correlates with BCR after RP.[23,24] Walz *et al.*[27] analyzed BCR-free survival according to clinical stage T3, biopsy Gleason score ≥8, and preoperative PSA ≥20.0 ng ml^{-1}. The authors reported that biopsy Gleason score ≥8 showed the worst BCR-free survival rate at 2, 5, and 10 years with 58.8%, 39.9%, and 26.4%, respectively. In the current study, 29.8% (25/84) of the patients with pathologic Gleason score 8–10 experienced BCR. In patients with PSMs and Gleason score 8–10, recurrence occurred in more than three-quarters as the estimated 5-year BCR-free survival rate was only 22.2%. In addition, these patients with PSMs and Gleason score 8–10 had no difference in BCR-free survival with regard to pathologic stage (≤T2 *vs* ≥T3, $P = 0.648$). In contrast, the combination of PSMs and pathologic stage ≥T3 was associated with the BCR-free survival when stratified by Gleason score (≤7 *vs* 8–10, $P = 0.047$). Taken together, these results show that the presence of pathologic Gleason score 8–10 should be used in counseling patients considering ART.

In contrast to the high pathologic Gleason score, the present study demonstrated no difference in BCR-free survival with regard to surgical margin ($P = 0.690$) and pathologic stage ($P = 0.353$) in patients with

Table 2: Uni and multivariate Cox regression analyses predicting BCR in 672 prostate cancer patients who underwent robot-assisted radical prostatectomy

Variables	Univariate		Multivariate	
	HR[b] (95% CI[c])	P	HR[b] (95% CI[c])	P
Age	1.054 (1.012–1.097)	0.012		
Preoperative PSA[a] (ng ml^{-1})				
>6.0 versus ≤6.0	1.922 (1.132–3.264)	0.016		
Pathologic stage				
≥T3 versus ≤T2	4.405 (2.617–7.414)	<0.001	2.106 (1.135–3.907)	0.018
Margin status				
Positive versus negative	3.670 (2.139–6.299)	<0.001	2.411 (1.338–4.343)	0.003
Pathologic Gleason score				
6	1.000 (Ref[d])	-	1.000 (Ref[d])	-
7	1.616 (0.798–3.273)	0.183	1.469 (0.701–3.082)	0.309
8–10	7.542 (3.857–14.746)	<0.001	4.715 (2.200–10.103)	<0.001

[a]PSA: prostate specific antigen; [b]HR: hazard ratio; [c]CI: confidence interval; [d]Ref: reference value; BCR: biochemical recurrence

the pathologic Gleason score 6. This observation is consistent with the body of literature that suggests that Gleason score 6 PCa has a relatively indolent course. For example, Savdie *et al.*[28] examined the association between pathologic Gleason score at the surgical margin and BCR with a median follow-up of 82 months. The results showed that the 5-year actual BCR-free survival for negative surgical margin and PSMs with Gleason grade 3 at the margin was 85.6% and 83.8%, respectively. Therefore, we recommend that the AUA/ASTRO should consider excluding all men with the pathologic Gleason score 6 regardless of the stage and surgical margin status in the context of ART.

Despite the potential clinical implications of the present study, there are some limitations. First, this is a retrospective, nonrandomized study and conducted at a single institution, thus raising concerns for selection bias. Notwithstanding, this study used a prospectively maintained database and reflects real clinical practice. Second, the follow-up period is relatively short and thus, BCR rate and the results of a multivariate analysis may be underestimated. It should be pointed out though, that early onset of BCR after RP is associated with poor prognosis. Thus, this study likely identifies those who will likely benefit the most from ART. Regardless, since the short follow-up period is a major limitation, this investigation should be considered a hypothesis generating study. Third, the sample size is relatively small. In the future, a large prospective multi-institutional study will be carried out to develop a stratification system that will help identify the optimal candidates for ART after RP.

CONCLUSION

Oncologic outcomes following RP in patients with adverse pathologic features are heterogeneous. Thus, the current AUA/ASTRO guideline on ART may be overly broad and raises the concern for overtreatment. In this regard, the pathologic Gleason score is an important prognostic factor. The current hypothesis generating study suggests that ART should be considered in patients with the pathologic Gleason 8–10 along with nonorgan confined disease or PSM. To the contrary, in patients with Gleason score 6, observation rather than ART may be more prudent regardless of stage and surgical margin status. A study with a longer follow-up is necessary to test this hypothesis.

AUTHOR CONTRIBUTIONS

WS participated in the design of the study, statistically analyzed the data, and drafted the manuscript. YSK reviewed the pertinent literature, revised, and reformatted the manuscript. JSS assisted with the design of the study, conducted the data acquisition, and revised the manuscript for important intellectual content. IYK participated in the design of the study, conducted the data acquisition, and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing financial interests.

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