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Original Article

Impact of Gleason Pattern 5 on outcomes of patients with prostate cancer and iodine-125 prostate brachytherapy

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ABSTRACT

Background: The Gleason grading system is a powerful predictor of prostate cancer (PCa) prognosis. Gleason scores (GS) of 8–10 are considered as a single high-risk grade category, and Gleason Pattern 5 (GP5) predicts biochemical recurrence. We report the clinical outcomes of patients treated with ^{125}I prostate brachytherapy for clinically localized PCa and prognosis in the presence or absence of GP5.

Methods: We enrolled 316 patients with T1c–T2N0M0 PCa and undergoing prostate brachytherapy treatment. All patients were followed up for ≥ 1 year. The primary endpoint was biochemical recurrence-free survival. Biochemical recurrence was defined by the Phoenix criteria. Survival curves were calculated by the Kaplan–Meier method, and the prognostic impact of biochemical recurrence was analyzed using a Cox proportional hazards model.

Results: The 5-year biochemical recurrence-free survival rate for all patients was 95.2%, and according to the D'Amico risk classification criteria, the rates were 98.7% for patients in low-risk, 96.9% in intermediate-risk, and 81.1% in high-risk groups ($P < 0.0001$). The 5-year biochemical recurrence-free survival rates for patients with GS8 or GS9–10 were 87.7% and 61.5%, respectively ($P = 0.0057$). Multivariate analysis found that GS and clinical T stage were independent predictors of biochemical recurrence.

Conclusions: The presence of GP5 in GS9–10 prostate cancer has a worse prognosis than GS8 prostate cancer in the absence of GP5 for patients undergoing prostate brachytherapy.

1. Introduction

Iodine-125 prostate brachytherapy (PB) is an established modality for treating localized prostate cancer (PCa), with favorable outcomes similar to those obtained by radical prostatectomy and external beam radiation therapy (EBRT).[1,2] The number of PCa patients with PB has been increasing rapidly in Japan.[3] Gleason grading is an important predictor of PCa outcome,[4] and Gleason scores (GS) of 8–10 represent a high-risk grade group. The presence of Gleason Pattern 5 (GP5) predicts for biochemical recurrence,[5,6] but there are few reports on the impact of GP5 on clinical outcomes of patients with brachytherapy. In this report, we summarize 7 years of clinical experience and outcomes of patients with PB at our institution, and evaluate the prognostic value of GP5 with regard to biochemical recurrence.

2. Materials and methods

We enrolled 316 patients with T1c–T2N0M0 PCa and treated with PB at the Kanazawa Medical Center (Kanazawa, Japan) between 2007 and 2014. We followed the patients for ≥ 1 year. Patients were stratified into prognostic groups by D'Amico risk classification criteria.[7] Low-risk patients had prostate-specific antigen (PSA) ≤ 10 ng/mL, GS ≤ 6, and clinical stage ≤ T2a tumors. Intermediate-risk patients had PSA > 10 ng/mL and ≤ 20 ng/mL, and/or GS = 7, and/or clinical stage T2b tumors. High-risk patients had PSA > 20 ng/mL and/or GS ≥ 8 and/or clinical stage ≥ T2c tumors. Most low-risk patients received PB without supplemental EBRT. High-risk patients received PB with EBRT, and intermediate-risk patients were given supplemental EBRT as determined by their physician depending on the PSA value and biopsy-positive core rate, i.e., the percentage of cores containing tumor. A total of 123 patients (30.1%) received neoadjuvant androgen deprivation therapy (ADT) for prostate volume reduction, to be worried the progression of disease until PB, or if it had already been started by

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another physician. PB alone was administered at a dose of 145 Gy; PB with EBRT was administered at a dose of 110 Gy with an additional 45 Gy of supplemental EBRT. Planned follow-up was by PSA blood tests every 3 months for the first 2 years, and every 3–6 months thereafter. The primary outcome was biochemical recurrence-free survival (bRFS). Biochemical recurrence was determined by the Phoenix criteria.[8] If biochemical recurrence was confirmed and it persisted, as shown by PSA increase, the patient was further evaluated by prostate biopsy, computed tomography, and bone scan so that recurrence could be assured and characterized by a physician. PSA bounce was defined as an increase of $\geq$ 0.4 ng/mL above an initial PSA nadir and a subsequent decline to or below that initial nadir without treatment, and patients meeting the bounce phenomenon were excluded from the analysis of recurrence. Survival curves were calculated by the Kaplan–Meier method, and differences in time-adjusted rates were evaluated for significance by log-rank test. The prognostic impact of biochemical recurrence was analyzed in a Cox proportional hazards model. All tests were two sided, and the statistical significance was set at $P < 0.05$.

3. Results

Patient characteristics are shown in Table 1. The median patient age was 69 years (range, 51–84 years) and the median follow-up duration was 48.2 months (range, 12–103 months). Of the 316 patients included in this study, 237 (75.0%) were in clinical stage T1c, 58 (18.4%) in T2a, 18 (5.7%) in T2b, and three (0.9%) in T2c. The median PSA level at diagnosis was 5.6 ng/mL (range, 0.67–84.44 ng/mL) and the GS were $\leq$ 6 (128, 40.5%), 7 (141, 44.6%), and $\geq$ 8 (47, 14.9%). According to the D'Amico risk criteria, 114 patients (36.1%) were at low risk, 144 (45.5%) at intermediate risk, and 58 (18.4%) at high risk. Of all patients, 221 (69.9%) were treated with PB without EBRT. A total of 123 patients (38.9%) were given neoadjuvant ADT for a median duration of 5 months. Only 10 patients (3.2%) received adjuvant ADT (data not shown). Additional patient characteristics, including GS, age, PSA, clinical T stage, combined EBRT therapy, and use of ADT are summarized in Table 2. Among high-risk patients, 34 (10.8%) had GS8 and all of them had no GP5.

Table 1
Patient characteristics.

Median age, y (range)	69 (51–84)	$n = 316$
Follow-up, mo (range)	Median	48.2 (12–103)
Clinical stage, *n* (%)	T1c	237 (75.0)
	T2a	58 (18.4)
	T2b	18 (5.7)
	T2c	3 (0.9)
Gleason score, *n* (%)	$\leq$ 6	128 (40.5)
	7	141 (44.6)
	$\geq$ 8	47 (14.9)
PSA at diagnosis, ng/mL (range)	Median	5.6 (0.67–84.44)
	$\leq$ 10	258 (81.7)
	10–20	39 (12.3)
	$\geq$ 20	19 (6.0)
Positive core rate, % (range)	Median	20.0 (7.1–100)
Prostate volume, mL (range)	Median	20.9 (7.0–46.5)
Neoadjuvant hormone therapy, *n* (%)	+	123 (38.9)
	–	193 (61.1)
Combined external beam radiotherapy, *n* (%)	+	95 (30.1)
	–	221 (69.9)
D'Amico risk classification, *n* (%)[a)]	Low	114 (36.1)
	Intermediate	144 (45.5)
	High	58 (18.4)

[a)] Low risk: PSA $\leq$ 10 and Gleason score $\leq$ 6 and stage $\leq$ T2a; intermediate risk: PSA > 10 and $\leq$ 20 and/or Gleason score =6 and/or stage T2b; high risk: PSA > 20 and/or Gleason score $\geq$ 8 and/or stage $\geq$ T2c, PSA, prostate-specific antigen.

Thirteen patients (4.1%) had GS9–10. As expected, patients with higher GS tended to have higher PSA values and a more advanced T stage.

Fig. 1 shows the survival curves calculated by the Kaplan–Meier method. The 5-year and 8-year overall survival rates were 95.7% and 91.6%, respectively, and the corresponding bRFS rates were 95.2% and 83.3%, respectively (Fig. 1A). The 5-year bRFS rates for low-, intermediate-, and high-risk patients (Fig. 1B) were 98.7%, 96.9%, and 81.1%, respectively ($P < 0.0001$). The 5-year bRFS rates for patients with GS $\leq$ 6, 7, or $\geq$ 8 were 98.9%, 95.8%, and 80.4%, respectively ($P < 0.0001$; Fig. 1C). Remarkably, the 5-year bRFS rates for patients with GS8 (87.7%) and GS9–10 (61.5%) were significantly different ($P = 0.0057$; Fig. 1D). Recurrence occurred in 16 patients (5.1%), and nine patients died during follow-up but only one patient died of PCa.

Table 3 shows the characteristics of patients who experienced recurrence. Ten of the 58 patients (17.2%) were in the high-risk group at inclusion, and six of the 258 (2.3%) were low- or intermediate-risk patients. One was a low-risk patient and five were intermediate-risk patients. Two recurrence sites were local (12.5%), three were lymph nodes (18.8%), and three were bone (18.8%). One recurrence was both local and in bone (6.2%), one was in both lymph nodes and bone (6.2%), and six were at an unknown site or sites (37.5%). Four of six patients with GS9–10 tumors experienced metastases.

Multivariate Cox regression analysis including age, GS, PSA, clinical T stage, and biopsy-positive core rate (Table 4) found that GS (hazard ratio = 3.43) and clinical T stage (hazard ratio = 4.59) were independent predictors of biochemical recurrence.

4. Discussion

Since 2003, when PB was first authorized, many cancer institutes throughout Japan have registered to administer PB therapy. The reported 5-year bRFS rates for patients in the low-, intermediate-, and high-risk groups are $\geq$ 90%, 80–90%, and 70–80%, respectively.[9–11] The corresponding bRFS rates at our treatment center were 98.7%, 96.9%, and 81.1%, respectively, which are similar to those of the previous reports.

Our high-risk patients had a poor prognosis, and those with GS9–10 PCa had a significantly worse bRFS rate than those with GS8 disease, who also had a relatively poor prognosis. In other words, the presence of GP5 predicted the worse clinical outcome. Sabolch et al[5] reported that the presence of GP5 predicted lower cause-specific survival and overall survival in PCa patients treated with EBRT compared with GS8 patients in cases without GP5. In that series, the presence of GP5 predicted worse clinical outcome and a short interval from biochemical failure to metastasis.[5] In our series, six of 13 patients with GP5 experienced biochemical recurrence and four experienced advanced metastasis. This suggests that GP5 may have characteristics that predispose to metastasis. Although the biological cause underlying worse outcomes in patients with GP5 is unknown, there are multiple alternative pathways that can drive a PCa toward the aggressiveness seen in the presence of GP5.[5] Horwitz et al[12] reported long-term results of Radiation Therapy Oncology Group Protocol 92-02 that demonstrate a survival advantage for 24 months of ADT plus radiation therapy in the treatment of locally advanced tumors with GS of 8–10. That result implies that the Protocol 92-02 regimen should be the standard of treatment for these high-risk patients. By contrast, androgen suppression probably contributes to the elimination of occult systemic disease while also potentiating external irradiation by an additive, or supra-additive, effect on local control through induction of apoptosis.[13,14] Hence, long-term ADT plus radiation therapy is considered more effective in high-risk cases

Table 2
Clinical features stratified by Gleason score.

	Gleason score			
	≤ 6	7	8	9, 10
n	128 (40%)	141 (45%)	34 (11%)	13 (4%)
Median age (range)	68 (51–84)	69 (54–84)	75 (54–83)	71 (56–77)
Median PSA (range)	4.98 (0.67–37.62)	5.69 (2.00–33.96)	7.90 (1.86–84.44)	10.08 (4.13–62.23)
Clinical stage				
T1c-T2a	100%	92%	88%	62%
T2b	0%	6%	12%	38%
T2c	0%	2%	0%	0%
D'Amico risk classification				
Low	89%	0%	0%	0%
Intermediate	8%	95%	0%	0%
High	3%	5%	100%	100%
Combined EBRT	5%	33%	85%	100%
ADT use	33%	43%	44%	46%

ADT, androgen deprivation therapy; EBRT, external beam radiotherapy; PSA, prostate specific antigen.

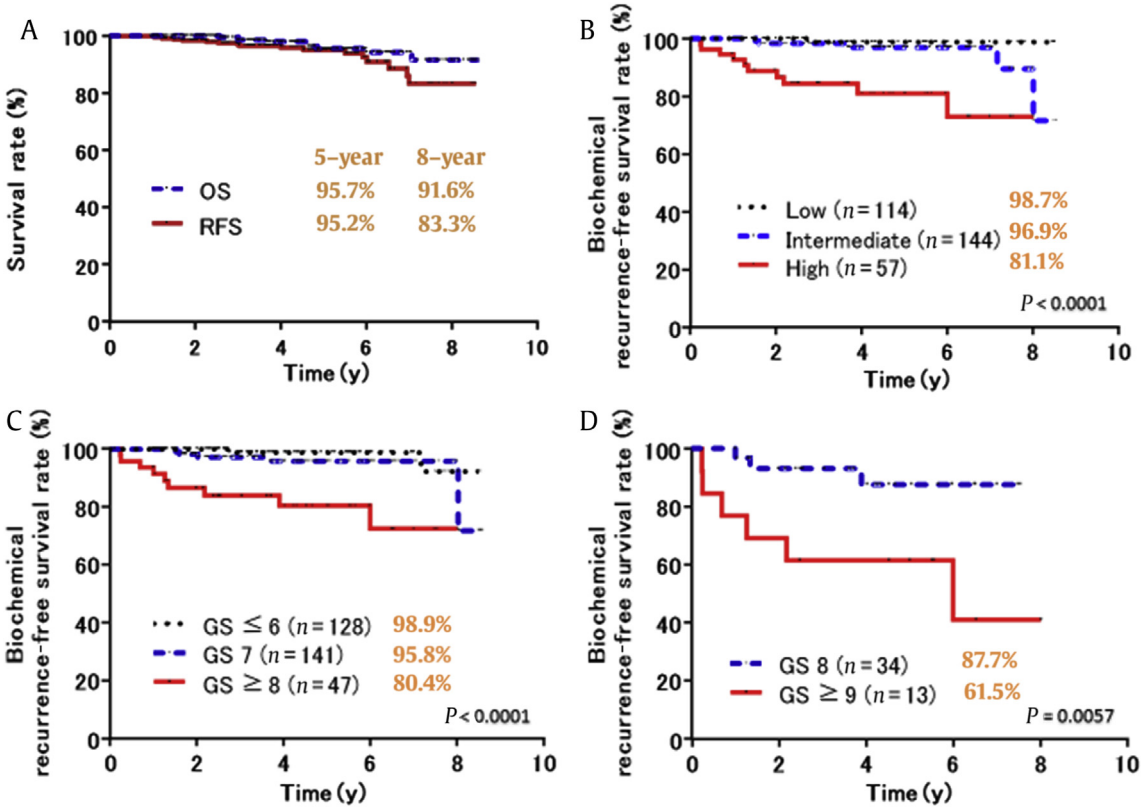

Fig. 1. Survival curves calculated by the Kaplan–Meier method. (A) Survival rates for all patients ($n = 316$). (B) Biochemical recurrence-free survival rates for all patients stratified by the risk group. (C) Biochemical recurrence-free survival rates for all patients stratified by the Gleason score. (D) Biochemical recurrence-free survival rate for high-risk patients with a Gleason score of 8 or 9–10, GS, Gleason scores; OS, overall survival; RFS, recurrence-free survival.

Table 3
Characteristics of recurrence patients ($n = 16$).

Risk group (No.of recurrence Pts)	Median age	T stage	Gleason score	PSA	Recurrence site
Low 1(/114; 0.9%) intermediate 5(/144; 3.5%) High 10(/58; 17.2%)	72	T1c: 5 T2a: 6 T2b: 4 T2c: 1	≤ 6:2 7:5 8:3 9–10:6	≤ 10:7 > 10, ≤ 20:5 > 20:4	Local: 2 LNs: 3 bone: 3 Local + bone: 1 LNs + bone: 1 Unknown: 6

LN, lymph node; PSA, prostate-specific antigen; Pts, patients.

Table 4
Multivariate Cox regression analysis for biochemical recurrence.

	P value	Hazard rate	95.0% CI	
			Lower	Upper
Age ≥ 70	0.196	2.321	0.647	8.328
GS ≥ 8	0.038	3.429	1.074	10.951
PSA ≥ 20	0.283	2.312	0.500	10.686
T stage *T2*	0.022	4.587	1.247	16.868
PCR ≥ 50%	0.932	0.940	0.227	3.888

CI, confidence interval; GS, Gleason scores; PCR, positive core rate; PSA, prostate-specific antigen.

such as those with GP5, in which distant micrometastasis may be present when primary therapy starts.

Gleason scoring is a well-established system for describing pathological stage and predicting oncological outcomes of men with PCa. Pierorazio et al[15] have recommended Gleason grades, and prognostic grade groups, including GS ≤ 6 (prognostic Grade Group 1); GS 3 + 4 = 7 (prognostic Grade Group 2); GS 4 + 3 = 7 (prognostic Grade Group 3); GS 4 + 4 = 8 (prognostic Grade Group 4); and GS9–10 (prognostic Grade Group 5). In that series, the 5-year bRFS rates were 96.6% in Grade Group 1, 88.1% in Group 2, 69.7% in Group 3, 63.7% in Group 4, and 34.5% in Group 5 ($P < 0.001$) after radical prostatectomy. Therefore, they suggested that men with GS9–10 tumors will more accurately be considered to have more aggressive tumors than those with GS8.[15] In our study, the 5-year bRFS rates were 98.9% in Grade Group 1, 96.2% in Group 2, 95.3% in Group 3, 87.7% in Group 4, and 61.5% in Group 5 ($P < 0.0001$; Fig. 2). As above, GS were independent predictors of biochemical recurrence. The 5-year bRFS rates for patients with GS8 (i.e., Grade Group 4) or GS9–10 (i.e., Grade Group 5) were significantly different. Thus, we can mention that Grade Group 5, based on the presence of GP5, is an independent predictor of biochemical recurrence. As the biochemical prognosis is significantly worse in GS9–10 than in GS8 groups, combined modality therapy such as PB, EBRT, and long-term ADT should be considered for high-risk PCa patients with GP5 disease. A Phase III, multicenter, randomized controlled trial of trimodal therapy with ^{125}I brachytherapy, EBRT, and short- or long-term hormone therapy for high-risk PCa is ongoing.[16] We expect that the results of the short- or long-term hormone therapy for high-risk PCa study will support trimodal therapy for patients in Grade Group 5 and GP5.

This study had some limitations. First, this was a retrospective study with duration of about 7 years. Second, the follow-up period was relatively short; therefore, only biochemical recurrence was examined. Only one patient died from PCa during the observation period in this study. Future studies are thus required to examine cancer-specific survival rather than biochemical recurrence.

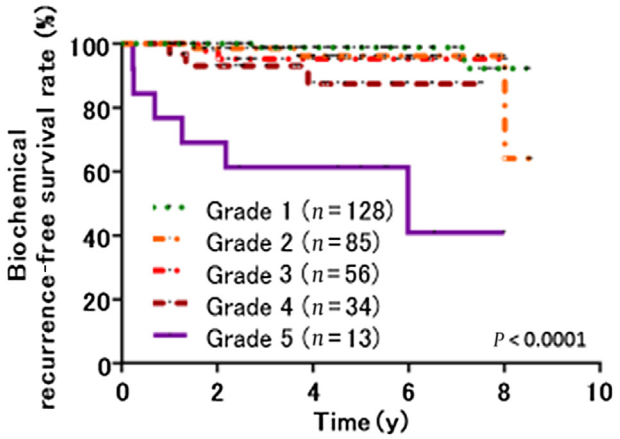

Fig. 2. Biochemical recurrence-free survival rates for all patients stratified by Gleason grades.

5. Conclusions

Although we achieved good outcomes with PB in low- and intermediate-risk patients with PCa, prognosis in the high-risk group was significantly worse. The prognosis of patients with GS9–10 based on the presence of GP5 (i.e., Grade Group 5) was worse than that for GS8 tumors (i.e., Grade Group 4), and Gleason grades may be useful for reflecting prognosis. Therefore, we should reconsider the strategy for treating patients with GP5 tumors.

Conflicts of interest

No potential conflicts of interest relevant to this article have been reported.

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