Integrating tertiary Gleason pattern 5 into the ISUP grading system improves prediction of biochemical recurrence in radical prostatectomy patients

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Abstract

Although the presence of tertiary Gleason pattern 5 is reportedly related to unfavorable prostate cancer characteristics, few data are available regarding the effects of tertiary Gleason pattern 5 on the new ISUP (International Society of Urological Pathology) grading system in radical prostatectomy patients. In this study, we evaluated the effect of tertiary Gleason pattern 5 on biochemical recurrence following radical prostatectomy in patients with prostate cancer. We retrospectively evaluated 1000 patients with prostate cancer who underwent radical prostatectomy. The ISUP Grades were as follows: Grade 1, 16.3%; Grade 2, 48.1% (with tertiary Gleason pattern 5, 8.0% and without tertiary Gleason pattern 5, 40.1%); Grade 3, 21.9% (with tertiary Gleason pattern 5, 9.1% and without tertiary Gleason pattern 5, 12.8%); Grade 4, 3.9%; and Grade 5, 9.8%. Biochemical recurrence-free survival differed significantly among the five groups (Grade 1–5) ($P < 0.0001$). Grade 2 with tertiary Gleason pattern 5 had a significantly worse prognosis than Grade 2 without tertiary Gleason pattern 5. Similarly, Grade 3 with tertiary Gleason pattern 5 demonstrated a significantly worse prognosis than Grade 3 without tertiary Gleason pattern 5. When Grade 2 and Grade 3 were divided with or without tertiary Gleason pattern 5, the survival curves differed significantly among Grade 1, Grade 2 without tertiary Gleason pattern 5, Grade 2 with tertiary Gleason pattern 5, Grade 3 without tertiary Gleason pattern 5, Grade 3 with tertiary Gleason pattern 5, and Grade 4 ($P < 0.0001$) (hazard ratios: 1, 1.14, 1.86, 2.23, 3.53, and 6.30). In a multivariate analysis, integrating tertiary Gleason pattern 5 into the ISUP Grade, PSA, and surgical margin status significantly predicted biochemical recurrence ($P < 0.0001$). Integrating tertiary Gleason pattern 5 into the ISUP grading system will improve the accuracy of patient outcome prediction following radical prostatectomy in patients with prostate cancer.

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Introduction

Gleason score is one the most important prognostic factors for prostate cancer. However, the original Gleason score has several issues to be resolved. For example, Gleason score 7 cases involve heterologous disease entities, and high-grade

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Gleason score cases, such as Gleason scores 9 and 10, have the similar clinical outcome [1]. The 2014 International Society of Urological Pathology (ISUP) consensus conference yielded a new grade group, ISUP grading system, to solve these issues, and subsequently, 2016 World Health Organization (WHO) classification has endorsed it [1, 2]. The Gleason score is now divided into five groups, and Gleason score 7 is divided into two categories: ISUP Grade 2 (Gleason score 3 + 4 = 7) and ISUP Grade 3 (Gleason score 4 + 3 = 7). The ISUP grading system has been validated only for radical prostatectomy specimens.

The ISUP grading system proposes replacing the term tertiary-grade pattern into a minor high-grade pattern and using it for cases with minor and limited extent instead of just the third most common pattern. Finally, minor high-grade patterns will not change the ISUP Grade [3].

Pan et al. found that the presence of tertiary Gleason pattern 5 was a worse prognostic factor in radical prostatectomy cases and proposed reporting the presence of tertiary Gleason pattern 5 [4]. Later, Trock et al. found the presence of tertiary Gleason pattern 5 was related to high pathological stage and was an independent prognostic factor for biochemical recurrence in radical prostatectomy cases [5]. These reports were based on pre-2005 or 2005 ISUP grading criteria.

Few data are available on whether the presence of tertiary Gleason pattern 5 influences biochemical recurrence in radical prostatectomy patients. Therefore, in this study, we evaluated the effect of tertiary Gleason pattern 5 on recurrence following radical prostatectomy in patients with prostate cancer.

Materials and methods

We retrospectively evaluated 1020 patients treated with radical prostatectomy from 2005 to 2013 at Nagoya University Hospital, Japanese Red Cross Nagoya Daini Hospital, JCHO Chukyo Hospital, and Komaki City Hospital. All patients had been diagnosed with localized prostate cancer and had undergone radical prostatectomy. After excluding the patients with missing data or slides, 1000 patients were enrolled in this study. Practice on a range of lymphadenectomy and the operative approach (open, laparoscopic, or robotic) were decided by each institution. The clinical T (cT) of each tumor was re-assessed based on the 2009 UICC TNM classification system [6]. All resected specimens were serially sliced with 3 or 5 mm interval and totally embedded. All prostatectomy specimen slides were reviewed by a single genitourinary pathologist (TT) according to ISUP 2014. The tertiary Gleason pattern 5 was defined to be just the third most common pattern. The percentage of tertiary Gleason pattern 5 was ranged between

1 and 10% of the tumor in this study, although most of them were ranged within 5% (167/172 cases).

Complete baseline and follow-up data were available for all 1000 patients. PSA was measured every 3 months over the 2 years following surgery and every 6 months thereafter. Biochemical recurrence following radical prostatectomy was defined according to the European Association of Urology guideline of rising PSA level >0.2 ng/ml [7]. Clinical progression was defined as verification of local recurrence, distant metastasis, and/or newly diagnosed lymph node metastasis by imaging studies. The primary endpoint of this study was the biochemical recurrence-free survival, which was defined as the time from prostatectomy to biochemical recurrence. Cumulative incidence curves were used in a competing-risks setting to calculate the probabilities of biochemical recurrence, treating clinical progression and death as competing risks [8]. The cumulative incidence curves for the biochemical recurrence-free survival among each group were compared using Gray's test [9]. The influence of prognostic factors for biochemical recurrence-free survival was evaluated by using the Fine and Gray's model [10]. Data on age, PSA level at diagnosis, clinical and pathological T stage, the presence of Gleason pattern 5, and surgical margin status were analyzed to predict PSA recurrence after prostatectomy. A *P* value < 0.05 was considered statistically significant. All statistical analyses were performed using the SAS software (ver. 9.3; SAS Institute, Cary, NC, USA). This retrospective study was approved by the Institutional Review Board of Nagoya University Graduate School of Medicine.

Results

Table 1 lists the patient demographics. Median age at diagnosis was 67 years (range 45–80 years). The median serum prostate-specific antigen (PSA) level was 6.9 ng/ml (range 0.4–82 ng/ml). The median follow-up period was 69 months (range 0.7–135 months). Pathological T (pT) occurred in 193 cases of pT2a, 110 of pT2b, 424 of pT2c, 233 of pT3a, and 40 of pT3b (Table 1). Overall, 262 patients (26.2%) had PSA-progression and 14 (1.4%) patients had clinical disease progression; one patient died of the disease (0.1%), and 32 (3.2%) patients died of other causes during the follow-up.

The number of patients in each grade was as follows: ISUP Grade 1, 16.3% (*n* = 163); ISUP Grade 2, 48.1% (*n* = 481) (ISUP Grade 2 with tertiary Gleason pattern 5, 8.0% (*n* = 80) and ISUP Grade 2 without tertiary Gleason pattern 5, 40.1% (*n* = 401)); ISUP Grade 3, 21.9% (*n* = 219) (ISUP Grade 3 with tertiary Gleason pattern 5, 9.1% (*n* = 91) and ISUP Grade 3 without tertiary Gleason pattern 5, 12.8% (*n* = 128)); ISUP Grade 4, 3.9% (*n* = 39); and ISUP Grade

Table 1 Clinical and pathological characteristics ($n = 1000$)

ISUP Grade		1	2	3	4	5
		$n = 163$	$n = 481$	$n = 219$	$n = 39$	$n = 98$
Age		67 (46–77)	66 (45–79)	68 (50–80)	67 (56–79)	69 (48–77)
Follow-up period	Months	77 (4.9–135)	68.4 (0.7–132)	67.9 (4.6–129)	83 (6.6–122)	64.5 (16.6–121)
PSA	ng/ml	5.7 (1.1–19.5)	6.5 (0.4–50.9)	8 (3.1–81)	7 (2.5–17)	8.3 (4–82)
Clinical T	cT1c, cT2	163	467	212	36	93
	cT3a		14	6	2	3
	cT3b			1	1	2
Pathological T	pT2a	70	78	32	6	7
	pT2b	20	55	25	5	5
	pT2c	71	244	69	13	27
	pT3a	2	97	80	12	42
	pT3b		7	13	3	17
Margin status	Positive	25 (15%)	193 (40%)	108 (49%)	9 (24%)	44 (44%)
Tertiary Gleason pattern 5		0/163 (0%)	80/481 (17%)	91/219 (42%)	1/39 (3%)	

5, 9.8% ($n = 98$). Only one patient classified as ISUP Grade 4 with tertiary Gleason pattern 5 was categorized into ISUP Grade 5 because this is a minor population and usually has a poor prognosis.

PSA progression-free survival differed significantly among the five groups (ISUP Grades 1–5) ($P < 0.0001$) (Fig. 1, Table 2). In ISUP Grade 2 and ISUP Grade 3, margin status, PSA, and tertiary Gleason pattern 5 were significantly able to predict the prognosis (Table 3).

ISUP Grade 2 with tertiary Gleason pattern 5 had a significantly worse prognosis than ISUP Grade 2 without tertiary Gleason pattern 5. Similarly, ISUP Grade 3 with tertiary Gleason pattern 5 had a significantly worse prognosis than ISUP Grade 3 without tertiary Gleason pattern 5 (Table 4). In contrast, ISUP Grade 2 with tertiary Gleason pattern 5 and whole ISUP Grade 3, and ISUP Grade 3 with tertiary Gleason pattern 5 and whole ISUP Grade 4 had the same prognosis ($P = 0.333$ and $P = 0.129$) (Supplement 1, 2).

When ISUP Grade 2 and ISUP Grade 3 were divided with or without tertiary Gleason pattern 5, the survival curves differed significantly among ISUP Grade 1, ISUP Grade 2 without tertiary Gleason pattern 5, ISUP Grade 2 with tertiary Gleason pattern 5, ISUP Grade 3 without tertiary Gleason pattern 5, ISUP Grade 4, and ISUP Grade 5 ($P < 0.0001$) (hazard ratios; 1, 1.14, 1.86, 2.23, 3.53, 6.30, and 5.62) (Fig. 2). In a multivariate analysis, integrating tertiary Gleason pattern 5 into ISUP Grade, PSA level at diagnosis, and surgical margin status significantly predicted the prognosis ($P < 0.0001$, < 0.0001 and < 0.0001 respectively) (Table 4).

Fig. 1 Cumulative incidence curves for prostate-specific antigen (PSA) progressive survival after prostatectomy on the ISUP grading system ($P < 0.0001$)

Discussion

The presence of tertiary Gleason pattern 5 is a well-known adverse prognostic factor in patients who undergo a radical prostatectomy [5, 11, 12]. The ISUP 2014 and 2016 WHO classifications recommend that minor high-grade patterns should not change the ISUP Grade [3]. However, this method using syntax seems to be less useful for urologists because tertiary Gleason pattern 5 seems to have a minor impact on patient outcome. A recent study concluded that this tertiary Gleason pattern 5 becomes stronger at Gleason score (GS) 3 + 4 and 4 + 3 cases but not for GS 4 + 4 cases

Table 2 Biochemical recurrence-free survival and variables in ISUP Grade ($n = 1000$)

Multivariate					
Variables	Category	Hazard ratio	95% Lower	95% Upper	<i>P</i> value
ISUP Grade	Grade 1	1			
	Grade 2	1.24	0.719	2.139	0.439
	Grade 3	2.68	1.53	4.694	0.0006
	Grade 4	6.118	3.246	11.532	<0.0001
	Grade 5	5.324	2.937	9.652	<0.0001
Age	65>	1			
	65≤	1.03	0.781	1.358	0.8353
Clinical T	cT2	1			
	cT3	0.881	0.458	1.696	0.7048
Pathological T	pT2	1			
	pT3	1.315	0.989	1.748	0.0597
Margin status	Negative	1			
	Positive	3.135	2.351	4.181	<0.0001
PSA	Continuous	1.027	1.017	1.037	<0.0001

Table 3 Biochemical relapse-free survival and variables in ISUP Grades 2 and 3 ($n = 700$)

Multivariate					
Variables	Category	Hazard ratio	95% Lower	95% Upper	<i>P</i> value
ISUP Grade	Grade 2	1			
	Grade 3	1.946	1.404	2.697	<0.0001
Age	65>	1			
	65≤	0.976	0.696	1.368	0.8874
Clinical T	cT2	1			
	cT3	1.227	0.589	2.556	0.5843
Pathological T	pT2	1			
	pT3	1.093	0.772	1.549	0.6149
Margin status	Negative	1			
	Positive	3.484	2.348	4.978	<0.0001
PSA	Continuous	1.029	1.017	1.041	<0.0001
Variables					
Tertiary Gleason pattern 5	Absent	1			
	Present	1.63	1.156	2.296	0.0053

[13]. Ozsoy et al. reported that upgrading the grade group by one grade when tertiary Gleason pattern 5 is present would more accurately predict the risk of biochemical recurrence for GS 7 [14]. Lucca et al. also reported that the risk of tertiary Gleason pattern 5 seemed to be comparable between patients with tertiary Gleason pattern 5 and their

counterparts in the next higher ISUP Grade without tertiary Gleason pattern 5.

A potential adverse effect of tertiary Gleason pattern 5 was first reported by Pan et al. [4]. Later, other groups also reported that the presence of tertiary Gleason pattern 5 was as an independent predictor of treatment failure after prostatectomy [11, 12]. Some studies found that GS 3 + 4 with tertiary Gleason pattern 5 had almost the same risk of biochemical recurrence as GS 4 + 3. Subsequently, Trock et al. demonstrated that GS 4 + 3 with tertiary Gleason pattern 5 behaved like GS 4 + 4 [5]. In contrast, Lucca et al. reported on 4146 prostatectomy patients by various pathologists at five institutions and found that GS 3 + 4 = 7 with tertiary Gleason pattern 5 was associated with a slightly higher risk of biochemical recurrence compared to GS 4 + 3 = 7 [15]. Adam et al. reported that the presence of tertiary Gleason pattern 5 was an independent predictor of biochemical recurrence after prostatectomy with the most potent prognostic effect in GS 3 + 4 and 4 + 3 cases [16]. Because these reports were evaluated before the 2014 ISUP conference, no data are available regarding the significance of tertiary Gleason pattern 5 in the current classification system. After the conference, several reports suggested that 5% is the upper limit of tertiary Gleason pattern 5, although they did not provide objective data to verify their statement [17]. A recent study also demonstrated that the minimal Gleason pattern 5 component has a substantial prognostic effect in Gleason 7 carcinomas. The authors also proposed an integrated quantitative Gleason score [18]. Another study reported that the presence of tertiary Gleason pattern 5 was correlated with higher PSA levels, a higher rate of lymph node metastasis, positive surgical margins, extraprostatic extension, and seminal vesicle invasion when compared with patients in the same grade without tertiary Gleason pattern 5.

It has been unclear to what degree tertiary Gleason pattern 5 can play a prognostic role. Initially, Pan et al. reported that tertiary Gleason pattern 5 occurs in very limited amounts in Gleason pattern 5 [4]. Some subsequent studies used a cut-off <5% [15, 19], and others reported no limit for the tertiary Gleason pattern 5 [16]. No definitive upper amount of tertiary Gleason pattern 5 and a minimal amount of Gleason pattern 5 has been proposed as leading to a significantly poor patient prognosis. Attendances at the 2014 ISUP consensus meeting did not vote for a specific cut-off value of 5% for tertiary Gleason pattern 5 [3]. The rationale for restricting the term tertiary to cases with <5% of the Gleason pattern 5 component is to equate a tertiary pattern, not only the third most common pattern; however, this has not been confirmed in a large cohort study [20]. A recent report found that the presence of <5% tertiary Gleason pattern 5 imparts an intermediate biochemical recurrence relative to the next highest grade in ISUP Grade

Table 4 Biochemical recurrence-free survival and variables in ISUP Grade with integrating tertiary Gleason pattern 5 ($n = 1000$)

Multivariate					
Variables	Category	Hazard ratio	95% Lower	95% Upper	<i>P</i> value
ISUP Grade	Grade 1	1			
	Grade 2 without tertiary Gleason pattern 5	1.142	0.654	1.994	0.6412
	Grade 2 with tertiary Gleason pattern 5	1.858	0.957	3.607	0.0672
	Grade 3 without tertiary Gleason pattern 5	2.233	1.222	4.08	0.009
	Grade 3 with tertiary Gleason pattern 5	3.537	1.928	6.488	<0.0001
	Grade 4	6.296	3.342	11.86	<0.0001
	Grade 5	5.618	3.098	10.186	<0.0001
Age	65>	1			
	65≤	1.02	0.773	1.346	0.8877
Clinical T	cT2	1			
	cT3	0.946	0.504	1.776	0.8637
Pathological T	pT2	1			
	pT3	1.243	0.934	1.653	0.1358
Margin status	Negative	1			
	Positive	3.139	2.354	4.186	<0.0001
PSA (ng/ml)	Continuous	1.025	1.015	1.035	<0.0001

Fig. 2 Cumulative incidence curves for prostate-specific antigen (PSA) progressive survival after prostatectomy on the ISUP grading system integrating tertiary Gleason pattern 5 ($P < 0.0001$)

2 and ISUP Grade 3 and could upgrade the category in ISUP Grade 4. In contrast, further expansion of tertiary Gleason pattern 5 has less of an effect on Gleason 7 carcinomas [18]. The definitive upper rate of tertiary Gleason pattern 5 seems to be controversial and will be elucidated in the future.

The present study had some limitations. First, the study population was small, and a nonrandomized retrospective design was used. Tertiary Gleason pattern 5 was found in 16.6% of ISUP Grade 2 (Gleason 3 + 4) and 41.6 % of ISUP Grade 3 (Gleason 4 + 3). The reported prevalence of tertiary Gleason pattern 5 ranged to 50% [11, 21–26].

Therefore, our study population did not deviate from those of studies reported previously. Second, the number of ISUP Grade 4 and ISUP Grade 5 cases was relatively small compared with other grades. Because our institutions underwent neoadjuvant therapy at one time for high-risk and very high-risk patients, the number of enrolled patients was limited. Therefore, only limited ISUP Grade 5 cases regarded as clinically localized and better prognosis could have been enrolled in this cohort. The primary purpose of this study is to investigate the impact of incorporating Gleason tertiary pattern 5 on ISUP Grades 2 and 3, and we don't believe this selection bias for high ISUP Grade cases influences on a significant impact on our conclusions. Third, the surgical approach including lymph node dissection was not standardized in all cases. Nevertheless, our study had some advantages including an extended follow-up period (about 1.5–2 times longer than previously reported ones [14, 15, 20]) and one central pathologist who standardized the pathological evaluation of the radical prostatectomy specimens compared with recent reports, so upgrading tertiary Gleason pattern 5 in ISUP Grade 2 and ISUP Grade 3 is becoming more likely.

Conclusions

Integrating tertiary Gleason pattern 5 into the ISUP grading system will improve the accuracy of patient outcome predictions. ISUP Grade 2 and ISUP Grade 3 were upgraded

by the presence of tertiary Gleason pattern 5 following radical prostatectomy in patients with prostate cancer.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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