



## Prostate Cancer

# Prevalence of a Tertiary Gleason Grade and Its Impact on Adverse Histopathologic Parameters in a Contemporary Radical Prostatectomy Series

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### Abstract

**Background:** The presence of a tertiary Gleason grade (TGG) pattern in radical prostatectomy (RP) specimens has been described as associated with adverse pathology and a higher biochemical recurrence (BCR) rate after RP.

**Objective:** To assess the prevalence of a TGG in a contemporary, consecutive, single-centre RP series and its association with adverse pathology.

**Design, setting, and participants:** From January to August 2007, 800 eligible patients (no prior neoadjuvant hormonal therapy) underwent RP for clinically localised prostate cancer (pCA) in our institution. The presence of the third most prevalent Gleason pattern was documented, regardless of whether it was better or worse than the two predominant Gleason grades.

**Measurements:** The overall prevalence of a TGG was described. Uni- and multivariate logistic regression analyses tested the association between the presence of a TGG <5% versus ≥5% of the whole tumour volume and extracapsular extension (ECE), seminal vesicle invasion (SVI), positive surgical margins (PSM), and lymph node invasion (LNI). Subanalyses were performed to assess the impact of different TGGs at various Gleason scores.

**Results and limitations:** A TGG was reported in 180 RP specimens (22.5%). In univariate analysis, the presence of a TGG ≥5% was significantly associated with ECE, SVI, PSM, and LNI ( $p < 0.001$ ). In multivariate analysis, a TGG ≥5% showed an independent association with ECE and PSM ( $p < 0.05$ ). Accordingly, in subanalyses, a significant association with adverse pathology was only documented if the amount of a TGG was at least 5% of the tumour volume. Our study is limited by the relatively low overall frequency of a TGG, thereby reducing the statistical expressiveness, especially for subanalyses.

**Conclusions:** Our findings confirm the association of the presence of a TGG with adverse pathologic features. Further follow-up is needed to assess the prognostic impact of a TGG on the risk of BCR and overall survival following RP.

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## 1. Introduction

Almost 40 yr ago, Donald F. Gleason pioneered his widely acknowledged grading system of prostate adenocarcinoma [1,2]. In the following years, the reliability of the Gleason system in predicting the outcome of patients with prostate cancer (pCA) undergoing surgery, radiotherapy (RT), or surveillance has been proven in several single- and multi-institution studies [3–6]. In its original version, the Gleason system considered only the most predominant and, if present, the second most predominant Gleason pattern. A potentially present third Gleason grade pattern (TGG), regardless of the tumour percentage or state of aggressiveness, did not contribute to the Gleason score. In 2005, the International Society of Urological Pathology (ISUP) decided that in prostate biopsies, a more aggressive TGG should replace a less aggressive secondary grade because of the assumption that this would reflect the aggressiveness of the whole tumour more accurately. Interestingly, in RP specimens, it was acknowledged that the presence of an aggressive TGG might be associated with an adverse prognosis. However, it was stated that, for example, renaming a Gleason 4 + 3 pCA with a tertiary pattern 5 into a Gleason 4 + 5 tumour would overestimate the aggressiveness of the cancer. Therefore, it was concluded that in RP specimens, a TGG should be mentioned but should not redefine the Gleason score [7,8].

Recently, different investigators defined the prevalence of a TGG and demonstrated a significant association with adverse histopathologic features and/or the risk of biochemical recurrence (BCR) after definite therapy for clinically localised pCA [7,9–14]. Limitations, however, arise in consideration of these study designs, most of which were retrospective and often limited by low statistical power resulting from small study populations. Furthermore, the data were derived from time intervals during which pathologic reporting of a TGG might not have been mandatory. Consequently, the prevalence and definition of the reported TGG differed substantially in the above-mentioned studies, ranging from 13–50%, which might hamper the assessment of their clinical impact. This was underlined by a recently published meta-analysis concerning the influence of a TGG on RP specimens. It was suggested that the available data are still too limited and too heterogeneous to affect the proposal of the 2005 ISUP conference on Gleason grading [15].

To address this void, we hypothesized that accurate assessment of TGGs in contemporary RP specimens may unequivocally demonstrate their

association with acknowledged adverse histopathologic features.

## 2. Methods

### 2.1. Patients and surgical approach technique

From January to August 2007, 863 consecutive patients underwent open retropubic RP for clinically localised pCA at a single institution, as previously described [16]. Patients who received neoadjuvant hormonal therapy were excluded from the study, leaving 800 patients for further evaluation. Lymph node dissection was only performed in patients who had a moderate or high risk for lymph node invasion (LNI) according to a published nomogram [17]. Margins of resection were determined to be positive if cancer cells extended to the inked surface.

#### 2.1.1. Histopathologic evaluation

The whole RP specimens were processed using serial step sections at 3 mm according to the Stanford protocol [18]. Grading was performed according to the Gleason system [2], including the entire prostate with every tumour focus. Considering the recommendations of the consensus conference on grading of pCA of 2005 [7], pathologists agreed before the study to report the presence of a TGG. Furthermore, the presence of the third most prevalent Gleason pattern was documented, regardless of whether it was better or worse differentiated than the two most predominant patterns. Overall, seven pathologists performed histopathologic evaluation, and every specimen was evaluated by only one pathologist. However, the majority of the specimens ( $n = 503$ , 62%) were evaluated by three uropathologists. For pathological staging, the 2002 TNM system was used [19]. There were two circumstances under which a Gleason grade was considered tertiary: (1) if a Gleason pattern consisted of <5% of the whole cancer volume and there was no presence of a secondary Gleason pattern >5% (eg, Gleason score 3 + 3 = 6 and <5% tertiary Gleason grade 4); and (2) if the primary and secondary Gleason grades were different, the third most prevalent Gleason pattern was considered tertiary, regardless of its percentage or differentiation (eg, 50% Gleason 4, 30% Gleason 3, and 20% Gleason 5: Gleason score 4 + 3 = 7 with tertiary Gleason pattern 5). A TGG exceeding at least 1% of the whole tumour volume was considered for evaluation. Among TGGs, stratification was performed into <5% versus  $\geq 5\%$  of the whole tumour volume and into higher versus lower TGG as the Gleason score.

### 2.2. Statistics

The overall prevalence of a TGG was described and the frequency noted according to pT classification, nodal status, and primary and secondary Gleason grades. Differences among groups were tested by using the  $\chi^2$  test.

Univariate logistic regression was performed to assess the association of TGGs <5% and  $\geq 5\%$  with extracapsular extension (ECE), seminal vesicle invasion (SVI), LNI, and positive surgical margins (PSM) for the entire cohort. Accordingly, in multivariate logistic analysis, the impact of TGGs <5% and  $\geq 5\%$  on ECE, SVI, and PSM was evaluated after correcting for the information on prostate-specific antigen (PSA), primary and secondary Gleason grades, ECE, SVI, and PSM. The

predictive accuracy (PA) of the TGG was quantified as area under the curve (AUC), using receiver operator characteristics (ROC) analysis. In multivariate analysis, the gain of PA by adding TGG to the base model (composed of the other variables but excluding TGG) was documented. Subanalyses were performed to test the impact of a TGG on adverse pathology at Gleason score <7 (composed of Gleason score 2 + 3, 3 + 2, 3 + 3, and 2 + 4), Gleason score 3 + 3, and for TGG 5 for the whole cohort. A *p* value <0.05 was considered significant. All statistical tests were performed using SPSS v.15 for Windows (SPSS Inc, Chicago, IL, USA).

### 3. Results

Clinical and histopathologic characteristics of the study cohort are provided in Table 1. Overall, a TGG was present in 180 of the 800 (22.5%) patients. In 89 cases (49.4%) the TGG was <5% of the whole tumour volume, whereas in 91 cases (50.6%) the volume was ≥5%. In 140 cases (78%), the tertiary Gleason component was higher than the two most predominant Gleason patterns, whereas a lower TGG was reported in 38 cases (21%). Two specimens (1%) showed both a higher and a lower third and fourth Gleason pattern with the same amount of tumour volume. A higher TGG was more frequently observed in well- or moderately differentiated tumours. An overview of frequencies for the different TGGs at various Gleason scores is given in Table 2. Regarding pT classification, TGG prevalence significantly increased with advancing pathology. It was present in 106 of 585 patients with pT2 tumours (18%), 48 of 168 pT3a tumours (29%), and 27 of 46 pT3b tumours (59%), respectively

**Table 1 – Descriptive clinical and histopathologic characteristics of the study cohort**

|                                 |            |
|---------------------------------|------------|
| Total number of patients        | 800 (100%) |
| Age (years)                     |            |
| Mean (median)                   | 63 (65)    |
| Range                           | 43–77      |
| PSA (ng/ml)                     |            |
| Mean (median)                   | 8.2 (6.2)  |
| Range                           | 0.65–120   |
| Clinical Stage                  |            |
| T1c                             | 624 (78%)  |
| T2                              | 170 (21%)  |
| >T2                             | 6 (1%)     |
| pT classification               |            |
| pT2                             | 586 (73%)  |
| pT3a                            | 168 (21%)  |
| pT3b                            | 46 (6%)    |
| Prostatectomy Gleason score     |            |
| ≤6                              | 239 (30%)  |
| 3 + 4                           | 402 (50%)  |
| ≥4 + 3                          | 159 (20%)  |
| pN status                       |            |
| pN0                             | 387 (48%)  |
| pN1                             | 30 (4%)    |
| pNX                             | 383 (48%)  |
| Margin status                   |            |
| Overall positive                | 17%        |
| pT2                             |            |
| Positive                        | 10%        |
| pT3a                            |            |
| Positive                        | 35%        |
| pT3b                            |            |
| Positive                        | 52%        |
| PSA, prostate-specific antigen. |            |

**Table 2 – Frequencies of different tertiary Gleason grade patterns according to different Gleason scores. Various Gleason scores were put together into the Gleason groups <7, 3 + 4, and ≥4 + 3**

| Gleason score and Gleason groups | Number of cases | Overall frequency of a tertiary Gleason pattern | Tertiary pattern 2 | Tertiary pattern 3 | Tertiary pattern 4 | Tertiary pattern 5 |
|----------------------------------|-----------------|---|--------------------|--------------------|--------------------|--------------------|
| 2 + 3                            | 1               | 1 (100%)  | –                  | –                  | 1 (100%)           | 0 (0%)             |
| 3 + 2 } <7                       |                 |   |                    |                    |                    |                    |
| 3 + 3                            |                 |   |                    |                    |                    |                    |
| 2 + 4                            |                 |   |                    |                    |                    |                    |
| 3 + 4                            | 402             | 39 (10%)  | 12 (31%)           | –                  | –                  | 27 (69%)           |
| 4 + 3                            | 126             | 40 (32%)  | 7 (18%)*           | –                  | –                  | 34 (85%)*          |
| 4 + 4 } ≥4 + 3                   |                 |   |                    |                    |                    |                    |
| 3 + 5                            |                 |   |                    |                    |                    |                    |
| 5 + 3                            |                 |   |                    |                    |                    |                    |
| 4 + 5                            |                 |   |                    |                    |                    |                    |
| 5 + 4                            |                 |   |                    |                    |                    |                    |

\*Both higher and lower tertiary Gleason grade patterns were found within the prostatectomy specimen.

**Table 3 – Prevalence of a tertiary Gleason grade pattern regarding pT classification, Gleason score, and lymph node status**

| Variable          | Number of cases |
|-------------------|-----------------|
| pT classification |                 |
| pT2               | 106/585 (18%)   |
| pT3a              | 48/168 (29%)    |
| pT3b              | 27/46 (59%)     |
| Gleason score     |                 |
| ≤6                | 76/239 (32%)    |
| 3 + 4             | 39/401 (10%)    |
| ≥4 + 3            | 65/159 (41%)    |
| Lymph node status |                 |
| pN0               | 150/606 (25%)   |
| pN1               | 18/30 (60%)     |
| pNX               | 12/163 (7%)     |

( $p < 0.001$ ). With respect to lymph node status, the presence of a TGG was more frequently observed in patients with LNI (23% pN0, vs 60% pN1;  $p < 0.001$ ). Evaluating RP Gleason score, a TGG was observed in 32% of patients with a Gleason score  $\leq 6$  (76/239), in 10% of Gleason 3 + 4 (39/402), and in 41% of Gleason  $\geq 4 + 3$  (65/159), respectively (Table 3). To account for the fact that seven pathologists examined the RP specimens, we checked the data for a potential interobserver bias. The frequency of a TGG differed between investigators but was not statistically significant (range: 14–29%;  $p = 0.129$ ).

In univariate analysis for the entire cohort, the presence of a TGG pattern  $< 5\%$  was not statistically associated with adverse pathology. Conversely, a TGG pattern  $\geq 5\%$  was a significant risk factor for

**Table 4 – Univariate logistic regression addressing the influence of a TGG  $< 5\%$  and  $\geq 5\%$  to adverse histopathologic features. For assessment of the influence on LNI, only the cases in which lymph node dissection was performed were considered**

| Histopathologic feature | TGG $< 5\%$ of the tumour volume     | TGG $\geq 5\%$ of the tumour volume              |
|-------------------------|--------------------------------------|--|
|                         | OR (95% CI), $p$ value               | OR (95% CI), $p$ value, PA*                      |
| ECE                     | 0.63 (95% CI: 0.34–1.14); $p = 0.13$ | 6.44 (95% CI: 4.05–10.24); $p < 0.001$ , PA: 61% |
| SVI                     | 1.72 (95% CI: 0.63–4.71); $p = 0.29$ | 8.21 (95% CI: 4.37–15.41); $p < 0.001$ , PA: 68% |
| PSM                     | 0.86 (95% CI: 0.45–1.64); $p = 0.65$ | 3.85 (95% CI: 2.41–6.15); $p < 0.001$ , PA: 58%  |
| LNI                     | 1.43 (95% CI: 0.31–6.65); $p = 0.65$ | 7.05 (95% CI: 3.25–15.26); $p < 0.001$ , PA: 70% |

CI, confidence interval; ECE, extracapsular extension; LNI, lymph node invasion; OR, odds ratio; PA, predictive accuracy; PSM, positive surgical margins; SVI, seminal vesicle invasion; TGG, tertiary Gleason grade.

\* Quantified by receiver operator characteristics (ROC) analysis.

**Table 5 – Multivariate logistic regression analysis addressing the influence of a TGG  $\geq 5\%$  of the whole tumour volume on adverse histopathologic findings after correcting for PSA, prostatectomy Gleason score, SVI, PSM, and ECE**

| Outcome               | Variable                    | OR (95% CI); $p$ value          | PA* (gain in PA)                |               |
|-----------------------|-----------------------------|---------------------------------|---------------------------------|---------------|
| ECE                   | TGG                         | 3.04 (1.66–5.57); $p < 0.001$   | 84.3% (+ 0.5%)                  |               |
|                       | PSA                         | 1.06 (1.03–1.09); $p = 0.001$   | 83.8%                           |               |
|                       | Prostatectomy Gleason score |                                 |                                 |               |
|                       | ≤6 vs 3 + 4                 | 7.12 (3.57–14.42); $p < 0.001$  |                                 |               |
|                       | 3 + 4 vs $\geq 4 + 3$       | 16.76 (7.85–35.77); $p < 0.001$ |                                 |               |
|                       | SVI                         | SVI                             | 10.61 (3.46–32.53); $p < 0.001$ | 92.8% (+0.3%) |
| SVI                   | PSM                         | 4.14 (2.59–6.62); $p < 0.001$   |                                 |               |
|                       | TGG                         | 2.05 (0.94–4.45); $p = 0.71$    |                                 |               |
|                       | PSA                         | 1.03 (1.00–1.05); $p = 0.03$    | 92.5%                           |               |
|                       | Prostatectomy Gleason score |                                 |                                 |               |
|                       | ≤6 vs 3 + 4                 | 6.04 (3.62–9.65); $p < 0.001$   |                                 |               |
|                       | 3 + 4 vs $\geq 4 + 3$       | 11.34 (6.35–22.18); $p < 0.001$ |                                 |               |
| PSM                   | ECE                         | 9.43 (3.11–28.62); $p < 0.001$  |                                 |               |
|                       | PSM                         | 1.73 (0.83–3.60); $p = 0.15$    |                                 |               |
|                       | TGG                         | 2.16 (1.23–3.78); $p = 0.007$   | 74.2% (+1.2%)                   |               |
|                       | PSA                         | 1.03 (1.01–1.06); $p = 0.018$   | 73%                             |               |
|                       | Prostatectomy Gleason score |                                 |                                 |               |
|                       | ≤6 vs 3 + 4                 | 1.37 (0.79–2.38); $p = 0.26$    |                                 |               |
| 3 + 4 vs $\geq 4 + 3$ | 1.05 (0.53–2.09); $p = 0.9$ |                                 |                                 |               |
| ECE                   | ECE                         | 3.92 (2.46–6.25); $p < 0.001$   |                                 |               |
|                       | SVI                         | 1.85 (0.9–3.8); $p = 0.09$      |                                 |               |

CI, confidence interval; ECE, extracapsular extension; LNI, lymph node invasion; OR, odds ratio; PA, predictive accuracy; PSM, positive surgical margins; SVI, seminal vesicle invasion; TGG, tertiary Gleason grade.

\* Quantified by receiver operator characteristic (ROC) analysis.

**Table 6 – Univariate logistic regression analyses addressing the impact of a TGG at Gleason score <7 (including Gleason score 2 + 3, 3 + 2, 3 + 3, and 2 + 4) versus Gleason score 3 + 3 alone on ECE and PSM\***

| Gleason score (with and without a tertiary Gleason pattern) | ECE        |                  | PSM         |                  |
|---|------------|------------------|-------------|------------------|
| <7  | 2/163 (1%) |                  | 9/163 (6%)  |                  |
| <7 with TGG   | 8/76 (11%) | <i>p</i> = 0.005 | 13/76 (17%) | <i>p</i> = 0.006 |
| 3 + 3   | 1/134 (1%) |                  | 5/134 (4%)  |                  |
| 3 + 3 with TGG  | 1/52 (2%)  | <i>p</i> = 0.5   | 6/52 (12%)  | <i>p</i> = 0.054 |

ECE, extracapsular extension; LNI, lymph node invasion; PSM, positive surgical margins; SVI, seminal vesicle invasion; TGG, tertiary Gleason grade pattern.  
\* None of the patients in this cohort had evidence of SVI or LNI.

**Table 7 – Influence of a TGG 5 <5% versus ≥5% of the whole tumour volume on adverse pathology\***

| Outcome | TGG 5 <5% of the tumour volume<br>OR (95% CI); <i>p</i> value | TGG 5 ≥5% of the tumour volume<br>OR (95% CI); <i>p</i> value |
|---------|---|---|
| ECE     | 2.41 (95% CI: 0.92–6.33); <i>p</i> = 0.74                     | 5.38 (95% CI: 2.85–10.16); <i>p</i> < 0.001                   |
| SVI     | 3.65 (95% CI: 0.79–16.8); <i>p</i> = 0.97                     | 3.41 (95% CI: 1.42–8.19); <i>p</i> = 0.006                    |
| PSM     | 1.17 (95% CI: 0.33–4.12); <i>p</i> = 0.8                      | 2.46 (95% CI: 1.28–4.71); <i>p</i> = 0.007                    |
| LNI     | 2.07 (95% CI: 0.25–17.15); <i>p</i> = 0.5                     | 2.10 (95% CI: 0.75–5.89); <i>p</i> = 0.16                     |

CI, confidence interval; ECE, extracapsular extension; LNI, lymph node invasion; OR, odds ratio; PSM, positive surgical margins; SVI, seminal vesicle invasion; TGG, tertiary Gleason grade pattern.  
\* For addressing the influence on LNI, only the cases in which lymph node dissection was performed were considered.

ECE (odds ratio [OR]: 6.44; *p* < 0.001, PA: 61%), SVI (OR: 8.21; *p* < 0.001, PA: 68%), PSM (OR: 3.85; *p* < 0.001, 58%), and LNI (OR: 7.05; *p* < 0.001, PA: 70%), respectively (Table 4). In multivariate analyses, a TGG pattern ≥5% showed an independent correlation to the presence of ECE (OR: 3.04; *p* < 0.001, gain of PA: 0.5%) and PSM (OR: 2.16; *p* = 0.007, gain of PA: 1.2%) but did not reach statistical significance for SVI after correcting for preoperative PSA, primary and secondary Gleason grade, ECE, SVI, and PSM (Table 5).

In subanalyses, we addressed the impact of a TGG on adverse pathology at Gleason score <7 (including Gleason score 2 + 3, 3 + 2, 3 + 3, and 2 + 4) and 3 + 3. Although a significant association of TGG on ECE and PSM was seen for the whole Gleason group <7, this effect vanished at Gleason score 3 + 3 only (Table 6), for which the amount of the TGG was <5% in all cases. In another subanalysis addressing the effect of a TGG 5 on ECE, SVI, PSM, and LNI in univariate analysis for the entire study cohort, a significant association to ECE, SVI, and PSM was also only seen if the amount of the TGG was at least 5% (Table 7).

#### 4. Discussion

Almost 40 yr after its introduction, the Gleason system is still a commonly used instrument for histopathologic grading of pCA. The Gleason system

accounts only for the two most predominant Gleason patterns. However, pCA is a heterogeneous disease, and the presence of multiple different tumour foci with particulate variable grades of aggressiveness within one prostate are frequently observed [20]. Among other studies that addressed the appearance of a TGG [21], Gleason himself reported in 1992 that more than half of RP specimens contain more than two patterns [22]. Nevertheless, a potential adverse influence of TGG on patient outcome was first reported only a few years ago by Pan et al [11]. In that study, patients with an RP Gleason score 5–6 and an additive worse differentiated tertiary grade had a significantly higher rate of BCR compared to their counterparts without a TGG [11]. In the following years, more studies uniformly confirmed the adverse impact of TGGs with respect to unfavourable histopathologic stage and/or a higher frequency of BCR after RP. Hattap et al [9] evaluated 228 patients with an RP Gleason score 7 (3 + 4 or 4 + 3) after prostatectomy for the presence of a tertiary Gleason pattern 5 containing at least 5% of the whole tumour volume. The presence of a TGG was an independent predictor for treatment failure. Van Oort and co-workers [13] showed that the presence of a TGG was likewise an independent predictor of PSA recurrence after RP. Interestingly, this applied to more and less aggressive tertiary components than the two predominant grades, indicating that a tertiary grade—regardless of

differentiation—is an expression of multifocality and, accordingly, of worse prognosis. Mosse et al [10] evaluated the influence of TGG 5 on adverse histopathologic features in a series of 223 RP specimens with a tertiary component compared to 603 cases without a tertiary grade. In their study, a Gleason pattern 5 of >5% of the tumour volume was reported as the secondary component. They found a significant correlation between the presence of TGG and advanced pathological stage at Gleason score 3 + 4 and 4 + 3 but not for Gleason score 4 + 4. They concluded that the influence of a TGG is strongest at lower Gleason scores but diminishes for more aggressive tumours because of naturally adverse biological behaviour. Whittimore et al [14] evaluated 214 RP specimens with Gleason score 3 + 4 or 4 + 3 that were reexamined by two blinded pathologists for the presence of a tertiary Gleason 5 pattern. Patients with a TGG showed statistically significantly higher pathological tumour stage and a significantly decreased BCR-free survival.

Limitations, however, to most of the aforementioned studies are that data were retrospectively analysed and that the definition of TGG was not invariably consistent, which may impede the interpretation and reproducibility of the results. Additionally, the numbers of patients were relatively small in most of the studies, alleviating the statistical expressiveness, especially for subanalyses.

To the best of our knowledge, our study is the first one in which the prevalence of a TGG in RP specimens has been evaluated in a single-centre, contemporary, consecutive patient population. The prevalence of TGG was 22.5% in our study and is accordingly lower than in most of the above-mentioned studies, where frequencies ranging from 15% to >50% were reported [21–23]. This discrepancy might be partly explained by different study designs (eg, only the index tumour was further evaluated).

In our study, the prevalence of TGG increased significantly with higher tumour stage ( $p < 0.001$ ), which is in accordance with previously reported results [13,24]. Recently, it was suggested that in multiracial populations, special subgroups may have unfavourable pCA characteristics at the time of RP [25]. Although we did not explicitly document race, we present data of a homogenous Caucasian referral group with a very low percentage of Asians and blacks, surely not exceeding 1% of the whole group, which corroborates the homogeneity of our study population.

In subanalyses, we stratified patients into TGGs <5% versus  $\geq 5\%$  of the whole tumour volume. Interestingly, in uni- and multivariate analysis, a

significant association with adverse pathology was only seen for TGG volume  $\geq 5\%$ , while volume <5% showed no significant correlation. This finding was emphasized by further subanalyses. Although a TGG for the entire Gleason group <7 (including Gleason score 2 + 3, 3 + 2, 3 + 3, and 2 + 4) showed significant association to ECE and PSM, this effect vanished for Gleason 3 + 3 only, for which the volume of TGG was always <5%. This also applied for subanalyses on TGG 5 to adverse pathology for the entire cohort. Again, a significant correlation was only detected when the TGG volume exceeded 5%, suggesting that a certain threshold of TGG must be exceeded to exert a meaningful influence. These findings are in contrast with the results of Mosse et al [10], where a tertiary volume <5% showed significant association with higher tumour stage. However, in their study, only the index tumour was considered, so our results may not be entirely comparable. Recently, Sim et al analysed the influence of a TGG 5 at Gleason score 7 on pathologic stage and time to BCR after RP [24]. Although a significant association with BCR was noticed for the entire cohort, on subanalyses for Gleason 3 + 4 + 5 and 4 + 3 + 5 versus their respective counterparts without TGG, both groups showed a trend towards a higher risk of BCR without reaching statistical significance. However, in their series, the authors did not consider the volume of the tertiary Gleason pattern, which may explain the lower significance. Nevertheless, this finding nicely demonstrates that the phenomenon of a TGG is complex, because an adverse association at a certain Gleason score must not necessarily withstand subanalysis. This is eminently interesting for reproducing the findings of van Oort et al [13], who stated that any TGG, regardless of its pattern, is an indicator for treatment failure. In our series, a worse tertiary grade was reported overall in 78% of all TGGs. Further substratification into higher versus lower tertiary grade and tumour volume <5% versus  $\geq 5\%$  would have ended in very small figures with accordingly reduced statistical power and so was not conducted. Therefore, the assumption that a better-differentiated TGG has a negative impact on patient outcome must be confirmed in further studies before a definite conclusion can be drawn, because the study by van Oort et al is the only one of its kind so far that addresses this issue.

In contrast to the results of other studies in which a TGG was not significantly associated with LNI, in our series, a TGG  $\geq 5\%$  of the tumour volume showed in univariate analysis a significant association to positive lymph nodes ( $p < 0.001$ ). However, our overall number of patients with positive lymph

nodes was only 30 (3.8%), and we did not perform an extended lymphadenectomy in most of the cases, so this finding should be interpreted with caution. Accordingly, we decided not to include LNI in multivariable analysis because we also included outcome parameters in the multivariate analyses. Inclusion of LNI would have lowered the number of cases for every parameter and was therefore not conducted.

Limitations of our study are, first, a relatively small number of overall TGGs, which consequently lowers the statistical power, especially for subanalysis. Second, no follow-up data are available to address the prognostic significance of TGGs on biochemical failure or survival. Finally, histopathologic evaluation of the RP specimens was performed by several pathologists, and each specimen was evaluated only once; therefore, interobserver percentage of agreement for classifying the same RP specimen cannot be given.

## 5. Conclusions

A TGG in RP specimens is significantly associated with advanced pathology. Our data indicate that a certain amount of TGG must be exceeded to affect pathological stage. A potentially negative impact of a TGG in RP specimens on patients' overall survival remains to be evaluated in further studies.

**Author contributions:** Hendrik Isbarn had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Isbarn, Steuber.

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*Analysis and interpretation of data:* Isbarn, Ahyai, Chun, Steuber.

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### Editorial Comment on: Prevalence of a Tertiary Gleason Grade and Its Impact on Adverse Histopathologic Parameters in a Contemporary Radical Prostatectomy Series

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Many pathologists feel themselves in a somewhat awkward position when identifying a tertiary Gleason grade in a prostatectomy, since the rules about how to incorporate this finding in a pathology report are not clear. Isbarn et al [1] report the finding of a tertiary Gleason grade in 22.5% of a contemporary series of 800 totally embedded prostatectomy specimens, not taking into account tertiary-grade carcinoma comprising <1% of the carcinoma. The presence of any (higher or lower) tertiary Gleason grade comprising >5% of the cancer in this contemporary series was shown to be associated with adverse pathological features in line with most previous studies [2]. As demonstrated by one other study [3], even a lower tertiary Gleason grade comprising >5% of the cancer was significantly more often associated with adverse pathological features. This finding could imply that pathologists should also report such a lower tertiary grade. In this series [2], tertiary-grade carcinomas, particularly Gleason score 6 adenocarcinomas, comprising <5% of the cancer did not show a significant association with adverse pathological findings. This further corroborates the so-called “5% rule” for Gleason scoring prostatectomy specimens: If a Gleason grade 4 or 5 component is present in the prostatectomy but comprises <5% of the cancer, this high-grade component is not factored in the Gleason

score [4]. The question still remains whether a pathologist should omit the reporting of any small high-grade (or lower grade) components. None of the above-mentioned findings provides evidence that a <5% proportion of high-grade cancer really lacks clinical significance, and only long-term follow-up studies will provide an answer. The retrospective design of the study involving several pathologists might further explain their considerable variation (from 14% to 29%) in reporting of tertiary grades. This variation emphasizes again the issue of inconsistent reporting of tertiary grades by pathologists, even within a single institution.

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### Editorial Comment on: Prevalence of a Tertiary Gleason Grade and Its Impact on Adverse Histopathologic Parameters in a Contemporary Radical Prostatectomy Series

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The concept of tertiary Gleason pattern remains an important issue in the urology field, mainly in the clinical situation in which its addition can increase the predictive value of Gleason grading. The study by Isbarn et al [1] addresses the prevalence of a tertiary Gleason pattern and the association to adverse histopathologic parameters in patients treated with radical prostatectomy. The paper is not original, since there are other studies on tertiary Gleason pattern [1–5]. What makes the study by Isbarn et al different is the fact that the sample series is prospectively selected; previous studies are retrospective and, therefore, more subjected to a selection bias.

The study of Isbarn et al [1] was aimed at prospectively assessing the rate of a tertiary Gleason grade pattern in a contemporary consecutive radical prostatectomy series and assessing the pattern's association with adverse pathology. By using a univariate statistical analysis, the authors confirmed a significant association between the presence of a tertiary Gleason pattern  $\geq 5\%$  of the whole cancer volume and extraprostatic extension, seminal vesicle infiltration, positive surgical margin, and lymph node infiltration. Moreover, on multivariate analysis, a tertiary Gleason pattern  $\geq 5\%$  was an independent predictor of both extraprostatic extension and positive surgical margin. Main conclusions in the current study are that (1)

tertiary grade pattern is more often higher than the standard Gleason score and (2) tertiary grade correlates with extracapsular extension and positive seminal vesicle disease.

Unfortunately, the absence of long-term outcomes to determine whether the additional information provides any prognostic information represents an important limitation of the current study. Therefore, the issue of the utility of tertiary Gleason pattern in patients with prostate cancer remains unclear and more research is needed.

In summary, the conclusion by Isbarn et al [1] is in line with published data that suggest tertiary Gleason pattern is an aggressive feature. Therefore, as recommended until more experience is made available, the presence of a tertiary Gleason pattern of 4 or 5 should be noted in the pathology report [1–5]. The utility of modifying the Gleason score to include the tertiary pattern in future may be imperative as new therapeutic strategies are incorporated into clinical practice.

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### Editorial Comment on: Prevalence of a Tertiary Gleason Grade and Its Impact on Adverse Histopathologic Parameters in a Contemporary Radical Prostatectomy Series

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In a recent European survey, 99.5% of uropathologists used the Gleason system for grading of prostate cancer in radical prostatectomy (RP) specimens [1]. The Gleason score was originally based on the two predominant Gleason grades, and patterns occupying <5% of the tumor were, by convention, ignored. The 2005 International Society of Urological Pathology (ISUP) consensus conference on grading of prostate cancer defined a set of rules that were thought to be more in line with current routines [2]. Based on the increasing understanding of the importance of tertiary Gleason patterns of higher grade (TGGs) [3], it was recommended that the highest Gleason pattern should be included in the score of needle biopsies, regardless of its amount, and mentioned separately for RP specimens. Isbarn et al demonstrate a correlation between TGG of RP specimens and adverse histopathology [4].

There are a few caveats. The definition of TGG is unclear. ISUP recommended that TGGs of lower grade and of <5% should be ignored [2]. Isbarn et al included these in the TGG concept and found that TGG was lower than the primary and secondary grades in 21% of TGG cases [4]. Furthermore, they based their grading on all cancer in the RP specimen as opposed to the ISUP recommendation to grade the main focus. In cases with large secondary, low-grade cancers, the impact of a

TGG may change by including all cancer in the Gleason score.

A key issue in assessment of TGG is to define a threshold for its identification. Prostate cancer is remarkably heterogeneous [5], and unless minute areas of deviating morphology are overlooked, a TGG will very often be found in RP specimens. More work is needed to reach consensus on this threshold. This study was done in a single institution, for which it is easier to define TGG than in a multi-institutional setting.

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