Practice Patterns in Reporting Tertiary Grades at Radical Prostatectomy: Survey of a Large Group of Experienced Urologic Pathologists

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Abstract

Context: In prostate cancer, “tertiary” higher grade patterns (TP) have been associated with biochemical recurrence after radical prostatectomy (RP).

Objective: To determine variation regarding definition and application of TP.

Design: Online survey regarding TP in a range of grading scenarios circulated to 105 experienced urologic pathologists.

Results: Among 95 respondents, 40/95 (42%) defined TP as “3rd most common pattern” and 55 (58%) as “minor pattern / <5% of tumor”. In a tumor with pattern 3 and <5% pattern 4, 35/95 (37%) assigned 3+3=6 with TP4, while 56 (59%) assigned 3+4=7. In a tumor with pattern 4 and <5% pattern 5, 51/95 (54%) assigned 4+4=8 with TP5, while 43 (45%) assigned 4+5=9. Six scenarios were presented in which the order of most common patterns was 3, 4, and 5 [group 1] or 4, 3, and 5 [group 2] with varying percentages. In both groups, when pattern 5 was <5%, 98% and 93% of respondents would assign 3+4=7 or 4+3=7 with TP5. In scenarios with 15% or 25% pattern 5, most respondents (70% and 80%, respectively) would include pattern 5 as the secondary grade, i.e. 3+5=8 (group 1) or 4+5=9 (group 2). For 85 of 95 (89%), a TP would not impact Grade Group assignment.

Conclusion: This survey highlights substantial variation in practice patterns regarding definition and application of “tertiary” grading in RP specimens. High consistency was observed in 3+4=7/4+3=7 scenarios with truly minor pattern 5. These findings should inform future studies assessing the standardization and predictive value of “tertiary” patterns.

INTRODUCTION

It is well known that some prostate cancers are comprised of more than two grades¹–⁵. While the majority of so-called “tertiary” grading reported in the literature refers to a higher grade – typically pattern 5 – the term has been used variably regarding extent, ranging from a more limited, minor, or <5% higher grade carcinoma component in initial publications³–⁴ to a third most common pattern of any percentage⁶–¹⁸. The accepted method for reporting
“tertiary” patterns also differs between needle biopsy and radical prostatectomy (RP). As codified by the International Society of Urologic Pathology (ISUP) 2005 and 2014 grading conferences, cases with 3 patterns on needle biopsy should be graded using a “1st plus worst” (most common + next highest grade) strategy\textsuperscript{19–20}. This reporting is employed to avoid losing key information regarding the highest pattern of cancer present in clinical decision-making / treatment planning, as needle biopsy predictive tools utilize only two grades\textsuperscript{21–22}. For RP specimens bearing three grading patterns, since the pathologist may assess the entire tumor, the “tertiary” terminology has been recommended\textsuperscript{19}. The latter recommendation is based on an array of studies\textsuperscript{3–4, 6–18} showing that cancers with a tertiary higher-grade pattern (TP) are associated with increased stage and/or biochemical recurrence following RP compared with their closest grading counterpart (e.g. 4+3=7 with tertiary pattern 5 compared with 4+3=7). Paradoxically however, TPs are not routinely incorporated into predictive clinical models\textsuperscript{23–25}.

While a majority of tertiary grading studies have defined the term as minor / less than 5%\textsuperscript{3–4, 11–18}, this is not universal\textsuperscript{6–10, 20}, and no study has ever documented practice patterns across a range of grading scenarios. Understanding how and when tertiary grades are assigned has become more intriguing with the introduction of a prognostic Grade Group system. First introduced in 2013\textsuperscript{27}, validated in multi-institutional analysis\textsuperscript{28}, corroborated in population-based, surgical, and radiation oncology data sets, and adopted by the World Health Organization and American Joint Cancer Committee\textsuperscript{29–34}, assigning a Grade Group is now standard practice in RP reporting. While the Grade Group system assigns each case to one of 5 groups, the ISUP 2014 grading conference, which endorsed the system, suggested that a tertiary/minor high-grade pattern should not alter the Grade Group\textsuperscript{20}. In this manuscript, we utilized an online survey platform to determine variation in practice patterns among experienced genitourinary (GU) pathologists through a series of grading scenarios focused on “tertiary” grading in RP specimens.

METHODS

In the spring of 2018, a survey was designed and circulated to 105 experienced international urologic pathologists via an online survey program, SurveyMonkey Inc. (San Mateo, California, USA). Pathologists invited to participate were identified solely by the authors as academically-engaged GU pathologists from a range of institutions. The ten multiple choice-style questions circulated are summarized in Table 1. The survey informed potential respondents that it would evaluate their perspectives/practice patterns related to tertiary grading in RP specimens. The first question assessed how participants define a “tertiary” pattern, which was followed by eight case-based grading scenarios. The final question asked if reporting tertiary patterns would affect assignment of Grade Group for an individual RP case. All replies were tabulated and analyzed with descriptive statistics.

RESULTS

Ninety-five pathologists responded to the online survey and are listed in Supplemental Table 1. Responses were tabulated on a per question basis as well as an interaction of responses.
(i.e. depending on how a respondent defined “tertiary”, were his/her subsequent responses consistent with that definition) as delineated below.

**Definition of Tertiary Grading Pattern**

Fifty-five of 95 (58%) pathologists responded that TP is a minor pattern/<5% of the tumor, while 40 (42%) defined TP as the third most common pattern.

**Scenarios with One Predominant Grade and a Minor Component (<5%) of Higher Grade**

In a tumor with overwhelming pattern 3 and <5% pattern 4, 56 of 95 (59%) would assign 3+4=7, with 40 also including a comment regarding % pattern 4, while 35 (37%) would assign 3+3=6 with a minor/tertiary component pattern 4. Four respondents would not document pattern 4 in this scenario, assigning 3+3=6.

In a tumor with overwhelming pattern 4 and <5% pattern 5, 51 of 95 (54%) would assign 4+4=8 with a minor/tertiary component of pattern 5, while 43 (45%) would assign 4+5=9, with 23 including a comment regarding % pattern 5. One respondent would not document pattern 5 in this scenario, assigning 4+4=8.

**Grading Scenarios Group 1: RP Specimens with Three Grades – 1st Most Common: pattern 3, 2nd Most Common: pattern 4, 3rd Most Common: pattern 5**

All respondents would address the presence of pattern 5. The responses for Group 1 are summarized in Table 2.

In a scenario with <5% pattern 5, 93 of 95 (98%) would assign 3+4=7 with TP5. In scenarios with either 15% or 25% pattern 5, 66/95 (69%) and 75/95 (79%) would assign 3+5=8, with half including a comment, respectively. Conversely, 29/95 (31%) and 20/95 (21%) would assign 3+4=7 with TP5.

**Grading Scenarios Group 2: RP Specimens with Three Grades – 1st Most Common: pattern 4, 2nd Most Common: pattern 3, 3rd Most Common: pattern 5**

All respondents would address the presence of pattern 5. The responses for Group 2 are summarized in Table 3.

In a scenario with <5% pattern 5, 88 of 95 (93%) would assign 4+3=7 with TP5, while the remaining seven would assign 4+5=9. In scenarios with either 15% or 25% pattern 5, 67/95 (71%) and 76/95 (80%) would assign 4+5=9, respectively, with one-third including a comment. Conversely, 28/95 (29%) and 19/95 (20%) would assign 4+3=7 with TP5.

**Did Definition of TP Predict Response to Grading Scenarios (Groups 1-2)?**

For Group 1 (order of most common patterns = 3, 4, and 5), among 55 respondents who defined TP as a minor pattern/<5% of the tumor, 98%, 9%, and 3% would assign 3+4=7 with TP5 in scenarios with percentage pattern 5 of <5%, 15%, and 25%, respectively. Among the 40 respondents who defined TP as the third most common pattern, 98%, 60%, and 45%, would assign 3+4=7 with TP5 in the same scenarios.
For Group 2 (order of most common patterns = 4, 3, and 5), among 55 respondents who defined TP as a minor pattern/≤5% of the tumor, 95%, 11%, and 4%, would assign 4+3=7 with TP5 in scenarios with percentage pattern 5 of <5%, 15%, and 25%, respectively. Among the 40 respondents who defined TP as the third most common pattern, 90%, 55%, and 43%, would assign 4+3=7 with TP5 in the same scenarios.

### Impact of Tertiary Grading on Grade Group Assignment

Eighty-five of 95 (89%) responded that a TP would not impact their assignment of Grade Group to an individual case.

### DISCUSSION

The application of prostate cancer grading has undergone significant evolution over the past two decades, in part due to systematic needle biopsy sampling as well as the centrality of tumor grading in predictive models\(^1,21–25\). The 2005 and 2014 ISUP grading conferences codified much of this evolution, including endorsement of a patient-centered prognostic Grade Group system\(^19–20\). Fundamentally, however, prostate cancer grading still relies on identifying the first and second most common histologic patterns to reach a Gleason score and corresponding Grade Group. For prostate glands harboring ≥2 grades, “tertiary” patterns, typically of higher grade, have a reported incidence of 4 to 50% in RP studies\(^2–3,13–14,35\). Several elements regarding TP remain controversial, including its definition (limited vs. no limit), association with recurrence rates (intermediate between grades vs. akin to next highest Grade Group), and more recently, its effect on Grade Group assignment. While the ISUP 2014 report suggested that a TP be defined exclusively as truly minor/limited (<5%) and should not alter the Grade Group, there is conflicting evidence in contemporary cohorts\(^9–12,15–16,18\).

Importantly, although reporting of tertiary higher-grade patterns is recommended for RP specimens, there is discordance with clinical predictive models that do not include TP in a standard fashion\(^23–25\). This is likely due to the reality that almost all TP studies are single institution reports, may be underpowered to show clear prognostic significance in multivariable analysis, often have short follow-up, and have not yet shown utility in clinical decision making. From the pathology perspective, there has been nearly no attention given to the variability of tertiary grading pattern definition and its application in specific grading scenarios. In that vein, the current survey of a large group of experienced GU pathologists reveals a range of practice patterns for TP reporting.

### Definition of Tertiary Grading Pattern

The definition of tertiary pattern and its upper limit have been a source of ongoing controversy. In an early article by Pan et al and subsequent manuscripts from Johns Hopkins Hospital, TP has exclusively referred to very limited amounts (<5%) of a 3rd most common pattern, usually pattern 5\(^3–4,11–12,18\). While some investigators have adopted this definition, this has not been universal, with other studies having no specific cut off\(^6–8,10\). In these latter reports, grading scenarios with up to ~30% pattern 5 could still be considered a TP. In a survey on Gleason grading published in 2005 preceding the ISUP grading conference, 46%...
(27/59) of genitourinary pathologists responded that they would use a 5% limit for inclusion of a TP, whereas 54% had no set limit. While there was consensus at the 2005 ISUP grading conference that the Gleason score for RP specimens is assigned based on the primary and secondary patterns with a comment as to a TP (if present), no limit for TP was specified.

In a report addressing practice-related issues resulting from the proceedings of the 2014 ISUP grading conference, it was noted that although no specific cut off was voted on, 83% of participants favored the term “minor high-grade pattern” over “tertiary grade” pattern, indicating that TP should not just be the 3rd most common pattern but that it should also be minor or limited in extent. In the current survey, conducted in 2018, 58% responded that TP refers to a minor pattern/less than 5% of the tumor, while 42% would still define TP as simply, the 3rd most common pattern. Therefore, while an increasing number of experienced urologic pathologists would limit the definition of TP, many would not. As tertiary grades are seldom incorporated within nomograms and prognostic tables, there remains a significant concern that not having a limit for TP could lead to under-estimation of risk in grading scenarios with relatively large amounts of pattern 5. Our findings indicate substantial variation in practice, with implications for comparing studies among institutions as well as prognostication post-RP.

Scenarios with One Predominant Grade and a Minor Component (<5%) of Higher Grade

Among the issues with the “tertiary” terminology are RP grading scenarios with only two patterns, in which the 2nd higher grade pattern is of very limited extent. At the 2014 ISUP grading conference, 75% favored reporting a percent pattern 4 for Gleason score 7 cases (Grade Groups 2-3), in both the needle biopsy and RP specimen types. Theoretically, adoption of this reporting parameter would allow cases reported as Gleason score 3+3=6 with TP 4 to be re-classified as Gleason score 3+4=7 with a % pattern 4 noted. Similarly, although not specifically addressed at the 2014 conference, it has been posited that for cases formerly reported as Gleason score 4+4=8 with TP 5, these cases might now be recorded as Gleason score 4+5=9 with a minor component of pattern 5. Our survey of practice patterns however, reveals that in these grading scenarios, 37% (for overwhelming pattern 3 and <5% pattern 4) and 54% (for overwhelming pattern 4 and <5% pattern 5) of survey respondents would still assign Gleason score based on the predominant grade alone and note the minor higher-grade component as a tertiary pattern. These findings reveal that reporting a % pattern 4 (and % of higher grade patterns more globally) in RP specimens has not been uniformly embraced.

Grading Scenarios Groups 1 & 2: RP Specimens with Three Grades:

**Group 1:** Most Common: pattern 3, 2nd: pattern 4, 3rd: pattern 5

**Group 2:** Most Common: pattern 4, 2nd: pattern 3, 3rd: pattern 5

In line with 2014 ISUP recommendations, we found that an overwhelming majority of respondents – 98% for group 1, 93% for group 2 – would report a TP 5 in grading scenarios with 3 grades, in which there was less than 5% pattern 5 (i.e. either 3+4=7 or 4+3=7 with TP 5). Substantial variation however was found in grading scenarios with a larger % pattern 5.
Specifically, for group 1 and 2 scenarios with 15% pattern 5, ~30% of respondents would still assign TP 5 – as opposed to incorporating pattern 5 as a secondary grade – and in those scenarios with 25% pattern 5, 20% of respondents would still assign TP 5, highlighting the degree to which the “minor/limited” definition of TP has not been universally adopted.

Unsurprisingly, when assessing responses to grading scenarios in groups 1 and 2 through the lens of the “tertiary pattern” definition chosen, we found that for those defining TP as a minor pattern/less than 5% of the tumor, ≥95% would assign either 3+4 or 4+3=7 with TP5. Concordantly, the rate of assigning TP5 fell to approximately 10% for group 1-2 scenarios with 15% pattern 5 and to less than 5% for scenarios with 25% pattern 5.

For those defining TP as the 3rd most common pattern, in scenarios with less than 5% pattern 5, ≥90% would assign either 3+4 or 4+3=7 with TP5. While one might have expected similarly high rates of assigning TP 5 due to the definition chosen, we found that for scenarios with 15% and 25% pattern 5, approximately 40% (group 1 scenarios) and 55% (group 2 scenarios) chose to include pattern 5 as the secondary grade, even though it was the 3rd most common pattern, indicating disparity between definition and utilization of TP. Stated differently, nearly half of respondents who defined TP as 3rd most common pattern adopted a “minor pattern” definition in application to specific grading scenarios.

**Impact of Tertiary Grading on Grade Group Assignment**

A further recommendation from the 2014 ISUP grading conference was that minor high-grade patterns should not change Grade Group assignment. The current survey results are in line with that recommendation, with nearly 90% responding that a tertiary pattern would not impact their assignment of Grade Group to an individual case. Literature following the 2014 conference – echoing work in the pre-Grade Group era – has produced divergent evidence regarding TP and its impact on Grade Group assignment, with some finding that a TP imparts rates of biochemical recurrence intermediate between grades (i.e. Grade Group 3 with TP 5 compared with Grade Groups 3 and 4) and others showing biochemical recurrence rates akin to the next highest Grade Group (i.e. Grade Group 3 with TP 5 similar to Grade Group 4). The latter findings have led some to argue that unlike the 2014 ISUP recommendation, tertiary patterns should be incorporated into the Grade Group system rather than left as a comment. Any such recommendation would be highly influenced by how the individual study defined TP and the uniformity in application of that definition in routine practice. The current practice pattern findings suggest great variability even among experienced urologic pathologists in this assessment.

Ultimately, data elements in standard pathology reports should have clinical import, for prognostication and/or management. To date, there has been only limited incorporation of TP in prognostic models and no studies incorporating a decision curve analysis to demonstrate a net benefit in clinical decision-making, e.g. for the provision of early adjuvant therapy post-RP. The current study highlights differences in practice patterns, some governed definitionally, for reporting TP grading. Importantly, while just over half of pathologists surveyed defined TP as a minor pattern/less than 5% of the tumor, the greatest reproducibility among respondents was observed in grading scenarios in which the degree of pattern 5 was truly minor, i.e. less than 5%, regardless of definition chosen. As a practice
recommendation, these findings suggest that practicing pathologist should consider reporting a tertiary pattern only when a limited amount of a higher grade, third most common pattern is present. At the same time, future practice might be informed by data from institutions in which % of all grading patterns are routinely recorded. Such studies can establish whether there is an optimal % above which tumors with three patterns no longer behave (i.e. biochemical recurrence, etc.) akin to cancers with the same primary and secondary grades but lacking a tertiary higher grade pattern. A final critical area for future study is how urologic oncologists utilize the presence of a tertiary higher-grade pattern in patient counseling and decision-making.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.
Survey questions evaluating practice patterns regarding tertiary grading in radical prostatectomy specimens.

1. How do you define a tertiary Gleason pattern?
   a. The third most common pattern observed; b. A minor pattern / less than 5% of the tumor

2. An RP specimen shows overwhelming pattern 3 with < 5% pattern 4. How would you grade this case?
   a. 3+3=6; b. 3+3=6 with a minor/tertiary component of pattern 4; c. 3+4=7; d. 3+4=7 with a note addressing the % pattern 4

3. An RP specimen shows overwhelming pattern 4 with < 5% pattern 5. How would you grade this case?
   a. 4+4=8; b. 4+4=8 with a minor/tertiary component of pattern 5; c. 4+5=9; d. 4+5=9 with a note addressing the % pattern 5

4. An RP specimen shows three grades; Based on the percentages in each scenario below, how would you grade the case?
   A. 80% pattern 3, 17% pattern 4, 3% pattern 5
      a. 3+4=7; b. 3+4=7 with a minor/tertiary component of pattern 5; c. 3+5=8; d. 3+5=8 with a note addressing the % pattern 5
   B. 60% pattern 3, 25% pattern 4, 15% pattern 5
      a. 3+4=7; b. 3+4=7 with a tertiary component of pattern 5; c. 3+5=8; d. 3+5=8 with a note addressing the % pattern 5
   C. 45% pattern 3, 30% pattern 4, 25% pattern 5
      a. 3+4=7; b. 3+4=7 with a tertiary component of pattern 5; c. 3+5=8; d. 3+5=8 with a note addressing the % pattern 5

5. An RP specimen shows three grades; Based on the percentages in each of the scenarios below, how would you grade the case?
   A. 80% pattern 4, 17% pattern 3, 3% pattern 5
      a. 4+3=7; b. 4+3=7 with a minor/tertiary component of pattern 5; c. 4+5=9; d. 4+5=9 with a note addressing the % pattern 5
   B. 60% pattern 4, 25% pattern 3, 15% pattern 5
      a. 4+3=7; b. 4+3=7 with a tertiary component of pattern 5; c. 4+5=9; d. 4+5=9 with a note addressing the % pattern 5
   C. 45% pattern 4, 30% pattern 3, 25% pattern 5
      a. 4+3=7; b. 4+3=7 with a tertiary component of pattern 5; c. 4+5=9; d. 4+5=9 with a note addressing the % pattern 5

6. If you would report a minor or tertiary pattern for any of the above scenarios, would it impact your assignment of Grade group (i.e. 3+4=7 with a minor or tertiary pattern 5 would be Grade group 2 v. Grade group 3)?
   a. Yes; b. No
Table 2.

Summary of practice pattern responses to scenarios involving RP specimens with three grades in which pattern 3 is the 1st most common, pattern 4 is the 2nd most common, and pattern 5 is the 3rd most common.

| Scenario                                      | 3+4=7 with minor / tertiary pattern 5 | 3+5=8 (+/- comment re: % pattern 5) |
|-----------------------------------------------|---------------------------------------|-----------------------------------|
| 80% pattern 3, 17% pattern 4, 3% pattern 5   | 93/95 (98%)                           | 2/95 (2%)                         |
| 60% pattern 3, 25% pattern 4, 15% pattern 5  | 29/95 (31%)                           | 66/95 (69%)                       |
| 45% pattern 3, 30% pattern 4, 25% pattern 5  | 20/95 (21%)                           | 75/95 (79%)                       |

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Table 3.

Summary of practice pattern responses to scenarios involving RP specimens with three grades in which pattern 4 is the 1st most common, pattern 3 is the 2nd most common, and pattern 5 is the 3rd most common.

| Scenario                                      | 4+3=7 with minor / tertiary pattern 5 | 4+5=9 (+/- comment re: % pattern 5) |
|-----------------------------------------------|--------------------------------------|-------------------------------------|
| 80% pattern 4, 17% pattern 3, 3% pattern 5   | 88/95 (93%)                          | 7/95 (7%)                           |
| 60% pattern 4, 25% pattern 3, 15% pattern 5  | 28/95 (29%)                          | 67/95 (71%)                         |
| 45% pattern 4, 30% pattern 3, 25% pattern 5  | 19/95 (20%)                          | 76/95 (80%)                         |