Tumour grading: communication is the key

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Tumour grade used in conjunction with other prognostic parameters, such as tumour type, stage and biomarker status, is a critical determinant of patient management in several cancers, especially those that are organ-confined. Pathologists therefore strive for precise grading and there have been ongoing efforts to facilitate grading reproducibility. We explain why this focus on precision may not be necessary in some cases and highlight the critical importance of optimally communicating the histopathological findings in cases where grading is borderline. We also discuss potential issues with the current trend to reduce the number of grading categories in some tumours such as urothelial and endometrial cancers.

Tumour grade is generally a biological continuum with a progressive increase in risk of adverse outcome and no quantum increase in risk at any particular cut-point. Although grade may determine management decisions, individual patients and clinicians may have a different perception of the minimum risk (and hence minimum grade) that would warrant therapy. Hence, the cut-points between grade categories are generally arbitrary. This is analogous to blood pressure and serum prostate-specific antigen (PSA) cut-points used to stratify patients with hypertension and prostate cancer, respectively. For example, PSA cut-points of 10 ng/mL and 20 ng/mL are used to stratify risk for patients with prostate cancer,[1] but it is unlikely that there is a significant biological difference between PSA levels of 9 ng/mL (low risk) and 10 ng/mL (intermediate risk).

Grade is also a morphological continuum with arbitrary and subjective cut-points, such as the 5% and 50% solid component in endometrial carcinoma.[2] Hence, there is an inevitable grey zone around the borders of each grade category that is associated with significant intraobserver and interobserver reporting variability. Several studies have shown only limited reproducibility in the reporting of tumour grade in many cancers.[3 4] However, it should be recognised that most of these reproducibility studies are inherently flawed as the results are biased by the selection of cases and participants. Interobserver variation would be greatest when a set of selected 'borderline' cases are graded by a group of participants who have not previously collaborated.

Numerous studies have demonstrated that grade is a proven powerful prognostic indicator for many cancers.[2 5 6] However, these results only inform the outcome of unequivocal cases. Cases with borderline grades would be distributed in different grade categories due to interobserver variability and their significance in outcome studies cancelled out, as they would have similar clinical outcomes.

While three-tier or four-tier systems are currently used to grade many cancers, there is a general trend to reduce the number of grade categories to the minimum required for patient management. In 2004, the WHO adopted a binary (low-grade/high-grade) grading system for urothelial carcinoma that had been proposed by the International Society of Urological Pathology to replace the three-tier (grades 1–3) WHO 1973 system.[7] The new two-tier system was considered to be simpler and more reproducible while precluding most tumours being 'dumped' in an intermediate (grade 2) category. It could also be in line with clinical requirements with potential BCG therapy for tumours at the bad end of grade 2 that would be categorised as high-grade.

Binary (low-grade/high-grade) grading of endometrioid endometrial carcinoma has recently been advocated by International Federation of Obstetrics and Gynecology (FIGO), the International Collaboration on Cancer Reporting and the International Society of Gynecological Pathologists and has been recommended in the updated 2020 WHO classification of endometrial carcinomas.[2 8–10] This entails grouping together grade 1 and 2 endometrioid carcinomas in the traditional three-tiered FIGO system as low-grade since these are generally treated in a similar manner.

As outlined above, potential advantages of a binary grading system are simplicity, reproducibility and clinical utility. Grading systems with fewer consensus-based cut-points are also useful for research and to guide therapies at a population level. However, there are also significant counter-arguments against such binary systems, and these may be suboptimal for deciding treatment of individual patients. While it is important to reproducibly distinguish obvious low-grade and high-grade cancers, precise grading may not be necessary in borderline cases. Tumours at the *bad end* of the low-grade spectrum and the *good end* of the high-grade spectrum are not biologically different. It would therefore be reasonable to treat such borderline cases as either low-grade or high-grade after consideration of other risk factors and patient preferences. This is analogous to the management of hypertension where patients with borderline blood pressure elevation may or may not be treated based on the presence or absence of other risk factors.[11]

Tumours at either end of the high-grade spectrum could have very different prognostic implications. Unlike radiology, clinicians do not review histology slides and hence it is critical that the histopathology report clearly indicates where a tumour lies within the grade spectrum so that patients and clinicians

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can make informed decisions regarding management options. This valuable information could be conveyed by increasing the number of grade categories or in the form of a succinct comment such as 'low-grade, bordering on high-grade' or 'just amounting to high-grade'. The generally reproducible distinction of the *good end* of high-grade from the *bad end* of high-grade is more important than the less reproducible distinction between the *bad end* of low-grade and the *good end* of high-grade.

A binary grading system would result in wider and more heterogeneous grade categories with a 'high-grade' tumour representing either a tumour at the upper end of the low-grade spectrum (that could be interpreted as high-grade by some experts on some occasions) or an unequivocally high-grade tumour. The former, but not the latter, could potentially be treated as a low-grade tumour, but this stratification would be poorly communicated in a system with fewer grade categories.

It is also unclear whether reducing the number of grade categories would simplify tumour grading. Reporting more categories could potentially make grading easier, as distinction between adjacent grade categories would become less important. The current practice of reporting the extent of pattern 4 in Gleason score (GS) 7 tumours has resulted in the GS 7 category being subdivided into 11 percentage intervals based on the amount of pattern 4 tumour present.[12] In the past, it was critical to distinguish between GS 3+4 and GS 4+3, but this is now less important as reporting the percentage of pattern 4 (eg, 3+4 (10% pattern 4), 3+4 (50% pattern 4), 4+3 (60% pattern 4) or 4+3 (90% pattern 4)) clearly communicates where the tumour lies in the grade continuum.[13] Thus, the distinction between 50% and 60% becomes less important when GS 7 is subcategorised by reporting the percentage pattern 4 present.

Another argument against increasing the number of grade categories is that clinicians need only a few categories to guide patient management. For example, in endometrioid carcinomas of the uterine corpus, there are essentially no management differences between grade 1 and 2 tumours, resulting in a proposal to designate these as low-grade malignancies.[2] However, if pathologists report more categories, clinicians could group these into fewer categories using cut-points based on whether the focus is to avoid undertreatment or overtreatment, which is often based on a combination of pathological and non-pathological parameters.[14] This histopathological approach could better inform the clinician as to where the tumour lies within the grade spectrum. A 3 cm size cut-point is used to risk-stratify non-muscle invasive bladder cancer.[14] Despite this, urologists record tumour size in 'cm' rather than simply record the tumour as ≤3 cm/>3 cm, so that it is clear whether the tumour size is 1 cm or 3 cm, or whether 4 cm or 10 cm.

Some grading systems have sought to improve communication by reporting a score that would indicate if a tumour is of borderline grade. As described above, reporting of percentage pattern 4 in a GS 7 prostate cancer would better inform the clinician and allow some patients with borderline GS 7 (eg, <10% pattern 4) to be managed with active surveillance.[12] The Nottingham breast cancer grading system categorises tumours as grades 1–3 but also records the score (3–9), and this enables clinicians to recognise that a tumour is of borderline grade (scores around 5 and 7).[6] Similarly, grading of gastrointestinal stromal tumours is based on the reported mitotic index (per 5 mm^2), thereby clearly indicating if the grade is borderline.[15] Other parameters, such proliferation index and molecular markers, could also help substratify borderline cases.

We conclude that effective communication of where a tumour lies within the grade continuum is necessary for informed decision-making. A greater number of grade categories could improve this communication and facilitate personalised medicine. An alternative is that in borderline cases a note could be added to the pathology report explaining where a tumour lies on the spectrum of a particular grade, and it is likely that different approaches will be necessary for different organs and tumour types. It is important that grading should be simple and straightforward, but simplicity should not be at the cost of clinical utility. We hope that this paper promotes debate regarding tumour grading across organ systems.

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