Histological grading in lung cancer: one system for all or separate systems for each histological type?

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Two recent studies show the importance of tumour budding and nest size in grading of lung squamous cell carcinoma http://ow.ly/WTaQ2

The grading of cancer is a histological method intended to help predict prognosis based on specific morphological features. It typically is based on architectural or cytological features (nuclear grade or number of mitoses), or in some cases, a combination of both. Grading is usually broken down into a spectrum from well differentiated (grade 1) to the most poorly differentiated (grade 3 or 4). The number of grades ranges from two to five [1–3]. The highest grade tumours (grade 3 or 4) lack any specific differentiation. The morphological criteria for grading usually differ from that used in histological classification, but in some systems, histological classification is a major component of grade.

Clinically relevant and reproducible histological grading systems have been well established for many years in cancers of the breast [4–6], prostate [1–3], endometrium [7, 8], soft tissue sarcomas [9] and kidney [10–12]. However, for lung cancer, a widely accepted histological grading system with clearly defined criteria and demonstrable clinical significance has not yet been developed, and there is a great need for this [13, 14].

In lung cancer, certain tumours are known to be high grade including small cell lung carcinoma (SCLC), large cell carcinoma, pleomorphic carcinoma, carcinosarcoma and pulmonary blastoma [13]. In addition, for lung neuroendocrine tumours, the histological subtyping is primarily based upon mitotic count and necrosis correlating with the low-grade typical carcinoid, intermediate-grade atypical carcinoid, and high-grade SCLC and large cell neuroendocrine carcinoma, where the latter two are distinguished primarily by cytological characteristics [13].

For lung adenocarcinoma, recent advances show emerging data that are likely to result in a grading system in the near future. This may best include a combination of architectural patterns or histological subtyping and nuclear features such as mitotic counts. Based on the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification of adenocarcinoma, five different histological subtypes were proposed [15] and based on the predominant subtype, significant prognostic differences have been demonstrated [16–22]. This provides a simple architectural grading system, most applicable to resection specimens, with grade 1 (well differentiated; lepidic predominant), grade 2 (moderately differentiated; acinar or papillary predominant) and grade 3 (poorly differentiated; solid or micropapillary predominant). Other proposed grading schemes include the two most predominant patterns, the highest grade pattern, or nuclear features such as size or mitotic count in combination with an architectural approach like the predominant subtype. In a study of stage I adenocarcinomas, Sica et al. [23]

proposed a grading system using a score created by summing the two most predominant grades and stratified tumours into a three-tiered classification, which also correlated well with prognosis. By using the predominant type to grade adenocarcinoma, it appears that the acinar pattern is the most common and the most heterogeneous. Several studies have suggested the acinar subtype can be divided further into prognostically significant subsets. Two studies, by KADOTA et al. [24] and VON DER THUSEN et al. [25], found the combination of predominant histological pattern and mitotic activity was helpful in separating the intermediate group into well and poorly differentiated tumours. In addition, the cribriform pattern has been identified to be a poor-prognostic subset of the acinar subtype, similar to the solid type [26–28]. NAKAZATO et al. [29] found that nuclear size was a valuable predictor of prognosis. However, this has not been confirmed by other investigators [24, 25].

Grading has implications beyond just predicting prognosis. Recent data suggest that the poorly differentiated solid and micropapillary histological subtypes not only correlate with poor survival but are also predictive of survival benefit with cisplatin-based adjuvant chemotherapy in patients with surgically resected adenocarcinomas [30].

Since a definitive grading system has not been established for resected lung adenocarcinomas and no grading system is recognised in non-resection specimens, there are limited data on the prognostic significance of histological features in this setting. However, a recent study in patients with advanced disease evaluated predominant subtype in core biopsies and classified tumours with papillary-, micropapillary- and solid-predominant patterns to be high grade. Patients with these high-grade patterns had better response rates to platinum-based therapy and progression-free survival than patients with lower grade adenocarcinomas [31, 32]. Further validation is needed to demonstrate clinical relevance for grading in non-resection specimens.

In this issue of *European Respiratory Journal*, WEICHERT et al. [33] have proposed a grading system for squamous cell carcinoma of the lung. It is based upon a scoring system by summing the scores for two independent prognostic markers including tumour budding and tumour cell nest size (table 1). This scoring system is based on a detailed clinical and pathological assessment of a large retrospective series of surgically resected lung squamous cell carcinomas and it demonstrates prognostic significance for overall survival by univariate and multivariate analysis.

Importantly, this study provides validation of the work by KADOTA et al. [34], who also found tumour budding and single cell invasion were independent prognostic factors for overall survival. The method of analysis for tumour nest size and tumour budding was slightly different in the two studies. According to KADOTA et al. [34], survival according to single cell invasion was significant and an independent prognostic factor, while in the WEICHERT et al. [33] study, poor prognosis was correlated with small (fewer than five cells) to intermediate (five to 15 cells) *versus* large nest size (>15 cells) rather than just single cell invasion. Also, the stratification of budding was significant in the KADOTA et al. [34] study with a cut off of 10 buds per high-power field (HPF), while in the WEICHERT et al. [33] study, budding was stratified according to no budding, <15 budding foci per 10 HPFs and ⩾15 foci per 10 HPFs. Future studies should further investigate the optimal stratification for tumour budding and tumour cell nest size according to both approaches. Interestingly, in contrast to lung adenocarcinoma, there is no consistent prognostic significance to the three main histological subtypes of

TABLE 1 Lung squamous cell carcinoma grade according to sum of scores for tumour budding and nest size

Morphologic feature	Score	Definition
Tumour budding	1	No budding in 10 HPFs
	2	<15 budding foci per 10 HPFs
	3	⩾15 budding foci per 10 HPFs
Tumour nest size	1	>15 cells (large nest size)
	2	5–15 cells (intermediate nest size)
	3	<5 (or 2–4) cells (small nest size)
	4	Single cell invasion
Combined score	2–3	Grade 1 (well differentiated)
	4–6	Grade 2 (moderately differentiated)
	7	Grade 3 (poorly differentiated)

HPF: high-power field. Reproduced and modified from [33].

squamous cell carcinoma: keratinising, nonkeratinising and basaloid. WEICHERT *et al.* [33] found a worse prognosis was associated with the keratinising subtype but KADOTA *et al.* [34] did not find any significant association between subtype and patient outcome. It is intriguing that, although others have reported poor survival for basaloid carcinomas [35], both of these studies were unable to demonstrate poor survival for the basaloid tumours [33, 34]. In the study by KADOTA *et al.* [34], basaloid tumours showed a trend for better overall survival (69% *versus* 58%, p=0.071). The study by WEICHERT *et al.* [33] showed significantly better overall survival for nonkeratinising and basaloid (71.5% and 68.8%, respectively) tumours compared to keratinising (62.1%) tumours (p=0.037). Compared to the MORO-SIBILOT *et al.* [35] study, which included 90 cases of basaloid carcinoma, the KADOTA *et al.* [34] study only had 33 cases and the WEICHERT *et al.* [33] study only had 18 cases, so further investigation is needed to address the clinical behaviour of this tumour. It is peculiar in the WEICHERT *et al.* [33] dataset why patients with keratinising tumours would have a worse outcome than the nonkeratinising or basaloid tumours because keratinising tumours are typically regarded as better differentiated. Also, in both studies, no prognostic significance was reported according to proliferation rate by Ki-67 staining [33, 34]. It is of interest that in both studies, survival analysis using overall survival rather than disease free survival or cumulative incidence of recurrence appeared to provide the most robust prognostic correlations.

Despite the similarity in results between the WEICHERT *et al.* [33] and KADOTA *et al.* [34] studies, there are some differences. Nuclear diameter was prognostically significant in the study by KADOTA *et al.* [34] but it had no impact on survival in the study by WEICHERT *et al.* [33]. In addition, WEICHERT *et al.* [33] found increased stromal content correlated with worse outcome but KADOTA *et al.* [34] did not. Although KADOTA *et al.* [34] did not find prognostic significance according to nuclear atypia, chromatin pattern, presence of nucleoli or mitotic rate, these features were not reported by WEICHERT *et al.* [33].

In summary, both the WEICHERT *et al.* [33] and KADOTA *et al.* [34] investigations demonstrate that unlike lung adenocarcinoma, the histological grading system for lung squamous cell carcinoma should not include histological subtyping or nuclear features such as mitotic rate, but rather the features of tumour budding and tumour nest size. Applying this system will be challenging for practicing pathologists who may have never given attention to the histological features of tumour nest size and budding. An inherent challenge in analysing these features is selecting the field with maximum tumour budding, and assessing tumour nest size both in the entire tumour and at the tumour edge. However, since two large studies have now demonstrated the prognostic importance of these features in squamous cell carcinoma, they may be the most important histological factors in predicting prognosis in this tumour and warrant further investigation. Another implication of these two studies is that they clearly show that the components of the grading system for squamous cell carcinoma must be different from that for other major lung cancers including adenocarcinomas and neuroendocrine tumours.

There is a great need for further study of histological grading in lung cancers, particularly lung adenocarcinoma and squamous cell carcinoma. Hopefully, over the coming decade, before the next World Health Organization classification revision, validated and reproducible systems will be established. Since writing this editorial, we have become aware of another similar study of resected lung squamous cell carcinomas where it was shown that tumour budding, single cell invasion, mitoses, and higher cytologic atypia were independent predictors of worse overall survival [36].

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