Reproducibility of colon tumor grade and relationship to recurrence in the context of clinical, pathologic, and genomic tumor features in 504 patients with stage II colon cancer treated with surgery alone at the Cleveland Clinic.

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Background: High tumor grade is included in practice guidelines as a marker of higher recurrence risk in stage II colon cancer. Multiple systems for tumor grading exist, without a standardized approach. We characterize agreement of 2 methods for tumor grading and association with recurrence in the context of clinical, pathologic, and genomic tumor features including mismatch repair (MMR) and the 12-gene recurrence score (RS).

Methods: Colon tumors were graded independently by 2 academic GI pathologists (P1, P2). Grade was defined by % tumor with gland-like structures: well (> 95%), moderately (50-95%) and poorly (< 50%) differentiated. P1 used this 3-tier system while P2 used 2-tier scheme with well and moderately differentiated tumors defined as low grade and poorly differentiated as high grade. All mucinous tumors were high-grade by P2 but not P1. Relationship to recurrence-free interval (RFI) was assessed by Cox regression.

Results: Primary tumors from 504 stage II colon cancer treated with surgery alone were included. 18% (P1) and 31% (P2) were high grade. High grade tumors were more likely right-sided (≥ 60%) and MMR deficient (≥ 35%) for P1 and P2 (all p < 0.001). Proportion of mucinous tumors was similar for high and low grade by P1 (25% vs. 21%, p = 0.39). P2 high grade trended to lower recurrence (HR = 0.63, p = 0.10) while P1 grade was not associated w/ RFI (p = 0.46). In multivariate analyses including grade and RS, P2 high grade was associated with lower recurrence (p = 0.007) but P1 grade was not associated w/ RFI (p = 0.30). Neither grade was associated w/ RFI (p > 0.30) after controlling for RS, MMR, tumor location and mucinous histology. Using the two-tier scheme, agreement b/w the 2 pathologists was low (kappa = 0.30, 95% CI 0.21-0.39) in all pts and moderate if mucinous tumors were excluded (kappa = 0.52, 95% CI 0.40-0.64).

Conclusions: High tumor grade was not found to be a marker of higher recurrence risk in stage II colon cancer. Other markers validated in stage II colon cancer, such as MMR and RS, should be considered. Interpathologist agreement on colon tumor grade is modest, even with central expert review.