Background

- High tumor grade was included in practice guidelines as a marker of higher recurrence risk in stage II colon cancer.
- Published studies of the prognostic power of tumor grade in colon cancer have reported variable findings.
- Recent large studies, including QUASAR (n=7,117) PETA-3 (n=4,584) and those from the NSABP and Cleveland Clinic (n=15,077) have consistently found that high tumor grade is associated with higher recurrence risk in stage II colon cancer.
- An added challenge is the existence of multiple systems for colon tumor grading, without an evidence-based approach.
- Standardized, reproducible assays are needed for decision-making in clinical practice.

The 12-gene colon cancer Recurrence Score® assay, as an example, is a standardized, clinically validated assay which has been analytically validated for reproducibility and precision.

There is little data regarding tumor grade inter-reader reproducibility.

Study Objectives

- Characterize the agreement of two methods for tumor grading and association with recurrence in the context of:
  - clinical and pathological covariates such as mismatch-repair (MMR), mucinous histology, and tumor location.
- The 12-gene colon cancer Recurrence Score® assay, previously validated in stage II colon cancer clinical and pathological covariates such as mismatch-repair (MMR), mucinous histology and tumor location.
- The association of grade with recurrence risk in stage II colon cancer treated with surgery alone or surgery plus adjuvant fluorouracil plus leucovorin.

Study Design and Methods

- Tumors from 504 stage II colon cancer patients treated with surgery alone at the Cleveland Clinic were graded independently by two academic pathologists (P1 and P2) who employed the grading methods used in their colon cancer clinical practice.
- For both pathologists, grade was defined by percent tumor with gland-like structures.
- The 12-gene colon cancer Recurrence Score® assay, previously validated in stage II colon cancer patients from QUASAR.

For both P1 and P2, grade was defined as high (>95%), moderately (50-95%) and poorly (<50%) differentiated.

Sections on glass slides.

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Using the two-tier scheme, agreement between grade assessments by two pathologists was assessed using Cohen’s kappa statistic.

In multivariate analyses including grade and RS, P1 grade was not associated with risk of recurrence while P2 high grade appeared to be associated with lower recurrence.

No evidence of interaction between either P1 or P2 grade and RS was observed (both p>0.36).

Confidence limits for HRs for P1 and P2 grade overlapped substantially.

Association of Grade with Recurrence Risk in conjunction with 12-gene Recurrence Score

Association of Grade with Recurrence Risk in Univariate Analyses

In univariate analyses, P2 grade was associated with risk of recurrence, while P2 high grade trended to be associated with lower recurrence.

Difference in HRs appeared to be relatively small and confidence limits overlapped substantially.

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