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Comparison of molecular and pathologic features of stage II and stage III colon cancer in four large studies conducted for development of the 12-gene colon cancer recurrence score.

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Background: An understanding of biologic similarities and differences between st II and III colon cancer is needed to inform clinical practice and trial design. We compare pathologic markers and gene expression by stage in 4 colon cancer studies conducted to develop the 12-gene recurrence score (RS): NSABP C01/C02, C04, C06, and CCF.

Methods: Gene expression was quantitated by RT-PCR from 30 µm manually microdissected FPE colon cancer tissue. St II colon cancer with < 12 LN examined was excluded to minimize under-staging. Pathologic markers and expression of 375 genes were compared b/w 634 st II and 844 st III pts, and stage-specific associations with recurrence were evaluated using Cox models.

Results: As expected, nodal status was a strong predictor of recurrence. St II pts were more likely to be MMR deficient (17 vs. 12%, p = 0.04) and have mucinous histology (19 vs. 14%, p = 0.007) while proportions of high grade and T4 were similar by stage (p > 0.5). Interaction of grade and stage was significant (p = 0.005) with HR for grade = 0.58 for st II and 1.27 for st III. Interactions of stage with T stage, MMR and mucinous histology as predictors of recurrence were borderline (p = 0.07-0.11), with indication of prognostic effects in st II but not st III. Absolute differences b/w st II and III in mean expression of 375 genes were small: median 0.09 C_T. 5 genes had significant (p < 0.05) differences in expression by stage in all 4 studies. 45 genes showed evidence of expression by stage interaction (p < 0.1), with 37 of these expected to be false discoveries. RS showed no interaction with stage (p = 0.87). Unsupervised cluster analysis revealed similar patterns of gene expression by stage. In st II colon cancer pts w/ ≥ 12 LN examined from the QUASAR validation study (n = 506), gene expression patterns paralleled those observed in the 4 studies.

Conclusions: Quantitative analysis by RT-PCR identified very similar expression in st II and III disease for the vast majority of genes tested. Future studies should examine the clinical significance of differences identified between st II and III, including MMR, grade, and a small number of individual genes.