

ASCO 2009 Abstract #4000

A quantitative multi-gene RT-PCR assay for prediction of recurrence in stage II colon cancer: Selection of the genes in 4 large studies and results of the independent, prospectively-designed QUASAR validation study

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Abstract:

Background: New clinical tools are needed to improve risk assessment and treatment decisions in stage II colon cancer. 4 development studies [Surgery (Sx) alone: NSABP C-01/C-02 (n=270) & CCF study (n=765); Sx+5FU/LV: NSABP C-04 (n=308) & C-06 (n=508)] were performed to select the genes for prediction of recurrence and 5FU/LV benefit. To determine clinical utility of the pre-specified assay, we performed a large independent, prospectively-designed clinical validation study in stage II colon cancer pts from the QUASAR trial.

Methods: Gene expression was quantitated by RT-PCR from 30 µm manually microdissected fixed paraffin-embedded primary colon cancer tissue. Recurrence-free interval (RFI), disease-free survival (DFS) and overall survival (OS) were analyzed using Cox regression.

Results: Combined analysis of the 4 development studies (total n=1,851; 761 candidate genes) identified 48 genes significantly associated with recurrence risk and 66 genes predictive of 5FU/LV benefit. Multivariate analysis, in the context of stage, grade, nodes examined and MSI status, yielded 18 genes (7 prognostic genes, 6 predictive genes, 5 reference genes) and separate prognostic Recurrence Score (RS) and predictive Treatment Score (TS) algorithms. In the QUASAR validation study, tumor blocks were collected for 68% of pts; 1,490 pts with blocks had stage II colon cancer and RT-PCR was successful in 1,436 eligible pts (711 Sx, 725 Sx+5FU/LV). Median FU=6.6 yrs. In the primary analysis of RFI in pts following Sx, the RS predicted recurrence risk (HR/25 units=1.58, 95% CI 1.15-2.15; p=0.004). The RS also predicted DFS (p=0.01) and OS (p=0.04). Recurrence risk increased monotonically with increasing RS. In multivariate analyses, RS retained prognostic significance (p=0.008) independent of mismatch repair (MMR), T stage, nodes examined, grade, and lymphovascular invasion. MMR deficiency (HR=0.31, 95% CI 0.15-0.63; p<0.001) and T4 stage (HR=1.94, 95% CI 1.35-2.79; p=0.005), together ~25% of pts, also were independently prognostic. 5FU/LV benefit was significant (p<0.001). However, TS was not validated as a predictor of 5FU/LV benefit (interaction p=0.19).

Conclusions: The colon cancer Recurrence Score is a validated, independent predictor of individualized recurrence risk for stage II colon cancer patients following surgery.