Abstract

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Lymphocytic response to tumour and deficient DNA mismatch repair identify subtypes of stage II/III colorectal cancer associated with patient outcomes.


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OBJECTIVE: Tumour-infiltrating lymphocyte (TIL) response and deficient DNA mismatch repair (dMMR) are determinants of prognosis in colorectal cancer. Although highly correlated, evidence suggests that these are independent predictors of outcome. However, the prognostic significance of combined TIL/MMR classification and how this compares to the major genomic and transcriptomic subtypes remain unclear.

DESIGN: A prospective cohort of 1265 patients with stage II/III cancer was examined for TIL/MMR status and BRAF/KRAS mutations. Consensus molecular subtype (CMS) status was determined for 142 cases. Associations with 5-year disease-free survival (DFS) were evaluated and validated in an independent cohort of 602 patients.

RESULTS: Tumours were categorised into four subtypes based on TIL and MMR status: TIL-low/proficient-MMR (pMMR) (61.3% of cases), TIL-high/pMMR (14.8%), TIL-low/dMMR (8.6%) and TIL-high/dMMR (15.2%). Compared with TIL-high/dMMR tumours with the most favourable prognosis, both TIL-low/dMMR tumours with the most favourable prognosis, both TIL-low/dMMR (HR=3.53; 95% CI=1.88 to 6.64; \(P_{\text{multivariate}}<0.001\)) and TIL-low/pMMR tumours (HR=2.67; 95% CI=1.47 to 4.84; \(P_{\text{multivariate}}=0.001\)) showed poor DFS. Outcomes of patients with TIL-low/dMMR and TIL-low/pMMR tumours were similar. TIL-high/pMMR tumours showed intermediate survival rates. These findings were validated in an independent cohort. TIL/MMR status was a more significant predictor of prognosis than National Comprehensive Cancer Network high-risk features and was a superior predictor of prognosis compared with genomic (dMMR, pMMR/BRAF^{wt}/KRAS^{wt}, pMMR/BRAF^{mut}/KRAS^{wt}, pMMR/BRAF^{wt}/KRAS^{mut}) and transcriptomic (CMS 1-4) subtypes.

CONCLUSION: TIL/MMR classification identified subtypes of stage II/III colorectal cancer associated with different outcomes. Although dMMR status is generally considered a marker of good prognosis, we found this to be dependent on the presence of TILs. Prognostication based on TIL/MMR subtypes was superior compared with histopathological, genomic and transcriptomic subtypes.

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