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Prognostic markers in early-stage colorectal cancer: significance of TYMS mRNA expression.

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Abstract

BACKGROUND:

Several studies have recently indicated the prognostic or predictive role of several biomarkers in colorectal cancer. We sought to investigate the prognostic value of prostaglandin synthase 2 (PTGS2), cyclooxygenase 2 (COX2), thymidylate synthetase (TYMS), thymidine phosphorylase (TYMP), dihydropyrimidine dehydrogenase (DPYD) and topoisomerase I (TOPO1) in colorectal cancer patients treated with 5-FU-based regimens, such as De Gramont and FOLFOX in the adjuvant setting.

MATERIALS AND METHODS:

In total, 96 formalin-fixed paraffin-embedded and 30 fresh-frozen tumor tissue samples were evaluated using immunohistochemistry, quantitative reverse transcription-polymerase chain reaction and microarray gene expression profiling, respectively.

RESULTS:

The majority of tumors exhibited protein overexpression of COX2 (69%), TYMS (75%) and TOPO1 (75%). There was a significant association of TYMP protein expression with T classification, gender and stage (p=0.040, p=0.041 and p=0.011, respectively). TOPO1 protein expression was correlated with TOPO1 mRNA expression and was positively associated with stage (p=0.002) and lymph node infiltration (p=0.004). In univariate analysis, patients with high TYMS mRNA expression were shown to have a significantly lower risk for progression and death (Wald's p=0.030 and p=0.015, respectively). However, in multivariate analysis, only a trend for decreased risk for death was shown in patients with high TYMS mRNA expression (Wald's p=0.083), while patients with high PTGS2 mRNA expression had a trend for lower risk for progression (p=0.064). Using supervised hierarchical clustering, based on the expression in fresh-frozen tumor tissue of PTGS2, TYMS, TYMP and DPYD, our 30 patients were separated into two clusters. One of the clusters was enriched with patients with infiltrated lymph nodes ($p<0.05$), suggesting that these genes might have an impact on the tumor's ability to metastasize.

CONCLUSION:

These findings indicate a possible prognostic role of TYMS mRNA expression and highlight a cluster of genes associated with nodal metastases that warrant further investigation in a larger cohort of patients with colorectal cancer treated with 5-FU-based adjuvant chemotherapy.