Hypoxia-inducible factor-1alpha expression in the gastric carcinogenesis sequence and its prognostic role in gastric and gastro-oesophageal adenocarcinomas.

Abstract:
Hypoxia-inducible factor-1 (HIF-1)alpha expression was studied in the gastric carcinogenesis sequence and as a prognostic factor in surgically resected gastric and gastro-oesophageal junction tumours. Protein expression was examined using immunohistochemistry on formalin-fixed biopsies of normal mucosa (n=20), Helicobacter pylori associated gastritis (n=24), intestinal metaplasia (n=24), dysplasia (n=12) and intestinal (n=19) and diffuse (n=21) adenocarcinoma. The relationship between HIF-1alpha expression and prognosis was assessed in resection specimens from 177 patients with gastric and gastro-oesophageal junction adenocarcinoma. Hypoxia-inducible factor-1alpha expression was not observed in normal gastric mucosa but increased in density (P<0.01) and intensity (P<0.01) with progression from H. pylori-associated gastritis, intestinal metaplasia, dysplasia to adenocarcinoma. The pattern of staining in the resection specimens was focally positive in 49 (28%) and at the invasive tumour edge in 41 (23%). Invasive edge expression was associated with lymph node metastases (P=0.034), advanced TNM stage (P=0.001) and was an adverse prognostic factor for cancer-specific survival (P=0.019). In univariate analysis and in comparison with
tumours not expressing HIF-1alpha, invasive edge staining was associated with a hazard ratio of 1.6 (95% CI 1.0-2.5) and focally positive staining a hazard ratio of 0.7 (95% CI 0.5-1.2). Hypoxia-inducible factor-1alpha lost prognostic significance in multivariate analysis. The results suggest HIF-1alpha is involved in gastric carcinogenesis and disease progression, but is only a weak prognostic factor for survival.