Altered expression of mdm-2 and its association with p53 protein status, tumor-cell-proliferation rate and prognosis in cervical neoplasia

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Recent results suggest that p53 inactivation is required for cervical-carcinoma development. The mdm-2 oncogene, which forms an auto-regulatory feedback loop with the normal p53 protein, has been found amplified in human carcinomas, thus abolishing the anti-proliferative function of p53. To investigate whether the mdm-2/p53 interaction plays a role in cervical neoplasms, we performed an immunohistochemical study in archival fixed, embedded specimens that included 178 pre-cancerous lesions (CIN) and invasive squamous-cell carcinomas of clinical stage IB. In addition to p53, we assessed the p53-associated protein, mdm-2, and the Ki-67 labelling index (LI). The presence of HPV was assessed by in situ DNA hybridization. Tumor expression of all nuclear proteins was scored as fraction of positive CIN or cancer nuclei. The analysis demonstrated a significant association of the Ki-67 LI with grade of atypia in cervical neoplasms. p53 accumulation and mdm-2 expression are higher in invasive carcinomas than in pre-cancerous lesions. No correlation was observed with HPV status. An inverse correlation was found between increased tumor-cell proliferation and mdm-2 expression in invasive carcinomas ($p < 0.0001$). mdm-2 expression was significantly associated with p53 accumulation ($p < 0.02$). However, the investigated nuclear proteins were not associated with overall survival in patients with invasive carcinomas. Cox stepwise-regression analysis revealed regional lymph node status and depth of invasion to be independent parameters.

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