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Potential prognostic significance of apoptosis related oncogenes: p53, bcl-2 and mdm-2 in early stage cervical carcinoma

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Introduction Evaluations of expression of apoptosis related oncogenes are being increasingly called upon in an attempt to better understand the carcinogenesis of cervical carcinoma and to provide possible prognostic information. The aim of this study was to analyze the expression of bcl-2, p53 and mdm-2 oncoproteins and cellular proliferative marker Ki-67 in early stage cervical carcinoma, with an emphasis on their association with human papillomavirus (HPV) infection, recurrence rate and lymph node status.
Material and methods Using immunohistochemistry, 69 radical hysterectomy specimens with cervical carcinoma (pT1b1/pT1b2) were studied. Evaluation of expression of p53, bcl-2, mdm-2 and Ki-67 was performed in surface area, center and invasion front of the neoplasms. The HPV presence was determined by CARD in situ hybridization.
Results and conclusion In the invasion front bcl-2 was expressed in 31 (45%), p53 in 37 (53%) and mdm-2 in 33 (47%) cases. HPV infection was detected in 40 (58%) cases. Carcinomas with a higher Ki-67 labeling index were more frequently HPV positive than HPV negative (82.5% vs 17.5%, $p<0.01$). No association was found between p53, mdm-2 or Ki-67 and either lymph node status or recurrence rate. Negative staining for bcl-2 was associated only with the presence of lymph node metastasis (74% vs 26%, $p=0.05$), and not with the recurrence rate. Significant correlation among expression of bcl-2, p53, mdm-2 oncoprotein and Ki-67 values was also observed. These results suggest that further study of a larger series is needed to confirm whether bcl-2, either alone or in combined evaluation with other markers, could be a useful marker to identify more aggressive behavior in early stage cervical carcinoma.

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Malignant potential of dysplastic endocervical epithelium assessed by ploidy status, S-phase fraction and c-myc expression

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Introduction During the past three decades, the incidence of cervical invasive primary adenocarcinoma (ACA) has increased. At the same time, incidence of squamous cell carcinomas of the cervix decreased, due to early detection of their well documented precursors lesions. The aim of this study was to determine if dysplastic endocervical cells (EC) have neoplastic potential as a precursor lesions of adenocarcinoma in situ (AIS) of the cervix. The malignant potential was determined by assessing the ploidy status, proliferative activity and c-myc expression in normal, dysplastic and malignant EC separately.
Patients and methods Serial sections from 49 patients with diagnosed AIS or primary invasive ACA were analyzed. One representative slide of cervix which showed normal, dysplastic and malignant endocervical glands simultaneously was chosen from each patient. Determination of ploidy status and S-phase by flow cytometry and expression of c-myc oncoprotein by immunohistochemistry in normal, dysplastic and malignant EC was done.
Results The morphologicaly normal EC were diploid, with normal proliferative activity and no expression of c-myc oncoprotein. The dysplastic and malignant EC had a significant proportion of cells with aneuploidy, higher proliferative activity and c-myc oncogene overexpression. The χ^2 test showed significant association of malignant EC with aneuploidy ($p=0.008$) and high proliferative activity ($p=0.042$). As one third of dysplastic EC are aneuploid, with high mitotic activity, they probably have malignant potential. Dysplastic endocervical cells had statistically significant association with c-myc oncogene expression ($p=0.028$).
Conclusion Our results support the existence of pre-malignant glandular lesions while the immunohistochemical detection of c-myc oncoproteine could be helpful in detection of EC with malignant potential even without dysplastic morphologic changes.

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Immunohistochemical expression of c-erbB-2 in early stage cervical carcinoma: correlation with human papillomavirus infection and prognosis

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Introduction The attempts to determine the prognostic significance of c-erbB-2 oncoprotein expression (OPE) and its relation to human papillomavirus (HPV) infection in cervical cancer have yielded controversial**.** The aim of this study was to evaluate the patterns of c-erbB-2 OPE in early stage cervical carcinoma and to assess its prognostic value by exploring its relationships to various clinicopathological characteristics, HPV status and recurrence rate.
Materials and methods Radical hysterectomy specimens from 71 cervical carcinoma patients (pT1b1/1b2) were investigated immunohistochemically for c-erbB-2 presence. The c-erbB-2 score (range: 0-400) was determined in the surface area, center and invasion front of each carcinoma. CARD in situ hybridization was used for HPV detection.
Results and conclusion Strong c-erbB-2 OPE was detected in 21, 20, and 32 cases in the invasion front, center and surface area of the tumor, respectively. There was a significant difference in positive staining rate of c-erbB-2 between squamous cell, mixed carcinomas and adenocarcinomas (23%, 50% vs 83%, $p=0.005$). C-erbB-2 OPE was significantly higher in carcinomas with abundant than in tumors with less abundant peri-tumoral lymphocytic infiltration (36.5% vs 10.5%, $p=0.032$). In HPV positive carcinomas (41), c-erbB-2 was detected more frequently in type 31/33 versus type 16/18 lesions (75% vs 18.8%, $p=0.002$). No association was found between c-erbB-2 expression and recurrence rate, lymph node metastasis or any other clinicopathological variable investigated (age, tumor diameter, depth of invasion, grade, vascular invasion). Therefore, immunostaining for c-erbB-2 is unlikely to be of use as a prognostic indicator in early stage cervical carcinomas, while further study is warranted to examine relationships between HPV infection and c-erbB-2 OPE.