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Ki-67 and vascular endothelial growth factor (VEGF) in prediction of tumor growth and lymph node metastasis in head and neck squamous cell carcinomas

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Background: The TNM staging is an important guide for treatment but does not explain biology of tumor growth and progression during clinical course. Molecular markers reflecting growth and metastatic potentials of a cancer would be helpful in directing better therapeutic decision.
Materials and methods: One hundred surgical specimens of head and neck squamous cell carcinomas were stainded by immunohistochemistry for expression of Ki-67 (K) and VEGF(V). Cutoff points for high and low marker expression were determined to allow grouping of the bifunctional markers into $K_{low}V_{low}$, $K_{high}V_{low}$, $K_{low}V_{high}$ and $K_{high}V_{high}$. Bifunctional marker profiles were analyzed for their associations with pathological T and N stages, tumor site and differentiation.
Results: Analysis of likelihood ratio (LR) to advanced T stage and lymph node metastasis when either or both markers were highly expressed revealed that $K_{high}V_{low}$ ($LR = 2.63$, $p < 0.001$) or $K_{low}V_{high}$ ($LR = 3.13$, $p < 0.001$) posed significant risk to T3/T4. Simultaneously enhanced expression of both markers not only facilitated tumor growth to T3/T4 ($LR = 2.86$, $p \ll 0.001$) but also promoted lymph node metastasis ($LR = 2.31$, $p \ll 0.001$). In two clinically extreme groups: patients with small tumors (T1/T2) and positive lymph nodes at presentation mostly expressed $K_{high}V_{high}$ ($p < 0.001$) as opposed to patients with large tumors (T3/T4) without node involvement in whom tumors tended to have low expression of either or both markers ($p < 0.05$). Differences in bifunctional marker profiles were observed among tumor sites ($p < 0.05$). Distributions of tumor staging in these sites could be accounted for this finding. For tumor differentiation, moderately and poorly differentiated tumors inclined to express $K_{high}V_{high}$ while well differentiated tumors showed no inclination for any marker profiles ($p < 0.05$).
Conclusion: Different patterns of Ki-67 and VEGF expression could help to explain biology of tumor growth and lymph node metastasis during pretreatment clinical course.

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Overexpression of HSP27 confers chemoresistance which is associated with cell growth delay and inactivation of p38 kinase in Hep-2 laryngeal cancer cells.

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Among the heat shock protein (HSP) families, Hsp70 and Hsp27 have been implicated in the tumorigenesis and chemoresistance, probably by regulation of cell proliferation and prevention of apoptosis. Hsp27 levels were often increased in large populations of tumors of head and neck, but the mechanisms of its chemoresistance are not clear yet. Here, we investigated the role of Hsp27 in resistance to cytotoxic stress using Hep-2 human laryngeal cancer cells overexpressing Hsp27. Hsp27 overexpression induced cellular resistance to heat shock at 45ºC for 1 hour as well as against several cytotoxic agents, such as cisplatin, staurosporin and H_2O_2. But there was no difference in the sensitivity against irradiation or serum starvation. Moreover, Hsp27 overexpressing Hep-2 cells showed delay in cell growth as compared with control cells. To examine if the decreased cell proliferation in Hsp27 overexpressing cells contributed to the chemoresistance, control Hep-2 cells were synchronized at late G1 phase by mimosine treatment. Synchronization of Hep-2 cells exhibited resistance to cisplatin, staurosporin and H_2O_2, but not to irradiation and serum starvation, correlating the protection effect shown in Hsp27 overexpressing cells. Therefore, the protective effect of Hsp27 against several cytotoxic agents was based on the cell growth delay. Interestingly, the cell growth and the cytotoxicity of Hep-2 cells were suppressed by SB203580, a specific inhibitor of p38 MAP kinase, but not by PD098059, a specific inhibitor of ERK, or specific inhibitor of JNK. Furthermore, overexpression of Hsp27 lead to suppression of drug-induced p38 kinase activation and subsequent Hsp27 phosphorylation, while ERK and JNK activities were not changed by overexpression of Hsp27. Taken together, our results suggest that overexpression of Hsp27 in Hep-2 cells confers chemoresistance which is associated with the cell growth delay and p38 kinase inactivation. However, the substrate of p38 kinase which induces growth inhibition should be identified to define the molecular mechanism by which Hsp27 induces growth inhibition in laryngeal cancer cells.

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Clinical significance of Bcl-2 expression at the invasive front of oral squamous cell carcinomas

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Background: Apoptosis is a genetically determined process playing an active role in tissue size regulation, morphogenesis and removing damaged cells that could be potentially dangerous for their host. Proteins of the Bcl-2 family play a key role in the control of apoptosis and carry out both proapoptotic and antiapoptotic functions. The previous study has reported that bcl-2 expression was the risk factor of oral squamous cell carcinoma. The present study evaluated the prognostic value of antiapoptotic protein expression at the invasive front of oral squamous cell carcinomas, considering the clinicopathological findings.
Materials and Methods: Forty-five specimens of oral squamous cell carcinoma were randomly selected. Bcl-2 expression was evaluated by immunohistochemistry in formalin fixed, paraffin embedded pretreated specimens at the invasive front of oral squamous cell carcinoma. Clinicopathologic data were gathered, and patient survival was analyzed.
Results: Immunohistochemical staining showed that nineteen of the forty-five specimens (42.2%) examined were positive for Bcl-2. Positive cells tended to be in the outer layer of round tumor nests and cord-like microtumor nests at the invasive front of oral squamous cell carcinoma. None of the Bcl-2 expression correlated significantly with age, gender, primary sites, T category, and N category. However, there was a correlation between Bcl-2 expression and the degree of cell differentiation ($p < 0.05$). Cases showing recurrence of oral squamous cell carcinoma demonstrated high rates of Bcl-2 expression, and there was a significant correlation between Bcl-2 expression and recurrence of oral squamous cell carcinoma ($p < 0.05$). Furthermore, the five-year survival rate of Bcl-2 positive cases was significantly lower than that of Bcl-2 negative cases ($p < 0.05$).
Conclusions: Cell differentiation is generally analogous to the normal cells and tissue. Cases showing a low degree of cell differentiation demonstrated the high rates of Bcl-2 expression. Cells deviating from normal might control the function of apoptosis. Therefore, Bcl-2 expression at the invasive front of oral squamous cell carcinomas is a significant indicator of prognosis.

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Relevance of the immunoexpression of galectin-3 in tumor cell compartments and its impact on the metastasis potential of the well-differentiated thyroid carcinoma

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Papillary and follicular carcinomas are primary epithelial malignant neoplasias of the thyroid gland, originating from follicular cells and are considered to be well-differentiated carcinomas (WDC). The diagnosis and therapy of choice are based on their classification, according to prognostic factors that are considered together with the results of biological-marker investigation. As applied to immunohistochemical investigations, galectin-3 has been amply studied and a wide range of functions that it carries out in the cellular compartments have been described. However, its role in WDC remains controversial. To investigate if galectin-3 can aid in the diagnosis and treatment choice of WDC, digital quantification of its immunoexpression in the different cell compartments was carried out in order to determine its difference in relation to following: local tissue free of tumors and the neoplastic tissue, tumors with local tissue invasion and metastasis and its relation to the cell proliferation index, apoptosis and angiogenesis. A retrospective study was carried out with 109 cases of WDC from 1995 to 1999 in "Hospital das Clínicas" of the University of São Paulo Medical School. A survey of clinical data and follow up of 73 ± 32 months was carried out, and in addition, morphological evaluation and digital immunohistochemical analysis with galectin-3, Ki-67, caspase-3 and CD-34 antibodies were done. It was demonstrated that: 1) there was no galectic-3 expression in the non-neoplastic epithelial tissue and there was nucleolar, nuclear and cytoplasmatic expression of galectin-3 in the tumor cells, with positive correlation among them; 2) according to a multivariate analysis, there was greater nucleolar expression as an independent factor associated to the presence of lymphatic metastasis ($P = 0.028$) and greater cytoplasmatic expression associated to the presence of lymphatic