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Value of Biological Factors for Prognosis in Maxillary Sinus Squamous Cell Carcinoma 2. P53 gene mutation and apoptosis

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2. p53 gene mutation and apoptosis

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Tumor progression is characterized by an imbalance between cell proliferation and apoptosis. One of the tumor suppressor genes p53 plays a crucial role in the induction of apoptosis in tumor cells. The p53-related apoptotic cell death is down-regulated by bcl-2 family including bcl-x. Bax is a proapoptotic protein to induce apoptosis. The interaction of Fas ligand and Fas stimulates an intracellular cascade of events that leads to induce apoptosis. Loss of p53 gene function due to mutation represents the most common genetic event known in human cancer. Down-regulation of the apoptotic pathway due to loss of p53 function and/or that of apoptosis-related protein probably contributes to treatment failure in patients with cancer by making malignant cells more resistant or sensitive to radiotherapy

and chemotherapy. In head and neck SCC, a number of reports have been documented about p53 overexpression and p53 mutation. However, conflicting results have been presented with regard to the correlation between prognosis and p53 status. We analyzed biological prognostic factors in maxillary sinus squamous cell carcinoma (SCC) from the standpoint of apoptosis. Our purpose of this study is to identify p53 mutations, the expression of apoptosis-related proteins such as p53, Fas, bax and bcl-x, and the incidence of apoptotic cells in maxillary sinus SCC. The goal of our study is to investigate the correlations among p53 mutation, expression of apoptosis-related proteins, apoptosis and to determine their relations to effectiveness of radiochemotherapy and prognosis.

The study group consisted of 70 Japanese patients with maxillary sinus squamous cell carcinoma (SCC). Fifty-seven patients were treated with radiochemotherapy followed by total or partial maxillectomy. The preoperative radiochemotherapy including local irradiation with total dose of 50 Gy (2.5 Gy x 20 fractions-5 days a week) along with concomitant intra-maxillary arterial infusion of 5-fluorouracil (5Fu) with total dose of 5000 mg (250 mg x 20 times). Tumor biopsy specimens at pretreatment status were examined for

expression of apoptosis-related proteins such as p53 protein, Fas, bax and bcl-x using immunohistological method. The proportion of apoptotic cells labeled by single stranded-DNA antibody was expressed as an apoptotic index (AI). P53 mutations at exon 5 through 8 were analyzed by direct sequence on PCR amplified products obtained from laser microdissected tissues. The effectiveness of radiochenotherapy was investigated histologically on surgically dissected specimens.

P53 mutations were identified in 20 (29%) of 70 patients. P53 protein was positive in 39 (56%) patients, Fas was in 20 (29%), bax was in 40 (57%), and bcl-x was in 33 (47%). Overexpression of bax was associated with high AI (p=0.024). Either low AI or p53 mutation at pretreatment status was significantly correlated with low histological effectiveness of radiochemotherapy (p=0.048, p=0.019, respectively). Kaplan-Meier analysis showed that low histological effectiveness of radiochemotherapy (p=0.028), p53 mutations (p=0.0095) and negativity of bax (p=0.0069), low AI (<2)(p=0.013) were significantly related with worse disease-free survival. Multivariate analysis showed AI as an independent factor predicting for disease-free survival (p=0.043).

We showed that the p53 mutation, expression of bax, and the levels of spontaneous apoptosis in pretreatment tissues have prognostic value in maxillary sinus SCC and that the apoptotic index is the independent factor predicting for disease free survival. The high level of spontaneous apoptosis induced by overexpression of bax may increase the sensitivity of radiochemotherapy resulting in good prognosis, while p53 mutation may lead to resistance against radiochemotherapy resulting in poor prognosis.

Proceeding

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