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Prognostic Implication of Hyaluronic Acid Expression in Oropharynx and Oral Cavity Cancer

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Background: Hyaluronic acid (HA) is a well-characterized component of extracellular matrix (ECM), which plays a critical role in a variety of cellular processes and regulates cell adhesion, migration, and proliferation associated with prognosis of various tumor types. However, the clinical prognostic significance in resected head and neck squamous cell carcinoma (HNSCC) is not well identified. **Methods:** The resected tissues from oropharynx or oral cavity cancer patients undergoing surgery were made for tissue microarray (TMA) divided into stroma and cancer panels. Including HA protein expression, HA synthases (HAS) and hyaluronidases (HYAL1) which degrading HA was also assessed by immunohistochemistry. **Results:** A total of 160 resected oropharynx or oral cavity cancer tissues between 1994 and 2012 were analyzed in this study. Stromal HA expression, positive in 31 (20.5%) of patients, was marginally significantly associated with advanced T stage ($p=0.051$). Other clinicopathological characteristics did not differ according to stromal HA protein expression. However, the expression in HA stroma were statistically associated with clinical outcomes. In the multivariate analysis for recurrence-free survival, stromal HA expression was found to be an independent indicator of poor prognosis (HR, 1.670; 95 % CI, 1.044 - 2.670, $p=0.032$) for disease recurrence. In addition, the multivariate analysis for overall survival, stromal HA expression showed a trend toward poor prognosis in patients ($p=0.169$) with marginal significance for overall survival. **Conclusions:** The positive expression of HA in stroma could be related with poor prognosis independently in surgically resected oropharynx or oral cavity. Thus, the finding suggested that HA in stroma may serve not only as a prognostic marker but also as a supposed target for HNSCC treatment.

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The value of p16 or HPV as predictive marker of anti-EGFR treatment in recurrent/metastatic HNSCC

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Background: The anti-epidermal growth factor receptor agent was approved and has been a mainstay of treatment of recurrent/metastatic head and neck squamous cell cancers. However, it is unclear whether human papilloma virus modulates the response to targeting the EGFR. Some subset analysis of the randomized phase III study are confusing and recent the cancer genome atlas data showed that EGFR gene is rarely abnormal in HPV positive HNSCC tumors while it is frequently altered in HPV negative HNSCC tumors. The purpose of our meta-analysis is to evaluate the effects of anti-EGFR agents regarding HPV status. **Methods:** We conducted a meta analysis to evaluate the association of p16 expression status with outcomes in patients with recurrent/metastatic HNSCC receiving palliative anti-EGFR treatment with or without chemotherapy. A literature search of PubMed, EMBASE, and meeting abstracts of the American Society of Clinical Oncology and European Society of Medical Oncology through December 2016 was conducted. Considered a relative risk on a treatment response for HPV+ vs. HPV- groups as a summary estimate of an effect size. **Results:** Six trials met the selection criteria. Median age in the individual studies ranged from 58 to 65 years old, and the proportion of males ranged from 80% to 88.2%. 6 studies of the pooled trials performed a retrospective biopsy. The total number of patients was 681 (554 with the HPV negative group, 127 with the HPV positive group). The treatment effect of anti-EGFR was significantly different between HPV+ and HPV- groups. The pooled RRs on a treatment response for HPV+ vs. HPV- groups were 4.21 (95% CI = 1.76-10.06, $p=0.001$) and 3.07 (95% CI = 1.10-8.53, $p=0.032$) in the fixed and random effect models, respectively. **Conclusion:** A meta-analysis of trials with anti-EGFR agents in p16 negative RMHNSCC patients versus in p16 positive recurrent/metastatic HNSCC patients yielded that p16 status could be a predictive biomarker for anti-EGFR treatment in recurrent/metastatic HNSCC. Prospective study is warranted to determine the value of p16 or HPV as predictive marker of anti-EGFR treatment in recurrent/metastatic HNSCC