Karolinska Institutet

Department of Oncology and Pathology

Studies on human papillomavirus and molecular markers in head-neck cancer

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i CCK lecture hall, Cancer Center Karolinska

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by

Cecilia Nordfors

Master of Science

Principal Supervisor:
Prof. Tina Dalianis
Karolinska Institutet
Department of Oncology and Pathology

Co-supervisors:
Associate Prof. Torbjörn Ramqvist
Karolinska Institutet
Department of Oncology and Pathology

Prof. Eva Munk-Wikland
Karolinska Institutet
Department of Clinical Science, Information and Technology (CLINTEC)

Opponent:
Massimo Tommasino
International agency for research on cancer (IARC)
Lyone, France

Chairman:
Associate Prof. Mikael Lindström
Karolinska Insitutet
Department of Oncology and Pathology

Examination Board:
Prof. Sonia Andersson
Karolinska Institutet
Department of Women and children's health

Prof. Klas Wiman
Karolinska Institutet
Department of Oncology and Pathology

Associate Prof. Lars Sand
Uppsala University
Department of Surgical sciences
Division of oral and Maxillofacial surgery

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ABSTRACT

Background. Oropharyngeal squamous cell carcinoma (OSCC), where tonsillar and base of tongue cancer (TSCC and BOTSCC) dominate, is associated with smoking and alcohol as well as human papillomavirus (HPV) infection. The incidence of TSCC and BOTSCC, has increased lately, mainly due to HPV infection. In addition, patients with HPV-positive TSCC and BOTSCC have a better clinical outcome compared to those with the corresponding HPV-negative tumors (80% vs. 40% 5 year disease free survival (DFS)). Recently, head and neck cancer treatment has been intensified with chemotherapy and more intensive radiotherapy. This is likely unnecessary for 80% of HPV-positive TSCC and BOTSCC patients.

Aims. Due to the increase in TSCC and BOTSCC, we wanted to follow oral HPV-prevalence in healthy sexually active youth as well as in patients with TSCC and BOTSCC. This in order to disclose e.g. whether there were specific traits of oral HPV infection in the latter group. In addition, the presence of different HPV16 E6 variants in TSCC were analyzed as well as new biomarkers, which could aid in the identification of patients with HPV positive TSCC and BOTSCC that could be eligible for de-escalated treatment.

Result. In Paper I we showed that oral HPV prevalence was 9.3% among youth attending a youth clinic in Stockholm. Oral HPV infection was more common in women with genital infection and there was also HPV-type concordance between the oral and cervical sites. When testing samples from patients with suspected HNSCC in Paper II, nearly all HPV_{DNA+} oral samples were derived from patients with HPV_{DNA+} TSCC and BOTSCC. For healthy subjects with oral HPV_{DNA+} infection, the relative viral load was very low. In Paper III we found that the HPV16E6 L83V variant was common in TSCC, cervical cancer (CC) and cervical samples (CS), while the rare HPV16E6 R10G variant was present in a proportion of TSCC, but absent in CC and only sporadic in CS samples. Neither L83V nor R10G had any significant impact on clinical outcome. In paper IV, high number of CD8+ tumor infiltrating lymphocytes (TILs) was correlated to a better clinical outcome, especially for patients with HPV_{DNA+} and HPV_{DNA+} /p16 positive TSCC and BOTSCC. $CD4^{+}$ TIL counts were not linked to clinical outcome or survival for patients with HPV_{DNA+} tumors, although there was a tendency of better survival for patients with HPV_{DNA-} and HPV_{DNA-} /p16-negative tumors. Finally in Paper V, patients with HPV_{DNA+} TSCC and BOTSCC and absent/weak as compared to medium/ strong CD44 intensity staining had a significantly better 3-year DFS and overall survival.

Conclusion. Oral HPV infection was relatively frequent in Stockholm youth as compared to other studies during the same time period, but the relative viral load was in general lower than that found for patients with HPV-positive TSCC and BOTSCC. HPV16E6 L83V variant was common in TSCC, CC and CS, while the R10G variant was present in a proportion of TSCC, but absent in CC and only sporadic in CS samples. Both high CD8+ TIL infiltration and absent/weak CD44 intensity staining seemed to be promising predictive markers for patients with HPV_{DNA+} TSCC and BOTSCC.