Increasing awareness and therapeutical options to improve prognosis of HPV positive and HPV negative head and neck cancer

Impact

The results of the first study of this thesis show that there is a lack of knowledge among the Dutch population about the role of HPV in oropharyngeal cancer. In addition, only 49.7% of the study population knew of the existence of an HPV vaccine, despite the current vaccination programme against HPV related cervical and oropharyngeal cancer. If the knowledge about the role of HPV in the development of oropharyngeal cancer and the role of the HPV vaccine in the protection against these cancer types increases, hopefully the vaccination grade will increase with a decrease of HPV related cancers in the future.
The results of our study have therefore been used for the national 'Make Sense Campaign' (see attachment), which is a yearly initiative from the Dutch Working Group on Head and Neck Tumors (NWHTT), in order to create more awareness about head and neck cancer among the Dutch population and in this specific case about HPV related oropharyngeal cancer.

General practitioners (GPs) in The Netherlands are relatively well aware of HPV as a causative factor for oropharyngeal cancer, but there is a gap in knowledge on the characteristics of patients at risk for HPV associated oropharyngeal cancer. Further education on these subjects could improve disease recognition and thereby early treatment and patient survival. The GPs who participated in this study received a fact sheet with information about HPV and the role of HPV in oropharyngeal cancer. In addition, the study results have also been published as an infographic in the Dutch journal 'Huisarts & Wetenschap' (designed by Studio Wiegers, see attachment). As a consequence, we expect that the knowledge about HPV and oropharyngeal cancer among GPs in the Netherlands will increase, which will contribute to an earlier recognition of patients with head and neck cancers and to an earlier refer for further diagnosis and treatment.

In addition, there is a need to improve treatment for HNSCC, as the 5-year overall survival rate is still around 40-50%. In contrast to some other types of cancer, improving treatment for head and neck cancer remains a challenge because HNSCC is a heterogenous disease. Nevertheless, recently some promising targetable pathways for new therapeutic approaches have been identified. We tested several PI3K pathway- and CDK4/6 inhibitors for their efficacy to inhibit cell growth in HPV positive and negative head and neck cancer cell lines. The results of these studies were promising and may stimulate further research to bring these substances into clinical practice. Furthermore,

it should be tested whether or not it may be useful to combine these agents with each other as well as with radiotherapy.
We also tested the antiviral agent Cidofovir and showed that the working mechanism is different than supposed until now. Treatment resulted in DNA damage and mitotic catastrophe in the head and neck cancer cell lines, independent of HPV status. This mechanism is also seen in radiotherapy.
The results of this thesis were published in high impact scientific journals and when possible as open access articles in order to create transparency and to target a broad audience. The results have also been shared through presentations at (inter)national congresses, for example at the International Academy of Oral Oncology World Congress (2019, Rome) and the International Symposium on HPV-infection in Head and Neck Cancer (2022, Amsterdam).

Earlier research has addressed that, in general, HPV positive tumors have a far more favourable prognosis than HPV negative tumors. However, the presence of HPV in tumor cells does not predict outcome in the individual patient. A subgroup of HPV positive patients shows a less favorable prognosis with a greater risk of recurrence or development of a second primary tumor. Therefor de-intensification of treatment for HPV positive tumors has not been possible until now and the treatment of these two different subtypes of HPV positive cancers is still identical while the intensity of treatment is linked to the severity of side effects and loss of quality of life. A possible mechanism leading to differences in biological behaviour of different HPV positive tumors is viral genomic integration. However, very little is known about this until now. We have shown that oropharyngeal cancer with HPV integration show an altered expression of genes involved in cell metabolism, resulting in upregulation of the enzyme AKR1C. These tumors with increased expression of AKR1C show an unfavourable prognosis. With this insight we've delivered an additional potential factor for identifying HPV positive tumors in which treatment de-intensification can be applied. However, these results have to be confirmed in a larger group of patient. Furthermore, for tumors with an unfavourable prognosis a potential new therapeutic agent, AKR1C inhibitors, has been identified. This offers the possibility to start new (pre) clinical studies.