Oral and oropharyngeal squamous cell carcinoma epidemiology and targeted treatment

Al-Jamaei, A.A.H.

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English summary

Oral and oropharyngeal squamous cell carcinoma (OOSCC), as described in the introduction section, are the most common HN malignancies that usually occur in elderly patients, having significant death rates. Within the last three decades, many studies suggest that OOSCC incidence is increasing in patients younger than 45 years old in several countries. However, the few number of cases in this young group, compared to the elderly patients, results in marginalization for this population in most of the epidemiological studies. Lack of sufficient data could eventually lead to disastrous outcomes particularly for the young cancer patients, with regard to prevention strategies and clinical interventions. Therefore, the best approach to start measuring these disease burdens in this age group specifically was to estimate their global occurrence (or incidence) and characteristics. In **Chapter 2** of this thesis we conducted a systematic review covering four decades, to include as much as possible of the published literature which intentionally or not estimated the incidence of OOSCC in patients younger than 45 years. The study did not only include population based studies, but also the proportion literature, and both estimations ultimately revealed a significant increase in incidence of these two malignancies worldwide. Further, the observations of that study indicated two unique gender-subsite associations. First, a significant increase in the mobile tongue carcinoma was clearly seen in women in their thirties or forties of age which were neither smokers nor drinkers, i.e. not exposed to the classic risk factors. The second association was the remarkable increase in tonsils and base of the tongue cancer in white, high class society men. Surprisingly when analyzing the data for Western countries, we found a significant reduction in incidence of these tumors in the Netherlands only.

The results of chapter 2 motivated us to know more about the incidence of these malignancies in the Dutch population. To create deeper understanding of these diseases, we also investigated the prevalence of the conventional risk factors such as smoking, drinking and HPV infection at the population level, and made gender specific estimates for each age group. **In chapter 3,** we studied for the first time the trend of incidence of oral squamous cell carcinoma by join point analysis regression that provides a complete evaluation for rate changes throughout the years. In that study we also for the first time classified the young Dutch patients into two subgroups (20-34 years and 35-44 years). The results showed a significant increase in annual incidence for patients younger than 35 years, while an opposite observation was found for the other young group (35-44 years). Additionally, a profound and surprising reduction in annual percentage changes for the adults population (45-59 years) since 1997 onwards was noticed . For the elderly patients (60 years and more), the incidence is increasing, with double rates in the women compared to the men. Regarding

the prevalence of smoking and drinking among the patients, the overall percentages were high for all age groups. However, it is important to keep in mind that we evaluated only risk factor data of the last two years of the studied period (2015,2016) because those were the years when the Netherlands Cancer Registry (NCR) launched risk factor data collection. In chapter 4, we focused on the incidence of oropharyngeal SCC and evaluated the related risk factors smoking and drinking, as well as, for the first time, the prevalence of HPV infection, in a population-based study. To study trend changes during the entire studied period of time which ranged from 1989-2016, we used join point regression software. As indicated previously, the NCR began collecting data for the classical risk factors of OOSCC as part of a national initiative toward a comprehensive registration in 2015. Therefore, the risk factor data for OPSCC were only available for the last two years of the studied period (2015,2016). Our results showed a significant decline in the annual percentage changes for the young patients with ages 35-44 years old and for those aged 45-59 years since 2000 onwards. In patients older than 60 years, incidence rates increased overall, with an annual percentage change for women being consistently higher than men. Importantly, we found that the percentage of Dutch patients with HPV-related oropharyngeal carcinoma is approximately 31%. Overall, the study found that the vast majority of the patients were tobacco smoker and alcohol drinker, which makes a pivotal role for HPV infection in the Dutch patients less likely.

Apart of the epidemiology, one aim of this thesis was to contribute in improving the outcome of the patients affected with tongue squamous cell carcinoma (TSCC). This is because TSCC is characterized by an aggressive clinical and biological behavior which is, however, often only diagnosed at a late stage and accordingly has the worst prognosis among all head and neck cancers. Currently, the highly improved understanding of the molecular pathways involved in malignant transformation facilitates the discovery of many valid biomarkers in different cancers. A biomarker by definition is an objective measure such as, a gene, a protein, enzyme, or hormone that can reflect the entire spectrum of the disease, from the earliest features to the end stages. It is important to mention that the journey of any biomarker from the bench to clinic is a very long and challenging one. At the simplest level, effectiveness of the biomarker cannot be measured by only one discovery study, but by the reproducibility of the results in different and independent populations. Hence, the initial key step to bring a newly discovered biomarker towards clinical implementation is independent replication. In **Chapter 5**, we assessed the validity level of the published studies concerning tongue carcinoma biomarkers. We included the relevant papers across different TSCC sample sources, i.e., body fluids (saliva, serum/ plasma) and tissues. Unfortunately, we noticed an

abundance of studies that described single or multiple biomarkers only in one publication (66%). Nonetheless, 10 biological markers demonstrated a consistent association between their presence and specific clinical outcomes. Collectively, these 10 biomarkers qualified as the most promising candidates for TSCC diagnosis and prognosis. Further research exploring the validity of these biomarkers in a prospective manner using single biomarker or a panel of biomarkers is urgently needed.

Although conventional treatment (chemo radiation therapy) is a commonly used modality for treating advanced TSCC, it often fails to eradicate the neoplastic cells. One reason is the need to deliver a higher dose of the radiation or drugs to kill the cancerous cells, but this ultimately will cause an irreversible damage to normal tissue cells as well. Hence, a potential solution is to enhance the selective intracellular delivery of the current medications in a higher dose to the tumor cells together with radiotherapy, thereby keeping the normal cells unaffected. This could be achieved by finding a suitable receptor which is highly expressed on the targeted tumor cells prior to, or upregulated after exposure to radiation, but absent or only present at low levels in normal tissues. In an attempt to identify a candidate receptor, we performed **in chapter 6** an analysis for c-Met expression upon exposure to irradiation. As a matter of fact, this receptor has been investigated in a set of cell lines of several tumors and a five-fold increase in its expression upon radiation exposure was observed, particularly in the cells showing radiation resistance. As a first step, we determined the intrinsic relative radiosensitivity character of the cells, using viability assays, by exposure of a panel of 6 TSCC cell lines to 4Gy of ionized radiation. Next, we investigated the c-Met expression pattern in our panel thoroughly by means of western blot and flow cytometry. In contrast to previous studies, we found variation in the overall expression of the c-Met that was not related to the intrinsic radiosensitive or radioresistant nature of the cells. Regarding the cell surface expression patterns, all but one of the cell lines showed abrupt downregulation in this receptor expression, but then increased with time. The remaining cell line showed an opposite pattern. For the intracellular expression, most of the cell lines showed a gradual increase in c-Met with time, peaking at day 5 after radiation which was obviously connected to mRNA synthesis. Since the cross talk between c-Met and EGFR has been widely demonstrated, we also investigated the expression of EGFR on the same cell lines. Strikingly, only in the radio resistant cell lines we found consistently c-Met and EGFR co-expression. Last but not least, we observed that the most radiosensitive cell line SCC-40 also acquires the highest invasive potential upon radiation. In conclusion, our analysis provides novel insights into the dynamic changes in the intracellular and extracellular c-Met profiles in native and radiation-exposed TSCC cells. Unfortunately, the relatively low surface expression percentages

disfavor the use of c-Met for nanoparticle-mediated targeted delivery, and shows the importance of surface expression analysis of cancer targeting candidates prior to developing targeted therapies. Further research is warranted to identify more suitable tumor cell surface markers for nanoparticle surface targeting.