Streszczenie w języku angielskim

Genetic determinants of Salivary Gland Carcinomas

Salivary gland carcinomas (SGCs) constitute a heterogeneous group of malignancies that are distinct both histopathologically and clinically. Although they occur rarely, they are characterized by an unpredictable disease course, numerous relapses and significant mortality. Distant metastases are presented in 10-40% of cases, with lungs being predominantly affected. Moreover, a significant increase in morbidity and mortality in SGCs is predicted in the near future. According to the World Health Organization (WHO), more than 20 histopathological types of SGCs are recognized. Thus, diagnostic accuracy might pose numerous difficulties. In the available literature, a number of cases of misdiagnosis of malignant tumours as benign have been shown. Nowadays, unique genetic alterations are considered in the differential diagnosis. However, studies have shown that exceptional lesions in particular type might not have a prognostic or predictive impact. Therefore, further comprehensive studies are required. Suspicious lesions, especially those with rapid growth, facial nerve palsy, ulceration or painful swelling, indicate malignancy and should be preferably investigated by multiparametric magnetic resonance imaging (MRI). Radical surgical excision is a standard of treatment, with further radiotherapy (RT) or chemoradiotherapy (CRT). Nevertheless, there is still a lack of reliable, evidence-based regimen methods, especially in recurrent or metastatic (R/M) cases. There are attempts to find more specific therapies in SGCs and to identify relevant markers, including molecular factors, therefore, it is imperative to optimize protocols and increase patients' access to more personalized therapies. However, the rarity of SGCs prevents clinical trials in this group, which creates a treatment gap. The chance for the patients is to join basket trials, where the therapeutic approach is tailored to the profile of specific molecular alterations. Additionally, there is an imperative need to determine prognostic markers in SGCs. However, the utilization of genetic analysis in clinical practice, including next-generation sequencing (NGS), is still limited. Wider usage of NGS contributes to better disease course predictions and more suitable and personalized treatment options. It also improves oncological supervision for SGCs patients.

The aim of this dissertation was to characterize genetic alterations in the most commonly occurring types of salivary gland carcinomas, especially those related to relapses or metastases, thus worse patients' oncological outcomes.

The study *Molecular landscape of salivary gland malignancies. What is already known?* is a comprehensive review that presents the genetic variety of selected histopathological SGCs types. The most frequently detected alterations in SGCs, including gene fusions, somatic mutations, and copy number variations (CNVs), were collected. Additionally, those that might be associated with unfavourable patients' outcomes were presented along with the clinical characteristics of SGCs.

The second study entitled *FGFR2 point mutation in 2 cases of pleomorphic adenoma progressing to myoepithelial carcinoma* is a case report with conducted genetic analysis of pleomorphic adenoma (PA) and myoepithelial carcinoma ex pleomorphic adenoma (MECA ex PA) tissues.. Comparison of tumour samples of both patients from benign and malignant lesions revealed various common CNVs and *FGFR2* point mutations. Taking into consideration the available literature, these genetic aberrations were established as related to carcinogenesis, quick disease progression and poor oncological outcomes.

The third, retrospective, original research entitled *Potentially actionable molecular alterations in particular related to poor oncologic outcomes in salivary gland carcinomas* is the NGS analysis of the most common histopathological types of SGCs. The additional aim of the study was to evaluate the relation of genetic changes to relapse or metastasis. The analysed material was obtained from 40 patients with the primary diagnosis of SGCs, who were hospitalized in the Otorhinolaryngology, Head and Neck Surgery Department of the Medical University of Warsaw between 2010-2017 and for whom surgical excision of malignancy with radical intent was performed. The clinicopathological data, including sex, age of diagnosis, localization of the tumour, tumour stage, as well as patients' outcomes were described. The predominant genetic alterations in the study cohort as well as in the group of patients with unfavourable outcomes, were *NF1* (24% vs. 32%), *TP53* (22% vs. 32%) and *CDKN2A* (14% vs. 21%), respectively. Moreover, *TP53* mutation was established as a relevant negative prognostic factor for overall survival (p=0.04). *TERT* promoter mutation and *TERT* amplification, p. Ile35Thr mutation in *CTNNB1 were found in* myoepithelial carcinoma *(*MECA), *and* adenoid cystic carcinoma (*AdCC), respectively. ERBB2 alterations were remarkable for salivary duct carcinoma ex PA (SDC ex PA). Moreover, abnormalities detected in the study presented the possibility of targeted treatment in the future, especially in patients with poor outcomes.*

In summary, salivary gland carcinomas belong to rare entities with diverse clinical behaviour and molecular landscape. They are characterized by an unpredictable disease course and

considerable mortality. The prognosis of increasing morbidity and mortality are predicted for the following years. There is still a lack of prognostic biomarkers as well as optimal therapy protocols based on scientific evidence, in particular for patients with R/M SGCs. The utilization of the NGS analysis in clinical practice for SGCs is essential for improving patient prognosis and providing opportunities for more personalized and precise therapy. However, further prospective multicenter research with a suitable cohort study is needed. It is expected that, in the near future, NGS analysis will be a standard tool in clinical practice in rare cancers and will enhance patients' outcomes.