Parotid Cancer

13

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Contents

Abstract

Salivary gland carcinomas are a heterogeneous group of tumors that comprise about 5–10% of all oropharyngeal cancers. Tumor classification and stage have a significant impact on patient survival. Primary treatment of salivary gland carcinomas is surgical resection in combination with postoperative radiotherapy and/or chemotherapies when required. Molecular abnormalities as potential therapeutic targets differ between certain tumor types.

13.1 Introduction

Salivary glands comprise three pairs of the major glands (parotid, submandibular, or sublingual) and hundreds of the minor salivary glands throughout the mucosa of the respiratory tract. Salivary gland carcinomas (SGCs) are relatively rare malignancies that occur in around 1 per 100,000 people per year counting, accounting for 5–10% of all oral and pharyngeal cancers. The majority of carcinomas occur in the parotid

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gland (70–75%) followed by the submandibular gland (10–15%), the sublingual gland (<1%), and minor salivary glands [1, 2].

Salivary gland neoplasms can be classified into 24 subtypes of malignant epithelial tumors. Mucoepidermoid carcinomas (MECs, 34%), adenoid cystic carcinomas (ACCs, 22%), and adenocarcinomas (ADNs, 18%) are the most common SGC although demographic and/or geographic aspects may have a significant impact on the incidence of tumors. Primary squamous cell carcinoma (SCC) of the salivary glands is described in the literature although some authors suggest that these tumors might be metastatic intraparotid lymph nodes originating from cutaneous SCC [3–5].

There is no clear evidence that SGC is associated with smoking or alcohol intake, while radiation exposure and UV light exposure are relevant risk factors. Nitroso compounds in rubbers may explain a higher incidence of SGC in rubber industrial workers [6–8].

SGC usually presents as painless swelling. The presence of facial nerve palsy, skin fixation, and cervical lymphadenopathy is highly suspect for malignancies. Clinical examination can be amended with fine-needle aspiration biopsy for cytological examination. Magnetic resonance imaging, computer tomography, and ultrasound are important for diagnosis although definitive diagnosis can only be performed with histologic examination.

The vast majority of malignant salivary gland tumors originate from acinar/ductal epithelial cells and/or myoepithelial/basal cells. Monophasic tumors have one cellular component (e.g., ACN, salivary duct carcinoma, and myoepithelioma), while biphasic tumors originate from both cell types (e.g., ADN, ACC, and epithelial-myoepithelial carcinoma) or demonstrate specific cellular differentiation (e.g., MEC) [5].

Primary treatment of salivary gland carcinomas is surgical resection in combination with postoperative radiotherapy and/or chemotherapies when required. Some authors have described positive effects of neutron-beam radiation due to its reduced toxic effects of the surrounding tissue [1, 9, 10].

SGC are a very heterogeneous group of neoplasms. Numerous general carcinogenic molecular mechanisms, including c-kit, EGF/EGFR, VEGF/VEGFR ErbB-1, ErbB-2, and Her2, are being examined in SGC. Furthermore, loss of the vascular protein sorting-associated protein 4b homolog (VPS4B) might promote carcinogenesis, leading to a prolonging effect of EGFR [11].

Molecular abnormalities, including Her2, c-kit, and EGFR as potential therapeutic targets in certain SGC types, are being investigated and will be discussed below in detail according to the most frequent tumor entities [1].

13.2 Mucoepidermoid Carcinoma

MECs originate from the main ducts and are composed of basal, intermediate, and differentiated cells and may also develop in the lung, skin, breast, cervix, and thyroid [3]. Carcinomas can be graded into low-, intermediate-, and high-grade tumors according to architectural formation and cellular and cytological features, which is

of essential prognostic importance [3]. MECs are usually positive for CK5, CK6, CK7, CK8, CK14, CK18, CK 19, EMA, carcinoma antigen, and p63, while negative for CK20, SMA, muscle-specific actin (MSA), and S100. Especially p63 is an important marker to differentiate MEC from ACC and low-grade MEC from mucous retention cysts and papillary adenomas [1].

A t(11;19)(q21-22;p13) tumor-specific gene alteration occurs in 40–70% of MEC. The occurrence of this translocation has been described in other organs, such as the lung and thyroid, but not in other SGCs. It involves the MECT1 gene and the MAML2 gene leading to a fusion gene. The effect on signaling pathways is largely unknown, although it has been shown that it leads to an upregulation of AREG as a ligand of EGFR. This autocrine process promotes MEC growth and survival [12, 13].

Similar to mammary carcinomas, Her2 is a biomarker overexpressed in about 20–40% of MECs. In contrast, rare cases of ACC express Her2. EGFR is overexpressed in about 50% of MECs. Agulnik et al. investigated the effect of lapatinib, an oral tyrosine kinase inhibitor of EGFR and Her2, but no responses were observed [2, 3, 14].

13.3 Adenoid Cystic Carcinoma

ACC develops in both, the major and minor salivary gland, as well as in other sites, e.g., the bronchial tree, breast, cervix, and skin. As in sinonasal carcinomas, three tumor patterns (tubular, cribriform {Swiss cheese}, and solid forms) have been described. Characteristically, tumors grow slowly with early perineural invasion (e.g., leading to paresis of facial nerve in parotid gland tumors). They show a high level of hematogenic metastasis; thus, these biphasic tumors are typically associated with poor outcome [3].

ACC typically expresses CK7, CAM 5.2, calponin, SMA, SMMHC, p53, SOX10, and S100. Overexpression of Ki-67, p53, and H3K9me3 and low expression of H3K9AC are associated with poor survival [1, 15, 16].

Persson et al. described a specific t(6;9) (q22-23; p23-24) gene translocation fusing the *Myb* oncogene to the transcription factor gene *NFIB* and consequent potential activation of *Myb* targets occurring in approximately 60% of ACC. Furthermore, *Myb* overexpression seems to be triggered by other unknown pathways because it occurs in approximately 90%. Due to the frequent expression in ACC, *Myb* appears to be a useful marker for the differential diagnosis of other salivary gland tumors [13, 17, 18].

C-kit is a transmembrane cell surface receptor encoded by the c-kit gene associated with cell migration, differentiation, and proliferation. Hotte et al. observed c-kit overexpression in 90% of ACC, but did not find any mutation or amplifications in the corresponding gene loci. In contrast to ACC, c-kit overexpression was not found in MEC. Especially the predominant c-kit expression in its inner ductal cells is useful to differentiate the ACC from its mimics, although it may also be expressed in low-grade adenocarcinoma. The use of Imatinib as a c-kit inhibitor is a new therapeutic approach but first clinical trials did not show evidence of tumour

response. Alternative target therapies may show more promising effects in the future [1, 19, 20].

EGFR overexpression appears in about 30–40%, but, similar to c-kit, no gene mutations or amplifications have been described; thus, the therapeutic impact of EGFR antagonists remains uncertain.

NF-kB being expressed in some ACC may be antagonized by bortezomib used for myeloma treatment. Argiris et al. reported disease stabilization in advanced tumors but no objective responses in a clinical trial using treatment protocols including bortezumib [21].

13.4 Acinic Cell Carcinoma

ACNs make up about 7–17% of all malignant tumors of SGC affecting the parotid gland in the vast majority of cases. Clinically, they often lead to local pain perception and occur bilaterally in 30% of the cases. "High-grade" and "low-grade" tumors can be differentiated, leading to dramatic differences in therapeutic outcome [1, 22].

ACN is a biphasic tumor mostly expressing CK7 and CAM 2.2. ACNs are usually negative for p63, SMA/SMMHC/calponin, and CK20. Originally described in gastrointestinal stromal tumors, the DOG1 protein is expressed in ACN and may be used to be distinguished from mimics, e.g., mammary analogue secretory carcinoma [23].

Very little is known about the genetic profile of ACC. Mitelman et al. reported 11 cases with abnormal karyotypic profile, while common changes were described in three trisomy eight cases only [24, 25].

The complex PI3K axis plays an important role in tumorigenesis, leading to upregulation of several regular tumor growth factors, including EGFR, HER2, and VEGF. Diegel et al. reported on the activation of the pathway in adenomatous polyposis coli (APC)/PTEN transgenic mice that lead to the formation of AZN [26].

13.5 Adenocarcinoma

ADNs show a very aggressive behavior. ADNs express hormonal and growth factors similar to mammary and epipharyngeal adenocarcinomas.

In contrast to ACC, EGFR overexpression (40%) and *EGFR* mutations have been described in ADN; consequently, EGFR inhibitors may play a therapeutic role in this subset of patient. Results of clinical trials using lapatinib, gefitinib, cetuximab and trastuzumab, all EGFR and Her2 antagonist showed limited success. Alternative treatment protocols may show more beneficial effects in the future [3, 27, 28].

Androgen receptors are a pathologic marker for salivary duct carcinomas found in about 20–40% of cases. Similar to antiestrogen therapies, the identification of these receptors might be therapeutically useful.

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