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Review

New concepts of personalized therapy in salivary gland carcinomas

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ABSTRACT

Salivary gland carcinomas are rare tumours and therapy strategies are less standardized than in lung, gastric or breast cancer.

Therapy is based on surgery, but not all carcinomas are completely resectable, e.g. because carcinomas often show infiltration of nerves. For further therapy decision pathology is recommended, but evaluation of potential targets for personalized therapy is not part of the routine panel. Many salivary gland carcinomas can be resistant to radio- and/or chemotherapy, which limits therapeutic options.

This review summarizes new concepts for personalized therapy in salivary gland carcinoma patients. Targeting growth receptors HER2, EGFR, AR and ER is possible but, in some studies, potential target molecules were not adequately tested before therapy. In addition, approximately 20–25% of carcinomas have RAS mutation (mainly H-RAS), which could explain resistance to therapy.

Possible therapy options in the future could be immunomodulation (inhibition of PDL1/PD1 signalling), nanoparticles (gold nanoparticles conjugated to cetuximab can increase radiosensitivity) and drug delivery systems (trastuzumab emtansine/T-DM1).

Introduction

During embryonal development, the primitive oropharynx epithelia form tubules which differentiate to adenoid tissues of salivary glands and lungs. Despite this similar ontogenetic origin, both tissues have different vulnerability to carcinogenic factors and may give rise to different adenoid cancer types. Most lung cancers can be grouped into neuroendocrine/small cell, adenocarcinomas and squamous carcinomas and the major risk factor is smoking. In contrast to lung cancer (smoking) but also in contrast to oral squamous carcinomas (smoking, alcohol, human papilloma virus), salivary gland carcinomas have no such common risk factors [1,2]. Remarkably, smoking is the major risk factor for benign Warthin tumours, but this salivary gland neoplasm almost never transforms to malignancy [1]. Predisposing risk factors for carcinomas are discussed [1] but radiation stress is uncommon, hormonal factors might also be less important, since there is no striking female predominance, and viral association is uncommon in most ethnic groups [2–4].

It is remarkable that salivary gland carcinomas are such a heterogeneous group of cancer with many different adenoid subtypes but also epithelial-myoepithelial and epithelial-mesenchymal differentiations. Among lung and breast carcinoma patients, only few develop salivary gland carcinoma-like neoplasms, such as adenoid cystic carcinomas (ACC) [5]. In concordance with these findings, the clinical course of salivary gland carcinomas varies enormously. While the majority of patients face a rather indolent course of disease, a fraction of patients faces rapid tumour growth and deterioration, indicating an aggressive course of the disease.

In general, in Europe, salivary gland carcinomas are rare tumours (<1% of all malignancies [1]), which mainly explains why therapy strategies are less standardized than in lung, gastric or breast cancer. In this review we summarize the therapy

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algorithm which is currently used. In general, treatment concepts are still based on surgery and, after histopathological examination, on radio- and/or chemotherapy. In contrast to common cancers targeted therapy is not a standard in rare salivary gland carcinomas. Therefore, we discuss the potential of new therapy options which are based on identification of molecular defects in a given patient tumour sample for selecting inhibitor molecules and therapeutic antibodies (see Fig. 1).

Current strategies for treatment of patients suffering from salivary gland carcinomas

Curative or palliative surgery or biopsy for tumour sampling

The mainstay of treatment of salivary gland carcinoma consists of surgery [6,7]. However, the surgical challenge remains the fact that salivary gland carcinomas, in particular ACC, often show infiltration of the facial nerve in the parotid gland or trigeminal nerve branches [8]. Furthermore, depending on the tumour localization, resection of bone, nerves and muscles requires complex strategies for reconstruction [9–12]. Improvement has been achieved by computed tomography-based 3D models before the resection which help to plan reconstruction by autologous tissue and individually adapted meshes [13–15]. Salivary gland carcinomas can be slow-growing and therefore patients can present at advanced stages with large primary tumours and/or metastasis. In these cases, curative resection may not be possible but at least a biopsy or partial resection should be taken for pathological evaluation. For further therapy decision, pathology is recommended, in order to clarify tumour subtype, grading of differentiation, nerve infiltration as well as status of the resection margins.

Current role of pathology: diagnosis but no standardized screening for molecular targets

In the last decades, the contribution of pathologists to further therapy planning has changed in many cancer types, in particular standardized evaluation of receptor protein expression in breast and gastric cancer samples and mutation analysis in lung cancer samples for therapy stratification. In contrast to breast, lung and gastric cancer, in salivary gland carcinomas, evaluation of potential targets for personalized therapy is not part of the routine panel. Diagnosis is still mainly based on conventional histopathology [1]. Until now, the aim of additional immunohistochemistry and fluorescence *in situ* hybridization (FISH) has been to verify the diagnosis, e.g. expression of the KIT receptor (CD117) or rearrangement of MYB transcription factor in ACC [16]. After the diagnosis has been established, radio- and/or chemotherapy may follow. In particular radiotherapy includes a variety of possible modalities.

Radiotherapy: many modalities but not defined standard

Neoadjuvant therapy is not standard in salivary gland carcinomas. After surgery, in the case of gross residual tumour, stage III/IV disease, microscopically positive margins, perineural invasion, bone infiltration, multiple involved lymph node metastases and/or extracapsular lymph node extension, additional adjuvant or additive radiotherapy can be applied [17–20]. Postoperative radiotherapy has been shown to improve locoregional control [18,19,21,22] with the potential to translate into improved overall survival [23,24]. Besides excellent outcomes, minimal side effects and preservation of good quality of life scores can be achieved [25]. However, in the absence of large randomized trials with

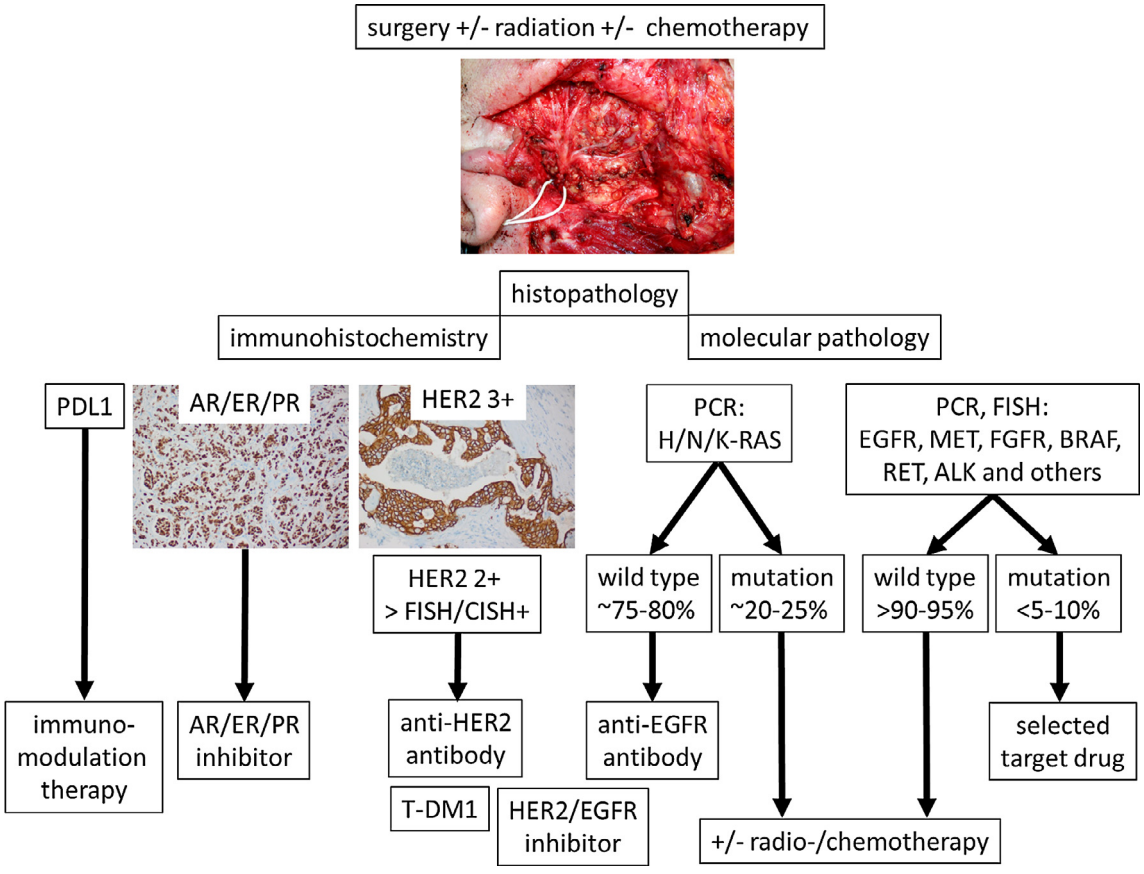

Fig. 1. Possible algorithm for salivary gland carcinoma patient stratification for individual therapy strategies.

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