Malignant salivary gland tumours

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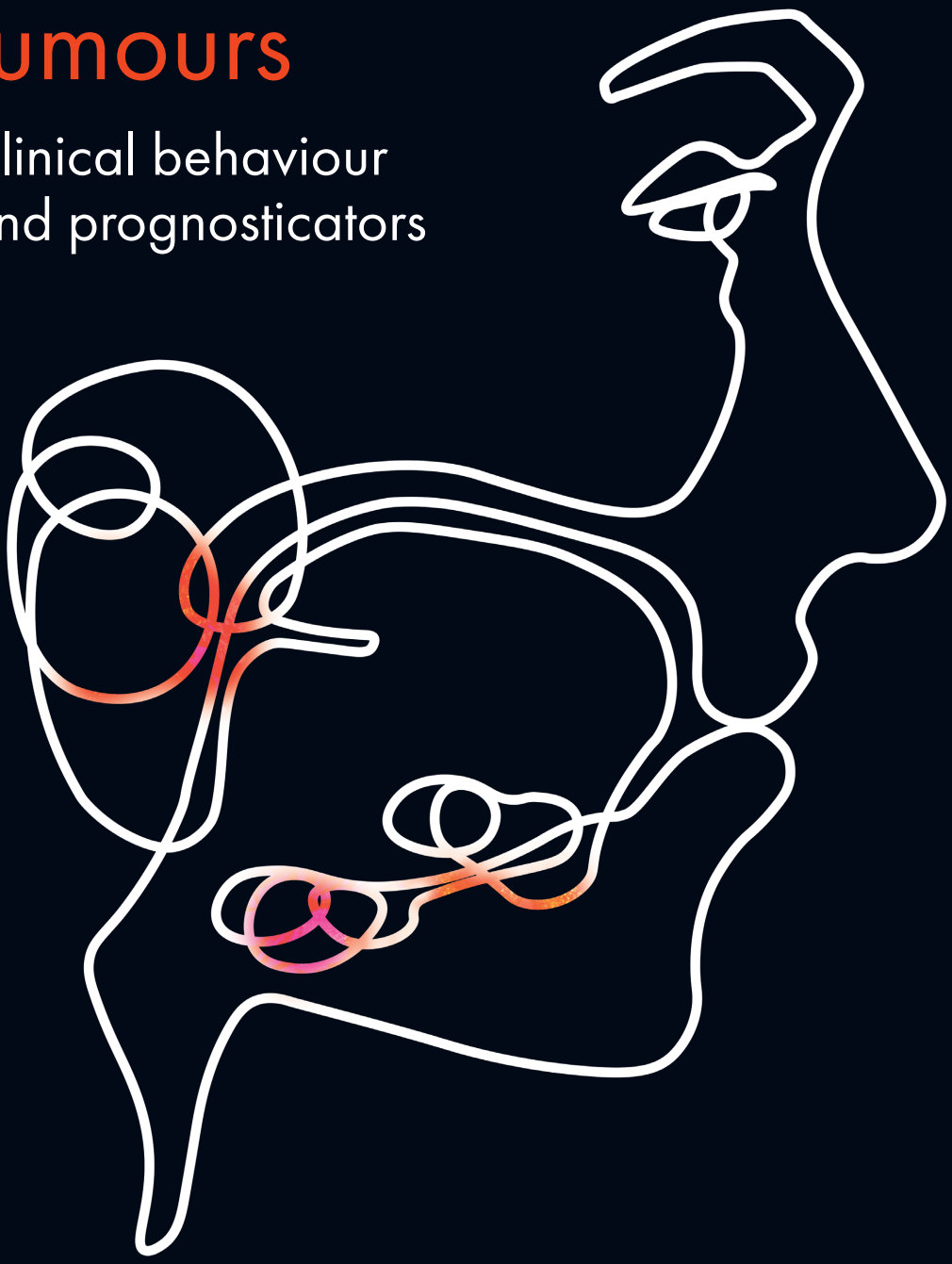

Stijn van Weert

MALIGNANT SALIVARY GLAND TUMOURS: CLINICAL BEHAVIOUR AND PROGNOSTICATORS

COLOFON

Malignant salivary gland tumours:
Clinical behaviour and prognosticators

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Clinical behaviour and prognosticators

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“Essut nie zonne wind waar zoggut nie zo hard wèien.”

Jos van Liempd

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CHAPTER 1.

General Introduction

General introduction

1.1 Anatomy and physiology of the salivary glands

The largest salivary gland is the parotid (par-otid= around the ear) gland. It is situated in the pre- and infra- auricular region. The zygomatic arch marks the cranial extent and the masseter muscle is situated anteriorly and is partially overlapped by the gland. Posterior boundaries are the external auditory canal, mastoid process and the upper part of the sternocleidomastoid muscle. Medially, the gland has a narrow relationship with the styloid process and its accompanying muscles as well as the external carotid artery. The parotid duct, known as Stensen's duct, runs over the masseter and pierces the buccinator muscle to end as the papilla in the cheek mucosa at the level of the second upper molar. The facial nerve, emerging from the stylomastoid foramen, divides the parotid gland into the superficial and the deep lobe of the gland. The retromandibular vein radiologically delineates the superficial from the deep lobe. Eighty percent of the parenchymal tissue lies in the superficial lobe. The gland itself is innervated by the glossopharyngeal nerve (ninth cranial nerve) for saliva production. Sensory innervation is supplied by the auriculotemporal nerve and the great auricular nerve.

The external carotid artery and its terminal branches within the gland, namely, the superficial temporal and the maxillary artery, supply the parotid gland. Venous return is to the retromandibular veins which is a unification of the superficial temporal and maxillary veins. The gland produces serous saliva which has a watery aspect.

The submandibular (sub- mandibular= under the mandible) gland is situated beneath the mandible in a triangle formed by the mandible superiorly, the anterior belly of the digastric muscle anteriorly and the posterior belly of the digastric muscle forms the posterior boundary. The duct, known as Wharton's duct, accompanied by a portion of "deep" lobe tissue, runs over the posterior border of the mylohyoid muscle, crosses it laterally and ends at the level of the anterior floor of mouth known as the caruncula just lateral to the lingual frenulum. The duct runs over the lingual nerve intra- orally. The gland is innervated by the chorda tympani, a branch of the facial nerve and joins the trigeminal nerve at the submandibular ganglion. This parasympathic pathway triggers excretion.

The gland receives its blood supply through submental and sublingual arteries and common facial and lingual veins.

The secreted saliva is more mucinous than the saliva produced in the parotid gland.

The sublingual (sub- lingual= under the tongue) gland is located at the level of the floor of mouth just beneath the mucosa. The anterior and lateral border is the mandible as it lies on top of the mylohyoid muscle. It has many excretory ducts known as Rivinus's ducts. The largest of these is Bartholini's duct which joins Wharton's duct at the level of the previously mentioned caruncula. The sublingual gland is innervated by the submandibular ganglion receiving fibers from the lingual nerve. The blood supply is similar to the blood supply of the submandibular gland and the type of saliva secreted is mixed but mainly mucinous. The salivary glands are exocrine saliva producing glands. The total daily saliva production ranges from 500- 1000 ml.

Figure 1 shows the anatomy of the major salivary glands.

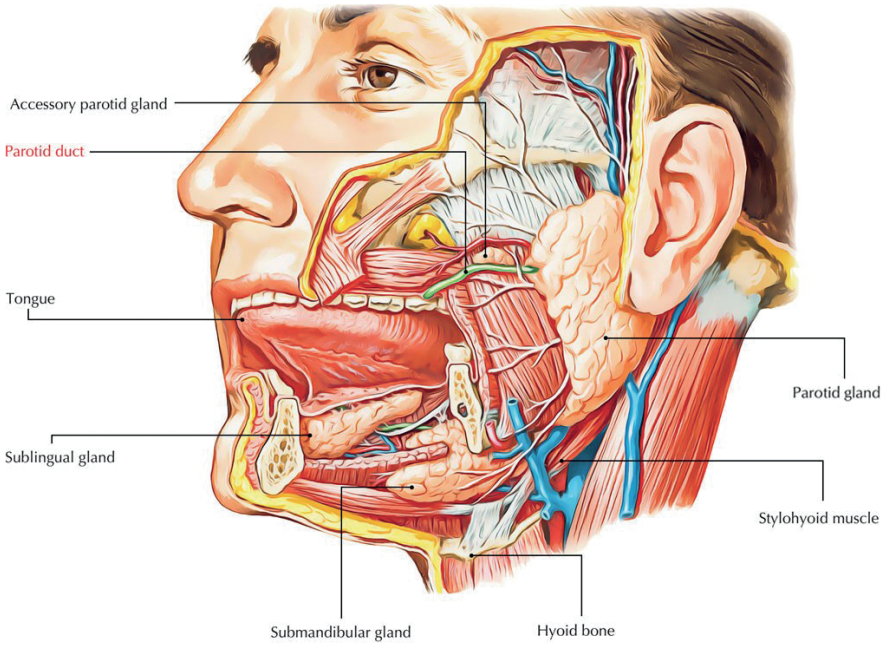

Figure 1. Anatomy of the major salivary glands. Source: © Elsevier, Inc., www.nettterimages.com

The lip, oral cavity, oropharynx as well as the larynx contain numerous minor salivary glands. These glands mainly produce mucous saliva.

Neoplasms of the salivary glands

Solid tumours of the parotid gland are predominantly benign (90%) with pleomorphic adenoma and Warthin's tumour being the most common. The parotid gland is however the most affected organ for salivary gland malignancy.

The ratio for malignant salivary gland tumours of the submandibular gland is clearly higher than for the parotid gland; approximately 50% of tumours of the submandibular gland are malignant.

Neoplasms of the sublingual gland are extremely rare. When they occur, approximately 90% of these lesions prove to be malignant.

With regard to neoplasms of the minor salivary glands, around 60- 80% of solid tumours are malignant (mainly mucoepidermoid carcinoma (MEC) and adenoid cystic carcinoma (ACC) where the most predominant benign tumour is pleomorphic adenoma (PA).

1.2 Epidemiology and histopathology of malignant salivary gland tumours

Malignant salivary gland tumours (MSGTs) constitute 1-4 % of all head and neck cancers and are therefore considered rare. After nasopharyngeal- and nasal cavity cancer it has the lowest incidence of head and neck cancer in the Netherlands.[1] Both the major (parotid, submandibular and sublingual; figure 1) and minor salivary glands are affected but different subtypes of MSGTs have a predilection for both major and minor glands. Clinical and pathological staging is done according to the TNM- staging system, eight edition, of the Union for International Cancer Control (UICC) and the American Joint Committee in Cancer (AJCC).[2,3] Minor gland disease is staged according to the subsite involved (e.g. oral cavity, oropharynx) whereas major gland carcinoma has its own staging.[2,3]

All age groups are affected with a peak incidence between the fourth and seventh decade. Salivary gland cancer is very rare in children. A recent analysis using the Surveillance, Epidemiology and End results database (SEER) in the U.S. showed 245 cases over a 10-year period in childhood, predominantly in the age group over 10 years old (92%).[4] The most common diagnosed MSGTs in children are mucoepidermoid carcinoma (MEC) and acinic cell carcinoma (AciCC).[4,5]

The age distribution for the Netherlands over the last three fully registered years (2016- 2018) is shown in figure 2 with a clear predominance in the seventh decade.

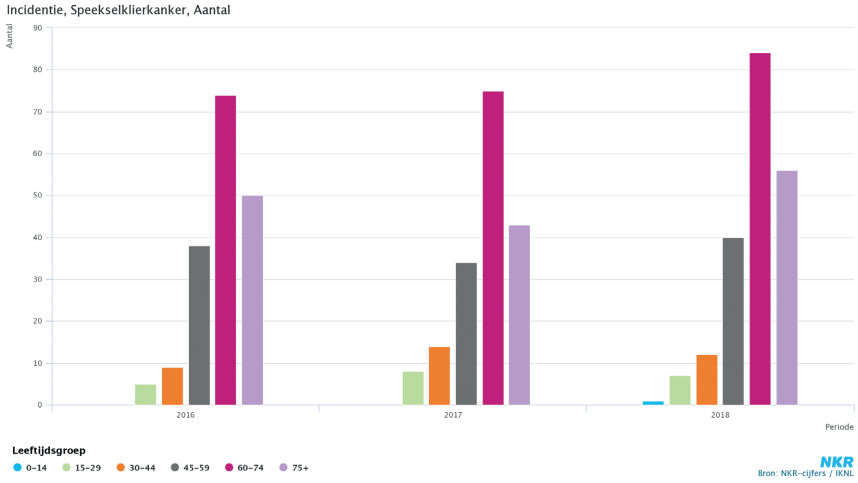

Figure 2. Age distribution relative to incidence for MSGTs in the Netherlands for 2016- 2018.

Yearly, around 200 new cases are registered in the Netherlands with an incidence of 1.4 per 100.000. The rarity of MSGTs is confirmed in figure 3 which shows the yearly incidence of MSGTs (green) in relation to the incidence of head and neck cancer overall (blue) in the Netherlands.

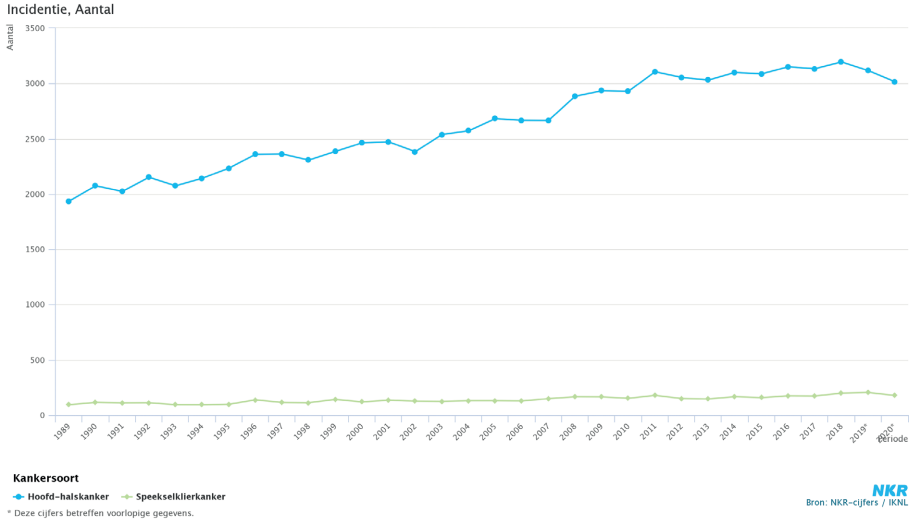

Figure 3. The incidence of MSGTs and head and neck cancer overall from 1989 to 2020*. MSGTs in green, head and neck cancer overall in blue. * Numbers are not definite due to ongoing registration.[6]

Figure 4 depicts the incidence of MSGTs relative to gender- male in blue, female in purple- in the Netherlands which shows a relatively equal distribution between sexes although there have been reports on a female preponderance in the literature. There is a trend observed for increasing incidence for both sexes over the last decades which is observed in other studies as well.[6,7]

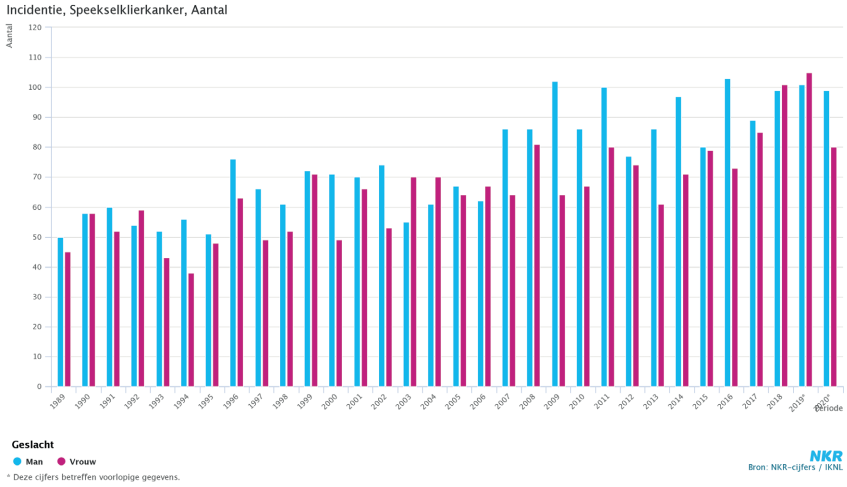

Figure 4. Incidence of MSGTs relative to gender from 1989 to 2020*. Blue is male, purple is female. * Numbers are not definite due to ongoing registration.[6]

A history of MSGT (and pleomorphic adenoma) in females may increase the risk for developing breast cancer most likely due to the similarity of salivary -and breast tissue and the influence of female hormones as salivary gland tissue is known to express hormonal receptors.[8] Previous radiation exposure of the head and neck area is another known risk factor for developing MSGTs.[9-13] In the Netherlands, overall survival (OS) is best in the age group between 18- 44 years with a 5- and 10-year survival of 96 and 94% respectively. OS declines with age with a 5- and 10-year OS of 54% and 32% in patients aged over 75. OS for all age groups combined is 65% for 5-year OS and 56% for 10-year OS. OS is negatively associated with high grade tumours and advanced stage disease. Figure 5 shows survival for patients diagnosed between 2001-2010 and 2011- 2018 respectively.[6]

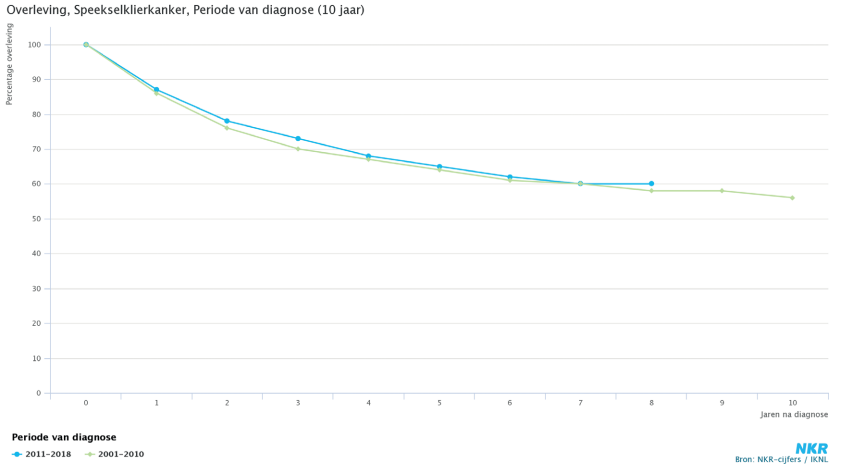

Figure 5. Overall survival (OS) for patients with MSGTs diagnosed between 2001- 2010 (green) and 2011- 2018 (blue)[6]

There is a near equal distribution of early and advanced cases (stage I-II vs. stage III-IV) at time of diagnosis. Stage I and IV are predominant in this respect.[1]

The spectrum of histopathological diagnoses in MSGTs is broad (20 known subtypes according to the 4th edition of the WHO classification for salivary gland tumours of the head and neck) and the clinical course varies from indolent to rapidly progressive disease with a high tendency for developing recurrent and metastatic disease.[14-16] All known histological types of MSGTs are shown in table 1 divided in low and high grade types. Some tumour types have both low and high grade features. Although adenoid cystic carcinoma (ACC) is considered high grade overall, it is a mixed type tumour with cribriform, tubular and solid nests where its solid component truly represents aggressive features.[17] For MEC, its high grade variant has a clearly more fulminant clinical course than the more prevalent low grade MEC.[18-21] The intermediate grade MEC is relatively hard to stratify due to different grading systems used for MEC possibly leading to over- and underestimation.[15,22-27] There have been recent updates in nomenclature.[28] The secretory carcinoma (previously known as mammary analogue secretory carcinoma (MASC); mimicking AciCC) described for the first time approximately 10 years ago is currently named secretory carcinoma. The current polymorphous adenocarcinoma was previously referred to as polymorphous low grade adenocarcinoma. High grade transformation (HGT) has gained more attention in the most recent (4th edition, 2017) classification of head and neck tumours by the World Health Organization (WHO) and is predominantly recognized in ACC and AciCC as well as in epithelial- myoepithelial carcinoma.[16]

Low grade	**High grade**
Acinic cell carcinoma (AciCC)	**High grade mucoepidermoid carcinoma (HG MEC)[a]**
Low grade mucoepidermoid carcinoma (LG MEC)	**Adenoid cystic carcinoma (ACC)[b]**
Epithelial- myoepithelial carcinoma	Mucinous adenocarcinoma
Polymorphous adenocarcinoma	Squamous cell carcinoma
Clear cell carcinoma	Small cell carcinoma
Basal cell adenocarcinoma	Large cell carcinoma
Low grade salivary duct carcinoma	Lymphoepithelial carcinoma
Myoepithelial carcinoma	Metastasizing pleomorphic adenoma
Oncocytic carcinoma	Carcinoma ex pleomorphic adenoma (invasive or high grade features)
Carcinoma ex pleomorphic adenoma (minimally invasive and low grade features)	Carcinosarcoma
Sialoblastoma	Adenocarcinoma met cystadenocarcinoma, NOS, high grade
Adenocarcinoma NOS and Cystadenocarcinoma, low grade	Sebaceous carcinoma and lymphadenocarcinoma
Secretory carcinoma	Salivary duct carcinoma

Table 1. Low and high grade stratification for subtypes of malignant salivary gland tumours (MSGTs). Subtypes described in this thesis in bold. [a]: intermediate grade MEC is difficult to stratify due to different grading schemes used. [b]: All types of ACC are high risk for local recurrence; solid type ACC is additionally high risk for metastasis.[16]

The MSGTs with the highest incidence are adenoid cystic carcinoma (ACC), mucoepidermoid carcinoma (MEC) and acinic cell carcinoma (AciCC) and are extensively described in this thesis.

The general rule in clinical practice is that the smaller the gland is the greater the chance of malignancy in case of a neoplasm. Overall, around 80% of neoplasms in the parotid gland (the largest salivary gland) are benign whereas up to 80% of neoplasms of the minor glands are malignant. The sublingual gland is an exception with an incidence of malignancy of approximately 90% for this major type gland which is the least affected.[29]

1.2.1 Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (ACC) is the tumour type which is most extensively described in this thesis. This is partly because its peculiar biological behavior and its relative high incidence within the group of MSGTs to reportedly as much as 28%.[30] In the Netherlands specifically, ACC is the most common diagnosed MSGT (16%) whereas in international literature mucoepidermoid carcinoma is considered the most prevalent type of MSGT.[31-33] ACC was first described by Robin, Lorain and Laboulbene in 1853 with their mention on microscopic cribriform growth pattern and perineural growth. The obsolete term for ACC was cylindroma as proposed by Billroth, where eventually Spies (1930) first mentioned the current nomenclature of ACC. Finally, Dockerty and Mayo recognized its true malignant potential in 1942.[34,35]

Although ACC is predominantly diagnosed in the salivary glands, it can also be found in the lung, lacrimal gland, breast, trachea, larynx and paranasal sinuses.[36-41] It is the most diagnosed MSGT in the minor salivary glands as well as in the submandibular gland.[17] ACC is typically a mixed type tumour with ductal and basal/myoepithelial differentiation with three possible growth patterns: tubular, cribriform and solid of which the latter is known to be correspond with increased risk of developing nodal and distant disease (figure 6). ACC is known for frequent perineural invasion (PNI) and forenamed distant metastasis (DM). Late local recurrences are no exception in ACC. High grade transformation (HGT), previously described as dedifferentiation is a rare but recognized feature in ACC with an even more relentless clinical course (incidence of cervical metastasis of near 60%, median survival of 12 months) than solid type ACC.[42-44] Although ACC is reportedly predominant in females, the contrary seems true for HGT-ACC.[44] In recent years, unraveling the molecular biology of ACC has gained interest in light of improved diagnostics and possible personalized therapies. The identification of the translocation leading to *MYB- NFIB* oncogene- a signature translocation for ACC- as well as *NOTCH1* mutations are possible factors in optimizing treatment in ACC patients.[45,46] High expression of Polycomb group protein EZH2 reportedly correlates with poor outcome.[47]

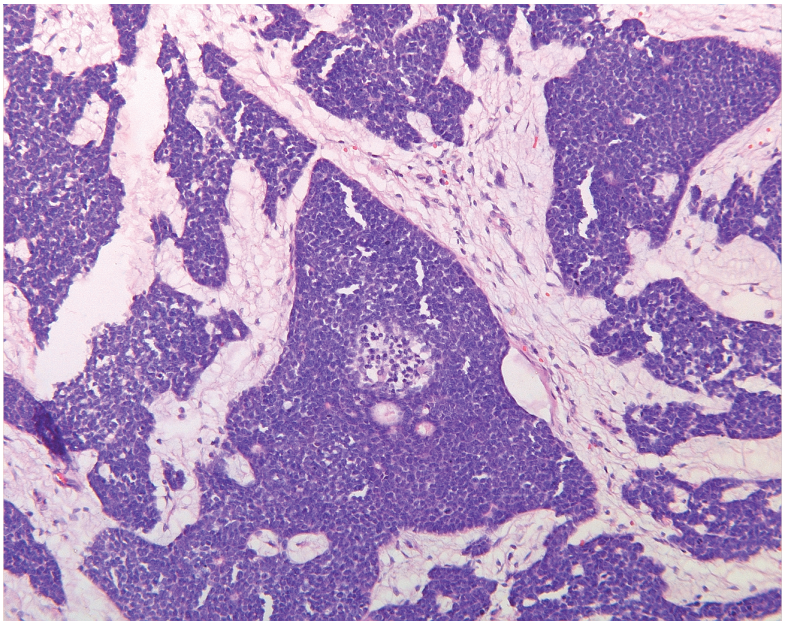

Figure 6. Solid type ACC.

1.2.2 Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma (MEC) is reportedly the most prevalent MSGT worldwide although incidence differs between countries.[18-21] It is a glandular epithelial neoplasm characterized by mucous, intermediate and epidermoid cells, with sometimes columnar, clear cell and oncocytic features. Its first mention was in 1924 by Masson and Berger and later Stewart and Foote and Frazell respectively further deciphered MEC although not yet recognizing it as a malignancy calling it a mucoepidermoid tumour.[48-51] Grading in MEC consists of three categories: low, intermediate and high grade. Multiple three- tiered schemes are applied (Armed Forces Institute of Pathology; AFIP, Brandwein and modified Healey) all harbouring the risk over over- and underestimating grade.[22-29] The parotid gland is the most sited organ where the palate is most affected with respect to minor gland involvement. Tumour localizations outside the major and minor head and neck salivary glands have been reported (lacrimal and ceruminous glands).[52,53,55] There is no gender predilection in MEC and all age groups are affected. Although rare, MEC is the most diagnosed MSGT in children.[4,54] MEC overall has a low tendency for regional or distant spread with the exception of high grade (HG) MEC. Dedifferentiation or HGT is described but is extremely rare in MEC.[55] Besides the most described *CRTC1-3/MAML2* fusion gene, other genomic abnormalities have been identified in MEC. In MEC without the *CRTC1-3/MAML2* translocation, a high number of chromosomal copy number abberations have been observed.[56] Other genetic aberrations, such as *TP53* mutation which is associated with high grade transformation have been described. EGFR expression is often seen in MEC and thus might be a target for EGFR inhibition.[57]

1.2.3 Acinic Cell Carcinoma

Acinic cell carcinoma (AciCC) is regarded as a low grade MSGT and is less prevalent than ACC and MEC compromising 11% of MSGTs where 15% of parotid MSGT are AciCCs.[58-59] The WHO describes AciCC as a malignant epithelial neoplasm of salivary glands "in which at least some of the neoplastic cells demonstrate serous acinar cell differentiation which is characterized by cytoplasmic zymogen secretory granules. Salivary ductal cells are also a component of this neoplasm."[14] Nasse was the first to report on AciCC in 1892 as a "blue dot tumour" where Buxton subsequently described its malignant features. Foote and Frazell described its morphology in more detail after which Abrahams (AFIP) studied al larger population and refined the description. Only later, the term acinic cell tumour was replaced by carcinoma.[60-64] There is no proposed grading scheme for AciCC and HGT is occasionally reported.[65,66] The preferred localization of AciCC is the parotid gland where minor glands are rarely affected. If AciCC occurs in minor salivary glands, it is mostly found in the buccal mucosa and upper lip, although the palate is also sited.[67] Rare localizations outside the head and neck area are the breast, lacrimal gland and pancreas. In the latter, AciCC is referred to as acinar cell carcinoma.[68,69] There is a slight female predominance and all age groups are affected with a peak incidence in the fourth and fifth decade with median age at diagnoses of around 50-52 years.[59,70-72] AciCC is the second most diagnosed pediatric MSGT after MEC.[4,5] Conventional AciCC has a low incidence of PNI or any other adverse feature and lymph node metastasis as well as DM are seldom diagnosed. HGT- AciCC however has a high propensity for regional and distant spread and a relatively high recurrence rate leading to poor long term survival.[73,74] There are no known risk factors associated with AciCC specifically.[59] To date, AciCC is the MSGT type with the least knowledge on genetic alterations. A recently described positive immunohistochemical staining for nuclear NR4A3 is diagnostic for AciCC in case the diagnosis cannot be properly made based on histomorphological characteristics.[75,76] There is some evidence supporting the overactivation of the mammalian target of rapamycin (mTOR) pathway which in turn may lead to trials with mTOR pathway inhibitors.[77]

1.3 Clinical presentation and diagnostic work up

A thorough case history can aid in diagnostics. Important features to touch upon are time since first notice of the swelling, speed of growth, pain, previous surgery or radiotherapy of the head and neck area and previously diagnosed skin cancer. Patients generally present with a painless mass in the neck, mouth or pharynx. In these cases, distinguishing between a benign lesion or a malignancy is difficult. If pain or a (marginal branch) facial nerve palsy in combination with a (submandibular) parotid lesion are present, malignancy is highly likely. In a minority of cases, a tumour can be diagnosed as an incidental sub-clinical finding on computer tomography (CT), magnetic resonance imaging (MRI), FDG-PET scan or ultrasound (US).

A complete head and neck examination should be done with an emphasis on palpation of the region of interest as well as a meticulous examination of the neck to assess possible enlarged lymph nodes.

In case of probability of metastatic skin cancer to the salivary gland patients should be referred to the dermatologist for further assessment and histopathology of previously removed skin lesions should be reviewed.

Further diagnostic work up is done by ultrasound guided fine needle aspiration (USgFNAC) when feasible. As a prerequisite, a center needs an expert head and neck pathologist for meaningful assessment of cytology in salivary gland lesions for this is notoriously challenging. A negative cytology results does not necessarily exclude malignancy as confirmed in previous research on cytology. A study on parapharyngeal salivary gland tumours at the Amsterdam University Medical Centers, Vrije Universiteit Amsterdam found a negative predictive value (NPV) for malignancy of 79%.[78]

In light of salivary gland cytology, the introduction of the 6-tiered Milan System for Reporting Salivary Gland Cytology (MSRSGC; figure 7) in 2018 has become widely adopted. This system was developed in analogy with existing tiered systems such as the Bethesda system in thyroid cancer. It has proven its added value in relation to conventional reporting of salivary gland cytology.[79-82]

Diagnostic category	Risk of malignancy	Management
1: Non- diagnostic	25% (0-67%)	Clinical/radiologic correlation or repeat FNAC
2: Non- neoplastic	10% (0-20%)	Clinical follow up and radiologic correlation
3: Atypia of undetermined significance	10-35%	Repeat FNAC or surgery
4: Neoplasm		Surgery or clinical follow up
a: Benign	<5% (0-13%)	
b: Salivary gland neoplasm of uncertain potential (SUMP)	35% (0-100%)	
5: Suspicious for malignancy	60% (0-100%)	Surgery
6: Malignant	90% (57-100%)	Surgery

Figure 7. The Milan System for Reporting Salivary Gland Cytology.[79]

When interpretation of cytology is inconclusive, core needle biopsy (figure 8) may provide sufficient tissue for histological examination and has reportedly superior diagnostic performance to FNAC in terms of lesser non- diagnostic results and higher sensitivity and specificity.[83] In case the lesion is not accessible for ultrasound, CT guided procedures should be considered. Translocation analysis may aid in further distinction in cytology as well as histology.[45,46]

Figure 8. Core needle biopsy of the submandibular gland. (Image reprint with permission; Wolters Kluwer Health , Inc. through Copyright Clearance Center's RightsLink service)

MR imaging can aid in diagnostics with its ability to distinguish malignant characteristics such as invasive growth, ill- defined margins, perineural invasion and involvement of the deep lobe in parotid lesions. A low signal on T2 weighted images of the parotid gland suggests malignancy.[84] The quality of imaging keeps improving and the added value of diffusion weighted MR imaging (DW-MRI) has been proven. A relatively low apparent diffusion coefficient (ADC) is suggestive for malignancy in salivary gland tumours and adds sensitivity and specificity to conventional MR imaging.[84-86]

Screening for distant disease seems indicated in high grade tumours with clinically high tumour burden in the neck at first presentation which increases the risk of distant metastasis. This is the recommendation in the Dutch Head and Neck Cancer guidelines for multiple or low level nodes in the neck in general (all head and neck cancer types). A 18F-FDG PET-CT is recommended.[87] The National Comprehensive Cancer Network (NCCN) guideline for salivary gland tumours differs from the Dutch guidelines and does not advocate 18F-FDG PET-CT but solely a CT of the chest to rule out DMs.[88] Another indication is adequate staging during treatment in the recurrent/ metastatic setting. 18F-FDG PET-CT for screening of distant disease in MSGTs can be useful, although standardized uptake values (SUV) in select tumours is relatively low and lesions may be poorly visualized due to physiologic uptake of salivary gland tissue.[89,90] Furthermore, 18F-FDG PET-CT does not perform well in distinction between benign or malignant salivary gland tumours. In conclusion, 18F-FDG PET-CT is complementary to conventional imaging with regard to staging and restaging but does not add to diagnostics with regard to the primary site.[91] Recent literature reported on the use of the ^{68}Gallium (^{68}Ga) prostate specific membrane antigen (PSMA) PET-CT

which might be specifically useful in the recurrent and metastatic setting for ACC and to a lesser extent for salivary duct carcinoma. It might show targets for PSMA radionuclide treatment in case of sufficient PSMA ligand expression in the tumour.[92,93]

1.4 Treatment of malignant salivary gland tumours

1.4.1 Surgery

MSGTs are treated surgically when possible. In parotid gland MSGT, the facial nerve should be spared when there is no clinical or peroperative involvement and the tumour can be macroscopically removed.[94] Contrary to the clear ratio for radical resection of the primary tumour, treatment of the neck has been a controversial topic mainly in case of the cN0 neck. As an alternative to elective neck dissection (END), observation or prophylactic radiation have been suggested. The reported incidence of (occult) nodal disease is at least 10% regardless of histology with large case studies and several reviews to prove for it.[95-98] There is general agreement to perform END in high grade and advanced tumour stage.[99] Tumours sited in the submandibular gland and pharynx seem to have a relative high incidence of occult lymph node disease so some advocate to take this into account.[99-101] The oral cavity is generally regarded as a low risk site for occult cervical involvement although a reported incidence of 38.9% for the buccal mucosa in MEC contradicts this.[98,102,104] Matched pair analysis has shown survival benefit in cN0 parotid carcinoma patients after END vs. observation.[103] The most controversial issue thus remains treatment strategy of the cN0 neck in early stage and low grade MSGTs. Since preoperative cytopathological assessment of MSGTs is difficult and not seldom inconclusive, pN+ outcome in the cN0 neck is relatively high and selective END carries relative low morbidity there seems enough ground to advise END with a low threshold. In case of tumours with low tendency for lymphogenic spread like ACC, END is also utilized to gain a proper margin due to direct infiltrative growth into adjacent lymph nodes.[104] With regard to parotid gland tumours, levels II-III and to a lesser extent level IV have been identified as harbouring the majority of (occult) nodal disease.[105,106] In case of a submandibular gland MSGT, levels I-III are generally dissected.[104-106] In specific high grade cases (e.g. salivary duct carcinoma) the incidence of regional metastasis is significantly higher (>50%) necessitating a more extensive (E)ND like a modified radical neck dissection in case of a level II positive node.[107,108]

1.4.2 Radiotherapy

Although in the past MSGTs were deemed radioresistant, adjuvant radiotherapy (RT) increases local control and is indicated in case of perioperative tumour spillage, advanced stage disease (f.e extracapsular spread, >N1), PNI, positive and close surgical margins and high grade tumours.[109,110] Photon radiation through intensity modulated radiotherapy (IMRT) or tomotherapy is the standard of care in this adjuvant setting. IMRT is used in an cumulative dose of 60-70 Gray (Gy) generally in 2 Gy fractions where in case of PNI the trajectory of the involved named nerve(s) should be

incorporated in the clinical target volume often up to the skull base.[111] In general, salivary gland cancers respond moderate to poor to radiotherapy as a primary treatment in case of unresectable disease but primary RT does improve locoregional control, specifically in a cumulative dose of ≥66 Gray (Gy).[112] Since vital structures need to be maximally spared with minimum toxicity, proton beam radiation and carbon ion (C12) therapy (ACC) are alternative primary treatment options in select cases (e.g. involvement of the skull base). C12 particle boost has also reportedly been combined with conventional photon IMRT with promising results in irresectable ACC. [113,114] Neutron beam radiotherapy has been identified as an alternative with comparable outcomes to conventional photon beam in the adjuvant setting and possible superior effect on short term survival. It is however not readily available and has reported higher toxicity.[115-117] Concurrent chemoradiation, either adjuvant or as a primary treatment and predominantly with cisplatin used as a radiosensitizer, has not been extensively studied but some small series studies indicate survival benefit in mainly young and healthy patients with MSGTs with adverse features, able to withstand induced toxicity. The evidence level for increased disease control by adding chemotherapy however remains limited.[118-121]

1.4.3 Systemic treatment

Besides conventional chemotherapy regimens like cisplatin, carboplatin and paclitaxel in general and cyclophosphamide, doxorubicin and paclitaxel (CAP) in metastatic ACC, there is extensive ongoing research in determining targets for systemic therapy in MSGTs.[122,123] Response rates with conventional chemotherapy in the recurrent/ metastatic setting are relatively poor and effects are short lived.[122] Multiple markers for potential treatment have been identified such as c- Kit, Ki- 67, human epidermal growth receptor-2 (HER-2), epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF) and the androgen receptor (AR) in salivary duct carcinoma (SDC).[123] Androgen deprivation therapy (ADT) in recurrent/ metastatic SDC has proven to be effective and is considered the primary treatment in this setting.[124] This equally accounts for the efficacy of trastuzumab in Her-2 positive cases.[125]ADT has also been proven effective in the adjuvant setting in advanced stage SDC.[126]

Recent reports on targeted therapies in MSGTs show promising preliminary results but also indicate that further research is necessary which is hampered by the low incidence of MSGTs.[127,128] Biological profiling of MSGTs is ongoing in the quest for identifying promising targets for therapy.

1.5 Outline of the thesis

The major setback in literature with regard to assessed possible prognosticators in MSGTs is the fact that different types of MSGTs are analyzed as one group and that sample sizes are small in case subtypes are separately reported on. In multi- center studies treatment strategies and histopathological grading systems used might differ thus influencing results.

The aim of this thesis was therefore to analyse outcome in relation to possible prognosticators in large single head and neck cancer referral center series at the Amsterdam University Medical Centers (Amsterdam UMC), Vrije Universiteit Amsterdam (and one multi- institutional study in cooperation with the Netherlands Cancer Institute; NKI; Chapter 6), for specific types of salivary gland cancer of the head and neck with an emphasis on adenoid cystic carcinoma (ACC), mucoepidermoid carcinoma (MEC) and acinic cell carcinoma (AciCC). Furthermore current concepts with regard to histopathological grading and survival with distant disease are critically weighed to gain better insight in these matters .

Chapter 2 describes a historical case series of 105 patients with adenoid cystic carcinoma (ACC) of the head and neck treated at the Amsterdam UMC over a 30- year period. In this retrospective survival analysis, outcome in relation to different possible prognosticators is analyzed such as T-status, N- status and perineural invasion (PNI). The outcome of this large single center analysis is reported.

In **chapter 3**, the current used histopathological grading systems (known as the Perzin and Spiro grading systems) for adenoid cystic carcinoma (ACC) are described and both applied to a cohort of patients at the Amsterdam UMC. Histopathological slides are reviewed by two expert head and neck pathologists to assess inter- observer variability and the practical applicability of these schemes. A novel grading system- the solid (S) +/- system- scoring the presence of a solid component in ACC regardless of its percentage, is introduced and assessed in a similar fashion as the two known grading systems.

Chapter 4 reports on survival in patients diagnosed with metastatic adenoid cystic carcinoma (ACC). Historically, ACC is considered an indolent type of disease with prolonged survival even in case of distant disease. This report analyzes survival in this specific group of patients to test this statement. Possible risk factors for developing distant metastasis are described and analyzed. Radiographs (chest and/ or abdominal CT) are reviewed according to the Response Evaluation Criteria in Solid Tumours 1.1 (RECIST) criteria to measure distant disease progression. The outcome in case of palliative treatment is described.

Chapter 5 represents an overview of 64 patients treated for mucoepidermoid carcinoma (MEC) at the Amsterdam UMC. Outcome with regard to prognosticators is assessed with a special emphasis on grade (low, intermediate and high) where high grade MEC is generally considered a different entity with poorer clinical outcome. A Fluor In Situ Hybridization- Polymerase Chain Reaction (FISH- PCR) analysis is performed to assess the presence of the translocation of t(11;19)(q21;p13) causing CRTC1/3- MAML 2 fusion gene. Presence of this translocation may influence prognosis.

In **chapter 6** a two center study of patients with head and neck acinic cell carcinoma (AciCC) is described. This combined cohort of 89 patients from the Amsterdam UMC, Vrije Universiteit Amsterdam and the Netherlands Cancer Institute (NKI) is retrospectively assessed through chart review for possible clinico- pathological prognosticators. The histopathological slides are reviewed by three expert head and neck pathologists and reported morphological features as described by the WHO are assessed with a special emphasis on high grade transformation (HGT). Outcome with regard to histopathological features is reported.

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CHAPTER 2.

Adenoid cystic carcinoma of the head and neck: a single-center analysis of 105 consecutive cases over a 30-year period

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Abstract

Background: Adenoid cystic carcinoma is a rare salivary gland malignancy with a poor disease free survival due to frequent distant metastases and late local recurrences. Previous single-center reports on outcome mostly encompass small series. In this report a relative large series of 105 cases is analyzed, all treated at the VU University Medical Center, Amsterdam, The Netherlands over a 30-year period in which treatment strategies remained unchanged.

Methods: All cases of ACC of the head and neck between 1979 and 2009 at our institution were analyzed through a medical chart review. Recurrence patterns and possible prognostic factors (T-stage, N-status, age, gender, type of salivary gland involved, histological grade, surgical margins, perineural invasion (PNI) and postoperative radiotherapy (RT)) were analyzed.

Results: One-hundred and five cases of ACC of the head and neck were identified. Five-, ten- and twenty year survival rates for overall survival were 68%, 52% and 28%, respectively. T-stage, N-status, surgical margins, histological subtype and age were highly significant predictors for survival. PNI was not a negative prognosticator.

Conclusions: T-stage, N-status, surgical margins, histological grade and age are the main predictors of survival- outcome in ACC of the head and neck. Distant metastasis frequently develop, mainly in the first 5 years post treatment. Local recurrences often develop even later on, warranting long term follow up of patients treated for ACC. Grade III ACC should be considered a specific entity within the group of ACC due to its typical aggressive biological behavior and relatively poor outcome, implicating the need for an improved adjuvant treatment.

Introduction

Adenoid cystic carcinoma (ACC) of the head and neck is one of the most prevalent salivary gland malignancies. It represents 10– 15% of all salivary neoplasms.[1] ACC is characterized by slow local growth, high incidence of perineural invasion (PNI), infrequent regional metastases and frequent development of local recurrences and mostly slowly progressive and relatively indolent distant metastases. Histopathology often shows mixed patterns of solid, cribriform and tubular types and usually the tumor is classified according to the predominant pattern.[2] Contrary to other types, solid type ACC is considered a high grade lesion which has a tendency to more aggressive behavior and relatively poor short term survival.[1–8]

ACC occurs in all decades of life and is not related to any known risk factor. Treatment of ACC consists of surgery, almost always followed by postoperative radiotherapy (RT) due to frequent positive and close surgical margins and perineural invasion (PNI).[1–7]

In case of non-resectable tumors cisplatin or carboplatin/paclitaxel based chemoradiation can be considered based on preliminary data.[9–11] Different chemotherapy schemes and targeted therapies showed poor response rates and short-lived effects if used as a single modality treatment. Chemoradiation in an adjuvant setting has not been proven to be superior to radiotherapy alone.[12]

Herein, we report a series of patients with ACC treated at the VU University Medical Center in Amsterdam, The Netherlands, between 1979 and 2009, with respect to survival and prognostic factors. In this period treatment concepts remained unchanged.

Materials and methods

Between 1979 and 2009, 105 patients with primary ACC were treated at the VU University Medical Center. Medical charts were reviewed and the following data were collected: gender, age, type of salivary gland involved, TNM stage (retrospectively staged according to UICC, 7th edition classification),[13] treatment modalities, PNI (defined as extension of epithelial tumor cells around nerves), metastases, surgical margins, histological grade and postoperative RT. The diagnostic work up consisted of complete head and neck examination, biopsy or fine needle aspiration of the primary lesion, routine laboratory analysis, MRI/CT imaging of the head and neck and a chest X-ray. When indicated ultrasound guided fine needle aspiration cytology of enlarged lymph nodes was performed. Treatment consisted of surgical excision in the vast majority of cases (83%). Frozen sections were not routinely performed. When facial nerve paralysis was present or if the nerve or one of its branches was surrounded by tumor the nerve or the branches was sacrificed and immediate dynamic facial reanimation or static reconstruction was performed depending on the clinical situation; in all other cases the nerve was preserved. Surgery was followed by RT in the vast majority of cases (93%).

Postoperative RT was generally given to a total dose of 60– 70 Gray (Gy), with an elective dose of 25 x 2 Gy to the whole surgical bed, followed by a boost of 10–20 Gy in fractions of 2–2.5 Gy to the tumor bed. Clear margin was defined as a tumor-free margin of ≥ 5 mm. A close margin meant a tumor-free margin of >1 and <5 mm. A margin was considered positive in case of tumor-free margin <1 mm.[7] With regard to histology, the grading system according to Perzin was used in which grade I represents a predominantly tubular pattern without a solid component, grade II represents a predominantly cribriform pattern with a maximum of 30% solid pattern and grade III is defined as a predominance of more than 30% of solid pattern.[2] All tissue samples were revised independently by two experienced head and neck pathologists. In case of discrepant grading, slides were reviewed by both and a consensus diagnosis was achieved. Follow up was done by frequent protocolized outpatient controls meaning two monthly in the first year, three monthly in the second, four monthly in the third and six monthly in the fourth and fifth year after treatment. After 5 years follow up was continued yearly for life. Imaging was not routinely performed during follow up.

Statistics

Outcome was analyzed by uni- and multivariate survival analyses for the surgically treated cases only (n = 87) using Log Rank and Cox regression testing in SPSS statistical software version 15.0 (IBM, New York, USA). Five-, ten- and twenty-year local control rate (LCR), distant disease-free survival (DDFS), disease-free survival (DFS), disease-specific survival (DSS) and overall survival (OS) were calculated, as well as hazard ratios (HRs) with 95% confidence intervals (CIs) for T-stage, N-status, surgical margins, histological grade and age.

Results

Patients' age ranged from 19 to 87 years (mean 57.3 years). Fifty-four patients were male (51%) and 56 cases involved the minor minor salivary gland (53%). The most affected major salivary gland was the parotid gland. With regard to the minor salivary glands, the oral cavity and oropharynx were the predominant sites for ACC. Eleven patients (10%) presented with positive lymph nodes. This group consisted of eight major gland tumors (submandibular gland n = 4, parotid n = 3, sublingual n = 1) and three minor gland tumors (tongue n = 2, ethmoid sinus n = 1). Distant metastases at presentation were seen in 4 patients (4%) with one primary tumor in the submandibular gland and three tumors in the minor glands (oropharynx n = 2, oral cavity n = 1). Advanced stage disease (UICC stage ≥ III) was diagnosed in 48 patients (46%). Eighty-one patients (77%) underwent surgery with postoperative radiotherapy. Six patients (parotid gland n = 3, submandibular gland n = 2, lip n = 1; 6%) underwent surgery alone. The different reasons for refraining from postoperative RT were T1 tumor with clear margins (n = 2), proven distant metastasis shortly after surgery (n = 1), successful re-excision with clear margins (n = 1), poor general condition after surgery (n = 1) and death due to co-morbidity (n = 1). Thus, 93% of surgically treated patients received postoperative RT. Thirteen patients (12%) were non-surgically treated with (chemo)radiotherapy because of a non-resectable tumor. Patients who underwent chemoradiation were treated with gemcetabine/cisplatinum, adriamycin and 5-FU, respectively. Five patients (5%) were not treated due to poor general condition or explicit wish. From the surgically treated group (n = 87), 77 cases (89%) showed positive or close surgical margins. In 10 cases (11%) the specimen had clear surgical margins: T1–3 major salivary gland tumors (n = 8) and advanced laryngeal tumors (n = 2). Considering histology, grade II was the most diagnosed subtype. PNI was seen in 70% of cases, where surgical margins were mostly positive (78%). In Table 1 details of the demographic, tumor and treatment related data are shown. The different tumor sites are shown in Table 2.

Gender	
Male	54 (51%)
Female	51 (49%)
Age	19-87 y (mean 57.3 years)
Type of salivary gland	
Major	46 (44%)
Minor	59 (56%)
UICC- Stage	
I	23 (22%)
II	34 (32%)
III	9 (9%)
IVA	27 (26%)
IVB	7 (7%)
IVC	5 (5%)
N- stage	
N1	3 (3%)
N2a	1 (1%)
N2b	5 (5%)
N2c	2 (2%)
N3	0
Histology	
Grade I	27 (26%)
Grade II	49 (47%)
Grade III	29 (27%)
Perineural invasion	
Yes	74 (70%)
No	25 (24%)
NR	6 (6%)
Surgical Margins	
Clear	10 (11%)
Close	9 (11%)
Positive	68 (78%)
Postop RT	
Yes	81 (93%)
No	6 (7%)

NR= Not reported

Table 1. Patient, tumour and treatment characteristics of the 105 cases of ACC.

Major salivary glands		Minor salivary glands	
Parotid	27	Oral cavity/lip	17
Submandibular	17	Oropharynx	28
Sublingual	3	Nasopharynx/Nasal cavity/Nasal sinus	8
		Larynx/Trachea	4
		Infratemporal fossa	1
Total	**47**	**Total**	**58**

Table 2. Distribution of primary tumour site.

Follow up ranged from 3 to 318 months (mean 78.1 months). During this period, 77% of all patients developed a recurrence. In 31% of these cases the recurrence was local, in 44% distant metastasis developed without local recurrence and 25% developed both local and distant recurrence. The predominant sites for distant metastasis were the lungs (56%), bone (27%) and liver (17%). The survival curve for DSS relative to margin status is depicted in Fig. 1.

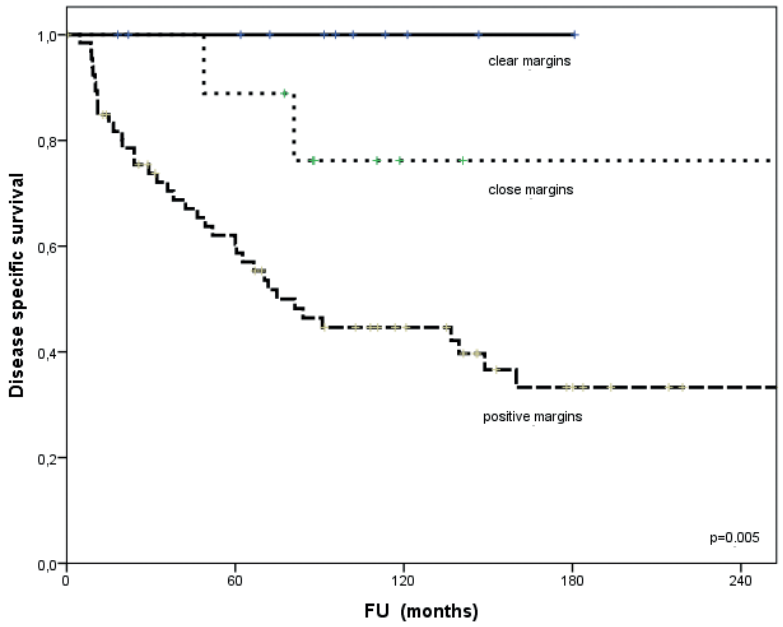

Figure 1. Disease specific survival (DSS) relative to surgical margins.

Survival relative to local control decreased from 82% at 5 years to 58% at 10 years. There was no major difference between 5-, 10- and 20-year survival for DDFS. Twenty-year overall survival rate (OS) for the whole population was 28%. Table 3 shows 5-, 10- and 20-year survival rates (LCR, DDFS, DFS, DSS and OS) and the prognostic significance of type of salivary glands involved (major vs. minor), histological grade, T-stage, N-status, surgical margins and PNI. In case of grade III ACC, most disease specific deaths (75%) occurred in the first five years after treatment. For grade I maximum follow up was 146 months (mean 74 months), for grade II 219 months (mean 89.9 months) and for grade III 288 months (mean 70.4 months). OS for maximum follow up was 18%, 40% and 31%, respectively. T-stage, N-status, histological grade and surgical margins were the most important predictors for all survival analyses, except for surgical margins with respect to LCR although a trend is observed. All survival rates decrease significantly with a higher stage of the primary tumor, as shown in Table 3.

	Local control	**Distant DFS**	**DFS**	**DSS**	**OS**
5-year (%)	82	60	56	68	68
10-year (%)	58	57	39	54	52
20-year (%)	39	49	26	43	28
Histology subtype (p- value)	**0.000**	**0.001**	**0.000**	**0.000**	**0.000**
Major/Minor gland (p- value)	0.354	0.994	0.487	0.832	0.764
T- stage (p- value)	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**
N+ (p- value)	**0.020**	**0.000**	**0.000**	**0.000**	**0.004**
Surgical margins (p- value)	0.082	**0.020**	**0.000**	**0.004**	**0.000**
Perineural invasion (p- value)	0.233	0.170	0.701	0.421	0.396

Table 3. Univariate analysis with 5-, 10- and 20-year survival and significance of analyzed prognostic factors.

DSS for T-stage and N-status is shown in Figs. 2 and 3, respectively.

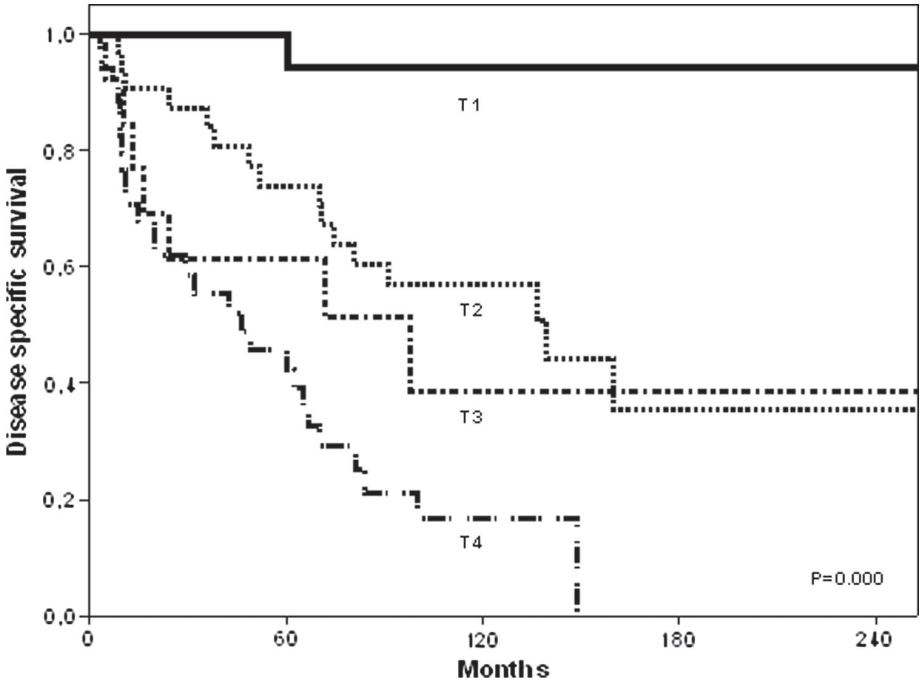

Figure 2. DSS relative to T- stage.

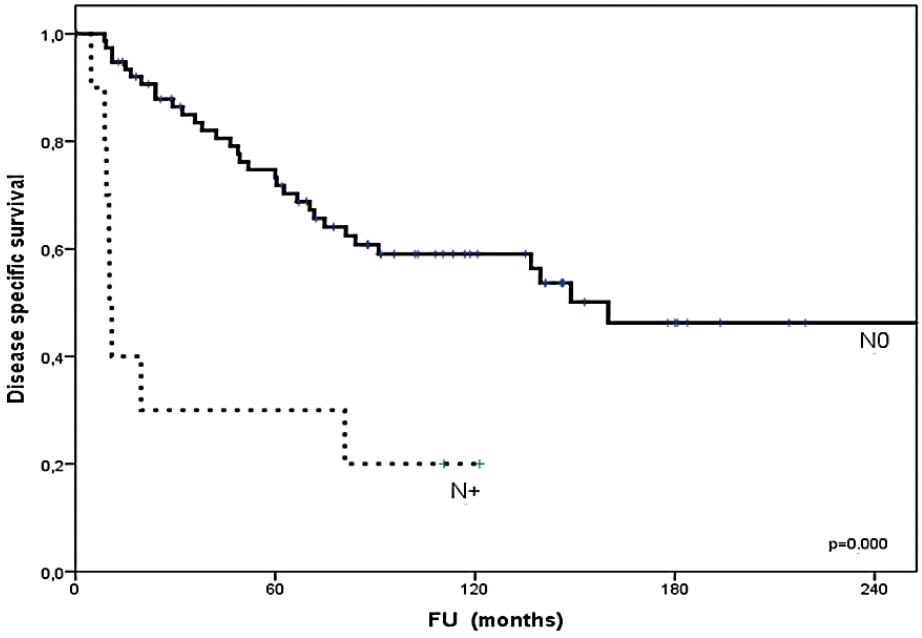

Figure 3. DSS relative to N- status.

Grade III ACC was a significant predictor for survival.

The OS curve for histological grade according to Perzin is shown in Fig. 4.

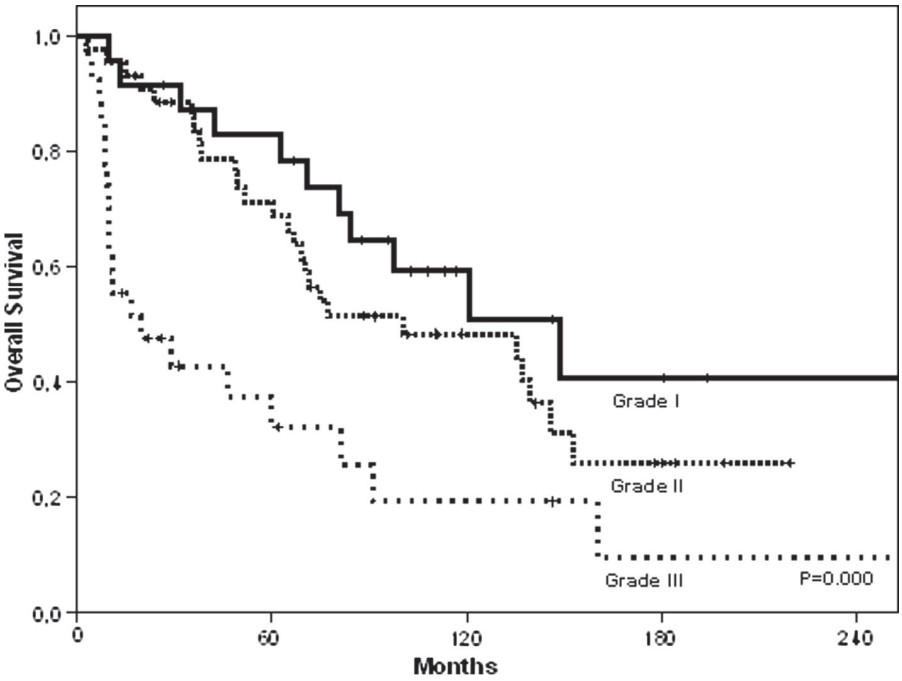

Figure 4. OS relative to grade according to Perzin.

As for the comparison between minor and major salivary glands no significant differences were found. Surgical margins was a strong prognostic factor. On multivariate analysis (Cox regression) for OS, T-stage, N-status, surgical margins, histological subtype and age were all important independent prognostic factors. The strongest prognosticator was T-stage with HR's of 5.2 (CI 1.2–8.7), 8.8 (CI 1.3–12.6) and 12.0 (CI 3.0–21.2) for T2, T3 and T4 relative to T1, respectively. HR for N+ relative to N0 was 3.5 (CI 1.4–8.3). The HR for close and positive margins were 2.3 (CI 0.2–26.5) and 8.1 (CI 1.1–58.7) relative to clear margins, respectively. Grade II had a HR of 1.8 (CI 0.8–3.6) and grade III of 4.4 (CI 1.7– 8.3) relative to grade I, respectively. For age this was 1.2 (CI 0.9– 1.5) for each next decade (Table 4).

	HR	CI
Age		
per decade	1.2	1.1- 1.6
T- Stage		
T1	1.0	
T2	5.2	1.2- 8.7
T3	8.8	1.3- 12.6
T4	12.0	3.0-21.2
N- status		
N0	1.0	
N+	3.5	1.4-8.3
Histology		
Grade I	1.0	
Grade II	1.8	0.8- 3.6
Grade III	4.4	1.7- 8.3
Margin		
Clear	1.0	
Close	2.3	0.2- 26.5
Positive	8.1	1.1- 58.7

Table 4. Outcome of multivariate analysis (Cox regression) for OS with covariates age, T-stage, N-status, histological grade and surgical margins (HR= Hazard Ratio, CI= confidence interval).

PNI, which was positive in 75% of cases in which this parameter was scored (n = 99), was not a negative prognosticator in the surgically treated group. As for postoperative radiotherapy, treatment with surgery plus postoperative radiotherapy for ACC resulted in comparable outcome as for patients treated by surgery alone. Table 5 shows a comparison with previous reports with regard to T- stage, N+ status and margins. [7,24,28]

	p-value
T-stage (OS)	
Oplatek et al. [24]	0.002
Present study	0.000
N+ (OS)	
Gomez et al. [28]	0.001
Present study	0.004
Margins (LCR)	
Garden et al. [7]	0.006
Present study	0.082

Table 5. OS by T-stage and N- status and LCR by margins compared to previous reports.

Discussion

In this single center cohort study of 105 patients with ACC we found that T-stage is the strongest prognosticator, adversely affecting survival as in all previous studies on prognostic factors in ACC.[7-26] In accordance to previous literature we found that OS is significantly correlated to high T-stage and N+ disease. Where with respect to local control rate (LCR) the margin status was not significant in the present study contrary to earlier reports.[7,24,27,28] Survival rate for local control continued to decrease significantly for all stages and sites between 5 and 10 years after treatment. In a study by Garden et al. LCR rates at 5- and 10 years were significantly better than in the present study (95% vs. 82% and 86% vs. 58% respectively). However, there was no information on T-stage distribution nor N-status in their cohort.[7] Distant metastases developed in 52% of patients, mainly within the first 5 years following diagnosis which is in accordance with previous reports. For example, Bhayani et al. reported a mean time to distant metastasis of 31.5 months while Spiro reported a mean time of 36 months, both well within the 5 years range.[29,30] Late local recurrence and slowly progressive distant metastasis caused disease specific survival to decrease from 68% after 5 years to 54% after 10 years. In comparison, Lloyd et al. report a 5- and 10- year DSS of 83% and 72% respectively. In their study the majority of patients had a major salivary gland ACC where in our series the majority had minor salivary gland ACC, which have a poorer outcome concerning LCR – although not significant in our series – in previous reports.[27] The latter is likely related to surgically wider tumor-free margins since these are apparently more often achieved in ACC of the major salivary gland type. Close and positive microscopic margins are strong predictors in all survival analyses except for LCR. The majority (72%) of excisions with clear margin were early T-stage (1–2) tumors, In case of a total laryngectomy wide margins for an endolaryngeal tumor (T3–4) are relatively easy established. These findings concur with the general concept of wide resection of ACC when feasible. To value the survival rates in this study, 5-, 10- and 20-year survival rates were compared with the results in the review by Dodd et al.[31] The results are shown in Table 6.

	Dodd et al. 2006	Present study
	range/ single value (%)	*(%)*
DFS		
5 y	35- 68	52
10 y	52	39
20 y	11	26
DSS		
5 y	58- 89	68
10 y	23- 74	54
20 y	22- 69	43
OS		
5 y	65- 73	68
10 y	39- 55	52
20 y	21- 25	28

Table 6. 5-, 10- and 20-year survival rates for DFS, DSS and OS from the review by Dodd et al. compared to outcome of the present study.

These show that the outcome in the present study is generally comparable with previous reports. PNI was no significant prognosticator in the surgically treated group but has proven to be in earlier studies. In previous reports, this was especially true in case of named nerve involvement, warranting more extensive surgery if possible followed by postoperative RT.[7,41] The role of adjuvant RT has been much debated. In this study, patients treated with surgery and adjuvant radiotherapy showed comparable outcome with patients treated by surgery alone. However, these results should be carefully weighed because the vast majority of patients received RT. This has also been a problem in earlier reports on the effect of postoperative RT in ACC.[32,33] Conventional RT as a single modality primary treatment has a limited role in ACC.[32] It should be considered in cases of inoperable disease or in patients unfit for surgery. Neutron radiotherapy seems to have a slightly better outcome than mixed beam or photon RT, however, availability of this technique is scarce.[32–36] As for proton beam RT, recent results for irresectable skull base localizations seem promising however this technique's availability is limited.[37] A recent study by Mizoe et al. showed favorable results for carbon ion RT in comparison to conventional RT in a series of 69 cases of advanced ACC of the head and neck.[38] These hadron therapies still need to become more readily available before becoming radiotherapeutic standard of practice for advanced stage disease. Furthermore, some reports discuss the possibility of brachytherapy, mainly in case of advanced stage tracheal ACC but also in case of recurrent oropharyngeal ACC.[39] Zhang et al. report about perioperative implantation of iodine 125 (125I) in twelve cases of malignant parotid gland lesions (ACC n = 3) with peri-operative involvement of the facial nerve. Although follow up was relatively short (maximum 74 months) no recurrences were seen.[40] Chemoradiation has only since recently been explored as a primary treatment for inoperable disease. In this study, 3 patients were treated with chemoradiation from

which little benefit was seen compared to RT alone. Although this outcome corresponds with the literature, one should keep in mind that the small chemoradiation- group (n = 3) and the different cytostatic agents used render this result somewhat arbitrary. Samant et al. report of favorable results with concomitant chemoradiation for cases not amendable for surgery. These results show good LCR, especially in cases of intra-arterial cisplatin administration. However, these results should be interpreted with precaution due to the multi-institutional character with different treatment regimens and the small number of cases (n = 16).[11] In another study, carboplatinum/placitaxel in combination with RT seems to yield acceptable response rates.[9] Given these results, further research is mandatory.

In case of recurrence, chemotherapy only is debatable and a recent review on different chemotherapy schemes showed low and short lived response rates.[10,12] In conclusion, ACC of the head and neck is challenging to treat because of its unique behavior. Although wide resection often followed by postoperative RT is the cornerstone of treatment, clear margins are difficult to achieve with high risk of PNI.[7,26,37] The strong negative predictive value of positive and close microscopic margins concurs with the latter. (Chemo)radiation as a primary treatment should only be explored in case of unresectability. ACC of the minor salivary glands has a predisposition for locoregional recurrence, where positive and close surgical margins are significantly correlated with poorer outcome. Almost half of patients develop distant metastasis within 5 years of diagnosis and local recurrences have a tendency to develop even later on. This finding warrants a long term follow up of these patients. Grade III (solid type) ACC has a significantly poorer outcome and should be considered a high grade tumor due to its more aggressive growth pattern, and tendency for early development of distant metastasis.[6–8]

Considering the significant differences in recurrence patterns and survival, grade III ACC should be considered a specific entity within the group of ACC. High T-stage, N+ disease, grade III histology, positive and close surgical margins and older age all have important negative prognostic value in ACC and should be taken into consideration while treating patients with ACC. Although the predominantly indolent course correlates with relatively acceptable survival rates, there is a small number of patients – mostly grade III histology – with poor survival rates and rapidly progressive tumor growth for which improved and more effective adjuvant therapy may be warranted.

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CHAPTER 3.

Histopathological grading of adenoid cystic carcinoma of the head and neck: analysis of currently used grading systems and proposal for a simplified grading scheme

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Abstract

Background: Histopathological grading of adenoid cystic carcinoma (ACC) is a controversial issue. It is generally agreed that solid type ACC has a relatively poor prognosis. However, the amount of solid regions within this often mixed type tumor that predicts a poor prognosis is not firmly established. Some authors stipulate that the presence of a solid component regardless of the amount is a poor prognosticator where others argue that the amount should be taken into consideration. Two grading systems most commonly used are those described by Perzin et al./Szanto et al. and Spiro et al., respectively. They report that prognosis of ACC is poor if >30% and >50% of the tumor volume has a solid growth pattern, respectively.

Material and methods: The described grading systems are applied to a series of 81 surgically treated cases of ACC at the VU University Medical Center, Amsterdam, The Netherlands. Moreover, we introduced an alternative grading system, in which the presence of a solid component, irrespective of its amount, is considered. All three systems of grading were tested for inter-observer concordance and prediction of prognosis.

Results: Inter-observer concordance for grading ACC according to Perzin et al./Szanto et al. and Spiro et al., proved to be moderate with Kappa Scores of 0.393 and 0.433, respectively. Our alternative grading system yielded inter-observer concordance with a Cohen's kappa result of 0.990. All systems were comparable in discriminating patients with poor clinical outcome. Histopathological grade proved to be an independent prognosticator.

Conclusion: The presence of any solid component in ACC is a negative prognosticator, and can histopathologically be diagnosed with a high reliability. These results suggest to merely register the presence or absence of a solid tumor component since its inter-observer variability is very low, its reproducibility is high and its predictive value is comparable to the traditional grading systems used.

Introduction

Adenoid cystic carcinoma (ACC) of the head and neck is one of the most prevalent malignant salivary gland neoplasms.[1] ACC in general has a protracted course. It is notorious for its poor disease free survival due to frequent local recurrences and – often indolent – distant metastases. The treatment of choice is surgery, when feasible followed by radiotherapy (RT). Regarding its histological features ACC predominantly presents as a mixed tumor, consisting of tubular, cribriform and/or solid growth patterns. The tumor is mostly classified according to the predominant pattern; the solid subtype is considered a high grade tumor with poor prognosis, first recognized as such in 1958 by Patey and Thackray.[2] Compared to cribriform and tubular types, solid type ACC shows a high percentage of loss of heterozygosity (LOH), more chromosomal aberrations and somatic mutations and a high expression of p53.[3-8] Some authors speculate that the risk of nodal metastases is higher when solid ACC is present.[9] For ACC, two different histopathological grading systems are currently used. These are one grading system described by Perzin et al.[10] and Szanto et al.[11] and one by Spiro et al.[12] We will refer to these grading systems as Perzin/Szanto and Spiro, resp. Both grading systems can discriminate patients with a poor prognosis, based upon the amount of solid component present in the tumor. In the Perzin/Szanto system, ACC is considered high grade if more than 30% of the tumor consists of a solid component. In the Spiro system, more than 50% of solid parts are considered high grade. In these grading systems, the amount of tumor to be investigated is not (clearly) defined.[10–12] Next to these established schemes, we studied the usefulness of a new histopathological grading system scoring the mere presence of solid type ACC in the histological specimen, irrespective of its amount. The main goal was to provide a reliable grading system with good reproducibility and with a low inter-observer variability, which are prerequisites for a practical grading system. Furthermore, the importance of histopathological grading relative to other known prognosticators such as T-stage and N-status is investigated.

Materials and methods

One-hundred and five patients with ACC attended our institution for treatment between 1979 and 2009, and of these, 87 patients were treated surgically. During this period, treatment strategies remained unchanged. Of these 87 patients, H&E stained slides were available for review in 81 cases which were included in this study. All available slides – almost always plural per case – were revised and graded independently by two expert head and neck pathologists (EB and IVDW). In case of discordant grading an agreement was reached. Grading was carried out according to the currently used systems by Perzin/Szanto and Spiro, respectively.[10-12] The definitions of these grading systems are shown in Table 1.

Perzin/ Szanto [10,11]	**Spiro&Huvos** [12]	**Present study**
Grade	Grade	solid/ no solid
I. Predominantly tubular, no solid	I. Mostly tubular or cribriform, occasional solid	
		S+
II. Predominantly cribriform, < 30% solid	II. Mixed with substantial solid (>50%)	
		S-
III. Solid component > 30%	III. Only Solid	

Table 1. Definitions of grading systems as used in current literature and the S+/- system.

The histopathological criteria of this predominantly mixed type tumor were scored according to the criteria of the World Health Organization (WHO).[1] The three types of ACC are shown in Fig. 1.

For analysis, specimens were subdivided in low and high grade ACC. This was done according to the definitions in the original papers.[10-12] According to these definitions, low grade ACC consists of Perzin/Szanto grade I (predominantly tubular, no solid) and II (predominantly cribriform, <30% solid) and Spiro grade I (mostly tubular/cribriform, occasional solid). High grade ACC thus consists of Perzin/Szanto grade III (>30% solid component) and Spiro grade II (substantial solid; >50%) and III (only solid). An additional scoring system was introduced which reported the presence or absence of solid type ACC in the specimen, regardless of the amount or further composition of this predominantly mixed type tumor. We considered this a new grading system, defined as Solid± (S±). A Cohen's kappa test was performed to analyse inter-observer variability for the different grading systems. The Cohen's kappa test is a reliable and often used test for measuring inter-observer variability with values ranging from 0 to 1.00, where values of >0.70 are considered satisfactory.[13]

Possible additional prognostic factors registered were TNM stage (retrospectively staged according to UICC, 7th edition),[14] treatment modalities, perineural invasion (defined as extension of epithelial tumor cells around nerves), metastases, microscopic margins, type of salivary gland involved,

gender and age. Uni- and multivariate survival analyses were performed using the Log rank and Cox regression test with SPSS statistical software version 15.0 (IBM, New York, USA). The different survival parameters scored were local control rate (LCR), distant disease free survival (DDFS), disease free survival (DFS), disease specific survival (DSS) overall survival (OS) and hazard ratios (HR) with confidence intervals (CI). A Harrell's concordance index (C-index) – a test for assessing prediction performance in survival analyses – was calculated to measure the predictive power of the three grading systems on survival.[15]

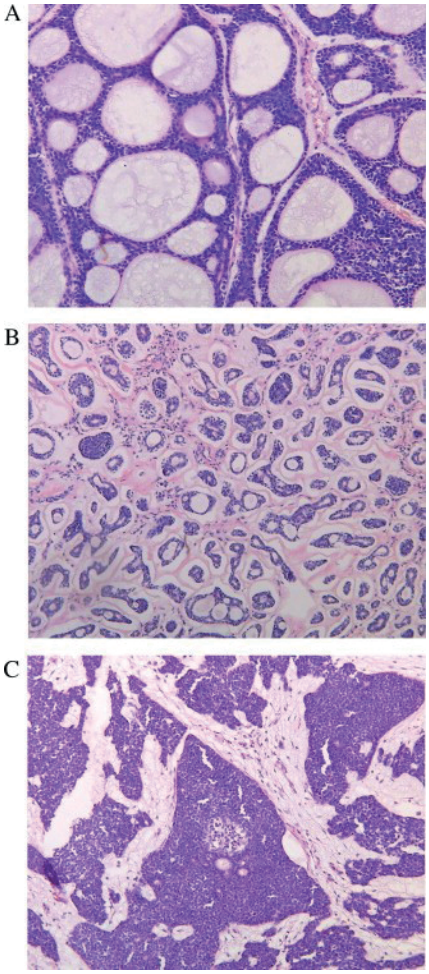

Figure 1. (A) Cribriform, (B) tubular and (C) solid type ACC.

Results

One hundred and five cases of previously untreated ACC were identified, of which 87 underwent surgery with curative intent, followed by radiotherapy in the majority of cases (93%). Patients' age ranged from 19 to 87 year (mean 57.3 year). Of the 87 surgically treated cases, 81 histological specimens were available for review. Forty-one patients were female (51%) and 41 cases involved the major salivary glands (51%). The demographic, tumor and treatment characteristics are shown in Table 2.

35/81 (43%) specimens contained solid type ACC regardless of the amount. Application of the grading systems according to Perzin/Szanto and Spiro resp. by two expert pathologists showed that the designation of grade in 50/81 (62%) tumors differed, solely on the basis of the different criteria in the two grading systems. This is due to the defined cut off point for the relative amount of solid tumor (30% vs. 50%, respectively). This sometimes even led to a two grade difference (i.e. a mixed tumor with >30% and <50% solid component is Perzin/Szanto grade III and Spiro grade I). Moreover, a Cohen's kappa test was done to analyse the inter-observer variability of the different grading systems based on the original grading. Results showed values of 0.393 (fair) for Perzin/Szanto, 0.433 (moderate) for Spiro and 0.990 (almost perfect) for S±. In order to actually determine the true clinical relevance of grading as such, both a univariate and a multivariate analysis were done. Univariate analysis showed that LCR, DDFS, DFS, DSS and OS all were significantly related (p-range <0.001–0.011) to tumor grade, irrespective of the grading system used, and to stage. Multivariate analysis for DSS with stepwise implementing of the prognostic factors T-stage and N-status was performed separately for the three grading systems. Table 3 shows a comparable outcome for all three grading systems.

Gender		
Male	40 (49%)	
Female	41 (51%)	
Age	19-87 y (mean 57.3 y)	
Major/Minor		
Major	41 (51%)	
Minor	40 (49%)	
Histology/ Grade	**Perzin/ Szanto**	**Spiro**
I	19 (23%)	58 (72%)
II	40 (49%)	12 (15%)
III	22 (27%)	11 (14%)
Solid		
Yes	45 (56%)	
No	36 (44%)	

UICC[a]- Stage	
I	20 (25%)
II	25 (30%)
III	8 (10%)
IV	28 (35%)
N- stage	
N1	2 (2%)
N2a	1 (1%)
N2b	4 (5%)
N2c	2 (2%)
N3	0
Perineural invasion	
Yes	63 (78%)
No	14 (17%)
NR[b]	4 (5%)
Surgical margins	
≥5mm	10 (12%)
1<5mm	9 (11%)
<1mm	62(77%)
Postoperative RT	
Yes	75 (93%)
No	6 (7%)

a= Union for International Cancer Control; b= Not Reported.

Table 2. Clinicopathological data of 81 reviewed cases of ACC.

	HR	**95% CI**		**HR**	**95% CI**		**HR**	**95% CI**
Perzin/Szanto			***Spiro***			***Solid***		
I	1.0		I	1.0		No	1.0	
II	1.7	0.6-4.4	II	3.6	1.6-8.2	Yes	3.9	1.7-9.1
III	5.7	2.2-15.2	III	6.2	2.5-15.3			
T- stage								
1	1.0			1.0			1.0	
2	12.3	1.6-95.0		13.1	1.6-102.0		5.7	0.7-44.9
3	24.8	2.8-219.0		25.6	2.9-227.7		9.9	1.1-85.5
4	26.7	3.4-206.8		29.3	3.7-230.2		13.3	1.7-103.6
N-status								
N0	1.0			1.0			1.0	
N+	4.1	1.7-9.7		4.1	1.7-10.0		5.1	2.0-12.8

Table 3. Multivariate analysis (Cox regression) with hazard ratio's (HR) and 95% confidence intervals (CI) for 81 histologically reviewed cases. Separate analysis for Perzin/ Szanto, Spiro and S+/-.

In 10 cases (11%), positive lymph nodes were found at first presentation. In 9 out of these 10 cases pathology specimens were available for revision and showed high grade tumor in 6/9 patients (67%) and presence of solid type tumor in 8/9 cases (89%). The 5, 10 and 20-year DSS and OS rates for the different grading systems (Perzin/Szanto, Spiro and S±) are shown in Table 4.

	Perzin/Szanto (p<0.001)			Spiro (p<0.001)			S+/- (p<0.001)	
	I	*II*	*III*	*I*	*II*	*III*	*No*	*Yes*
5y DSS[a] (%)	90	75	36	82	39	27	90	53
5y OS[b] (%)	90	75	36	82	39	27	90	53
10y DSS (%)	73	60	22	66	26	13	73	37
10y OS (%)	73	55	22	62	26	13	70	34
20y DSS (%)	58	48	11	52	0	0	64	26
20y OS (%)	50	20	11	35	0	0	45	19

a: Disease specific survival; b: Overall survival.

Table 4. Five, ten and twenty-year disease specific- and overall survival for Perzin/Szanto, Spiro and Solid+/-.

Figs. 2 (A,B,C) show the Kaplan Meier curves for DSS for a maximum follow up of 20 years for Perzin/Szanto, Spiro and S±, respectively.

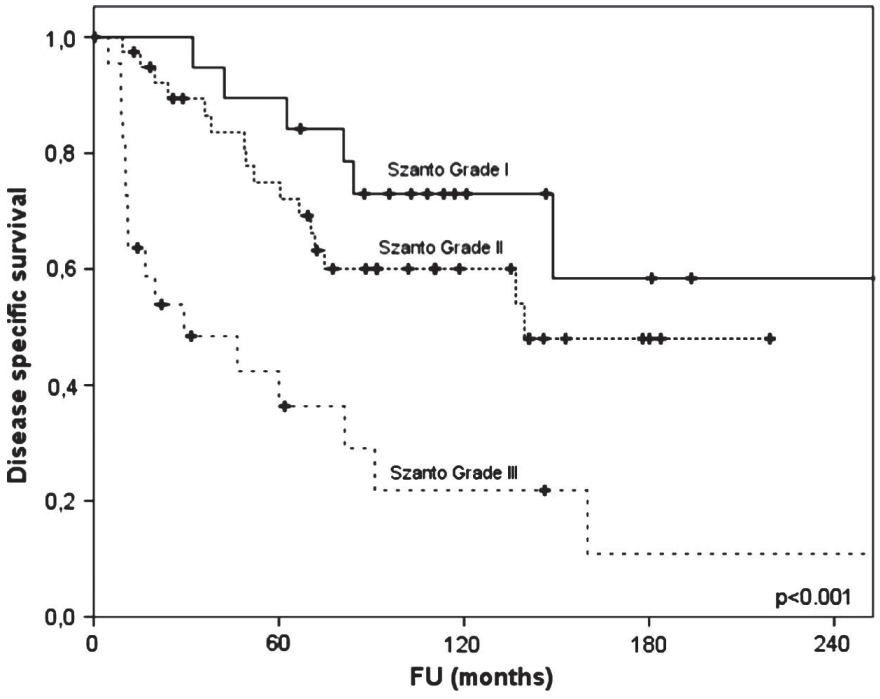

Figure 2A. DSS for grading according to Szanto (Log rank; significance p<0.05).

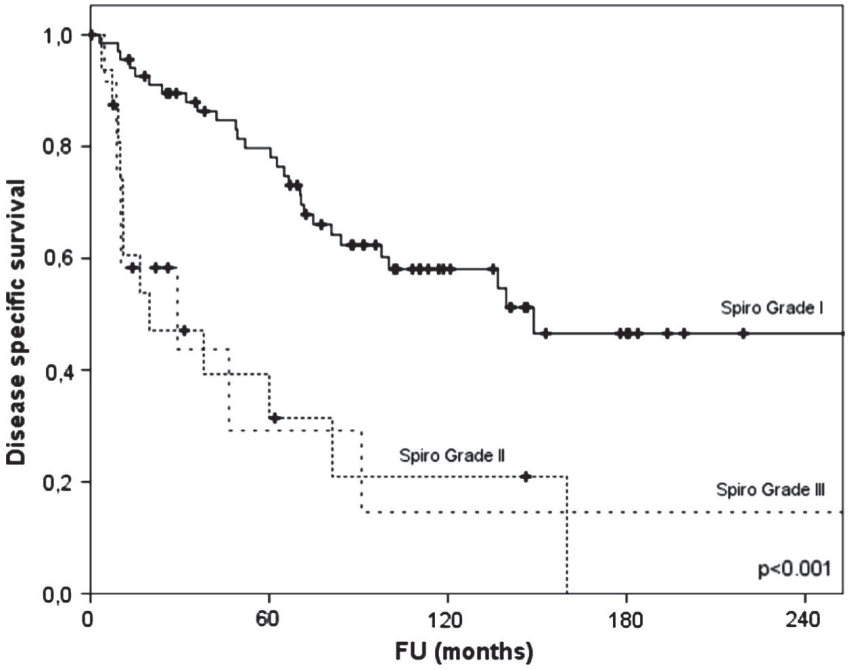

Figure 2B. DSS for grading according to Spiro (Log Rank, significance p< 0.05).

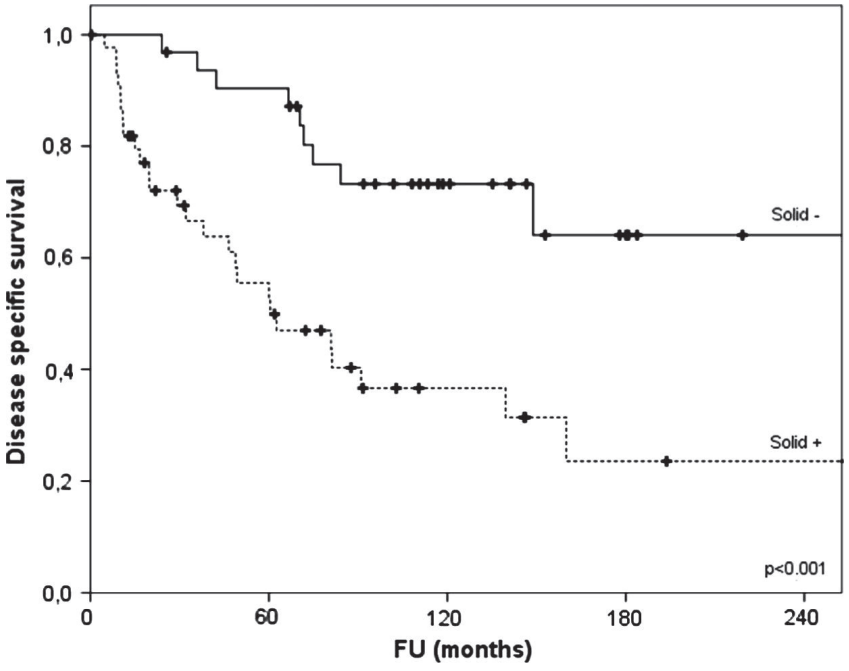

Figure 2C. DSS for grading according to S+/- (Log Rank; significance p< 0.05).

The results all show high significance with a poor survival for high grade (Perzin/Szanto grade III, Spiro grade II and III and S+) tumors. DSS and OS are also related to tumor stage (data not shown). Since it is generally assumed that stage is the strongest prognosticator for ACC,[16] effects of stage on survival in low and high grade tumors is shown separately (Figs. 3A–3D).

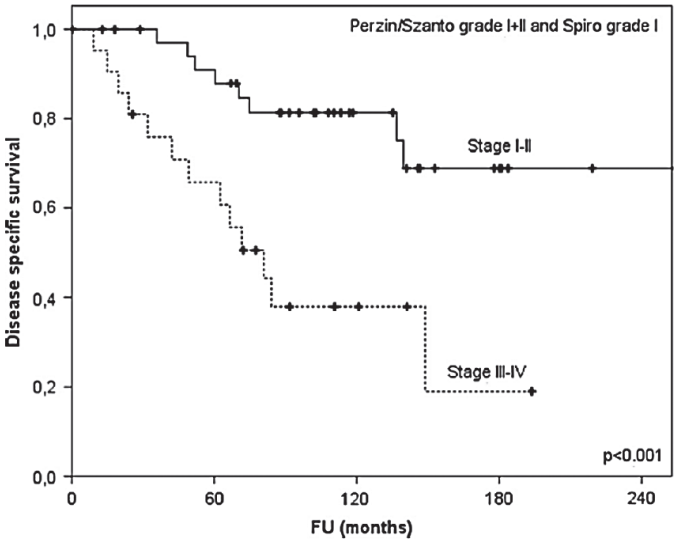

Figure 3A. DSS for low grade ACC subdivided for early (I-II) and advanced stage (III-IV) disease (Log Rank, significance p< 0.05).

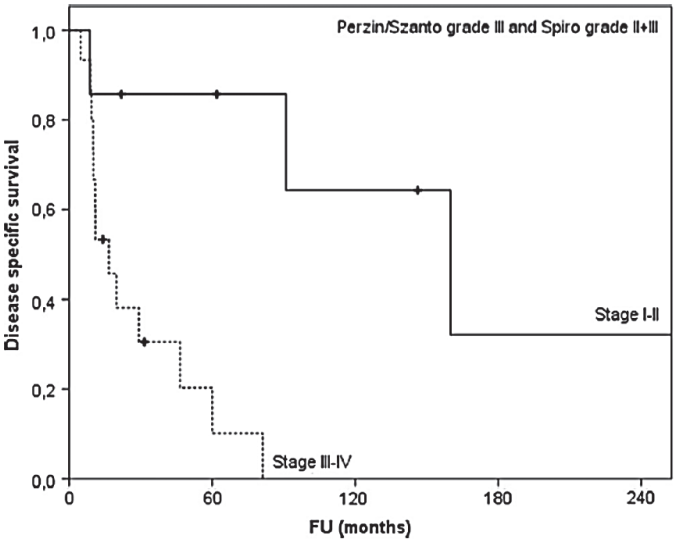

Figure 3B. DSS for high grade ACC subdivided for early (I-II) and advanced stage (III-IV) disease (Log Rank, significance p< 0.05).

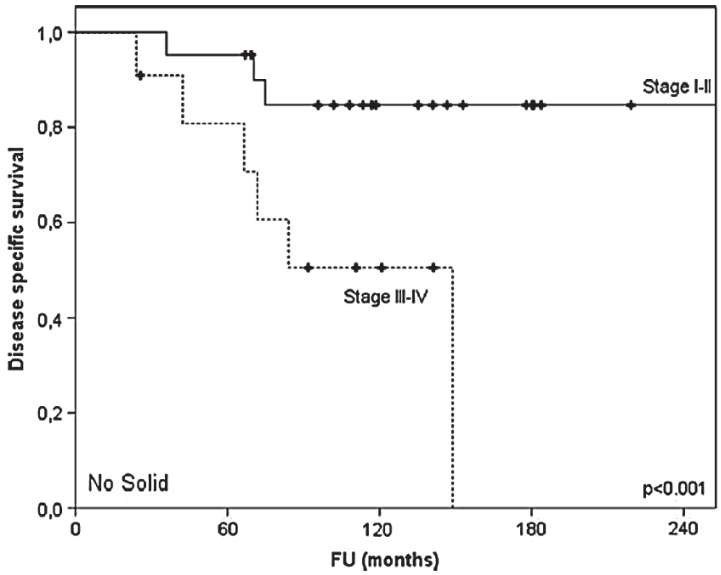

Figure 3C. DSS for non- solid ACC subdivided for early (I-II) and advanced stage (III-IV) disease (Log Rank, significance p< 0.05).

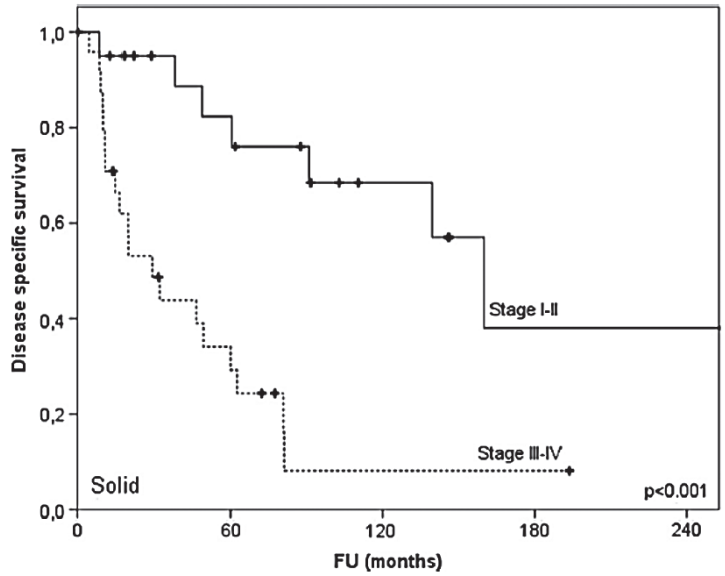

Figure 3D. DSS for solid ACC subdivided for early (I-II) and advanced stage (III-IV) disease (Log Rank, significance p< 0.05).

Finally, a Harrell's C-index was calculated to evaluate the actual predictive power of the grading systems used in this study. This shows that all three grading systems have a comparable predictive strength (Table 5).

	Perzin/Szanto		Spiro		S+/-	
	H C	95% CI	H C	95% CI	H C	95% CI
LCR[a]	0.62	0.52 - 0.72	0.63	0.55 - 0.71	0.61	0.51 - 0.70
DDFS[b]	0.64	0.56 - 0.73	0.63	0.56 - 0.70	0.62	0.54 - 0.70
DFS[c]	0.64	0.56 - 0.72	0.63	0.57 - 0.69	0.60	0.52 - 0.67
DSS[d]	0.66	0.58 - 0.74	0.65	0.59 - 0.72	0.65	0.57 - 0.73
OS[e]	0.66	0.58 - 0.73	0.64	0.58 - 0.70	0.64	0.57 - 0.71

[a] Local Control Rate, [b] Distant Disease Free Survival, [c] Disease Free Survival, [d] Disease Specific Survival, [e] Overall Survival

Table 5. Harrell's C- index (H C) for all three grading systems.

Discussion

The debate on the role and actual importance of histopathological grading of ACC has been ongoing for some decades. Some authors advocate that ACC should be predominantly solid to be of influence on outcome where others stipulate that the presence of a solid pattern regardless of its quantity encompasses a high grade tumor.[17-22] The results of the present study concur with the latter. One could argue that its importance is limited, for treatment strategies – surgery ± RT – remain unchanged so it bears no clinical consequence. On the other hand, the quest for identifying adjuvant treatment targets for ACC has been disappointing so far. Grading based upon the presence of solid growth pattern seems to be an independent prognosticator according to the present study and should be taken into account as such, as is the case for T-stage and N-status, thus providing the clinician and the patient with additional prognostic information. Although the definition of the currently used grading systems is rather different, they are both used. Difficulty is however encountered using these systems.[17] For both grading systems used, the defined cut-off point is difficult to calculate and prone to error. These could be reasons that tumor stage is considered more indicative for prognosis than grade – as reported by Spiro et al. – and that histology is often described according to the predominant pattern rather than as a numeric grade.[16] In the present study, all but one case with lymph node metastases contained solid type tumor, supporting the assertion by Myers et al. that there is a higher likelihood of lymph node metastases in solid type ACC.[9] Besides the histological subtype, recent reports emphasize the possible importance of the proliferative marker Ki- 67, where a high index correlates with poorer outcome.[23,24] We suggest to exclude or confirm the mere presence of a solid component and to report it as such through the S± grading system. The Cohen's kappa test – a proven reliable measure for inter observer variability – shows a slightly better outcome for Spiro compared to Perzin/Szanto which is in accordance with the study by Therkildsen et al..[14,25,26] However, both results show only fair to moderate values for inter-observer variability. The S± grading system however has a Cohen's kappa result of 0.990, which resulted in an excellent correlation. The Harrell's C-index shows that the predictive power of this grading system is equal to that of the other two grading systems. In previous studies,

contradictory results are reported on the clinical relevance of grading.[24,27] However, the present study confirms through multivariate analysis that grade is an independent prognosticator which is in accordance with the study from da Cruz Perez et al. who report somewhat the same HR for solid type ACC (3.9 vs. 3.6, respectively).[27] According to the results in this study, it is rather questionable to describe ACC histology according to its predominant pattern for the mere presence of solid type tumor despite predominance of another subtype seems to be of significant influence on survival. According to the present study, high T-stage and N+-status remain the most powerful negative prognosticators. Because of the reliability, reproducibility and predictive power of the S± grading system we regard this grading system as a meaningful adjunct to the currently used grading systems, for grade has a significant impact on survival.[11,12,24,27,28]

Acknowledgement

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CHAPTER 4.

Differences in patterns of survival in metastatic adenoid cystic carcinoma of the head and neck

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Abstract

Background: We examined the assumption in conventional teaching about metastatic adenoid cystic carcinoma (ACC) being an indolent type of disease.

Methods: A single center analysis of 105 cases of ACC was performed. Radiographs were reviewed and tumor response to chemotherapy was measured. Distant disease-free survival (DDFS) and time to death since distant metastases diagnosis were analyzed.

Results: Forty-two percent of the patients were diagnosed with distant metastases. DDFS showed significant negative associations with advanced T classification, N1 classification, solid type tumor, and positive surgical margins. Distant metastases (91%) developed in the first 5 years after presentation. Median distant metastatic survival was 13.8 months. The most frequent organ sited was the lung. Solid type ACC showed a preponderance for multiorgan metastases (17/28; 61%). Distant metastases seemed not to occur in case of clear surgical margins. Solid type ACC had a significant poorer survival after development of distant metastases.

Conclusion: Metastatic ACC is not always an indolent disease.

Introduction

Adenoid cystic carcinoma (ACC) accounts for approximately 15% of all malignant salivary gland tumors.[1] It is generally recognized for its typical indolent behavior of late onset locoregional recurrences (years) and frequent and often silent diagnosis of distant metastases.[1,2] According to earlier reports, patients tend to survive for a substantial period after being diagnosed with distant metastases and, therefore, distant metastatic ACC is generally deemed "indolent."[2–7]

Although risk factors for developing distant metastases in ACCs have been described previously, studies on survival prognosticators for patients with distant metastatic ACC have not been published in abundance.[3–6] In clinical practice, there are, however, striking differences in disease progression and, thus, survival in patients with distant metastatic ACC. Fordice et al.[7] previously described 2 populations of patients with ACC, one having an indolent type and the other an aggressive type of disease, possibly partly represented by high-grade transformation (HGT) in ACC.[7–9] The search for treatment targets and agents, so far, has been unsatisfying. This study analyzes both the possible prognostic factors for the likely development of distant spread and the likely survival consequence on the diagnosis of distant metastasis.

Materials and methods

In this retrospective analysis, 105 cases of ACC were identified over a 30-year period (1979–2009), of which 44 (42%) developed distant metastases. Several possible prognosticators were identified and documented, such as T classification, N classification, extranodal spread (ENS), surgical margins, perineural invasion (PNI), histopathological grading, and site of distant metastases.[10] The histopathological grading was carried out using the systems described by Szanto et al.[11] and Spiro et al.,[12] as well as a third system, recently described, in which any presence versus absence of solid type tumor is used.[13,14] Because of the moderate applicability – and resulting high interobserver variability of the Szanto and Spiro systems – a reliable comment on the actual influence of grade has been historically difficult. Therefore, the presence or absence of solid type ACC was documented in this study, which has proven to be more reliable under the assumption that grade does have a substantial role in survival. We did not specifically look for HGT in ACC because its incidence is relatively low and no reliable statistical analysis could be performed.

Imaging of the primary site (MRI/CT) and chest (Xray) were routinely performed at the first visit. In case of enlarged lymph nodes, ultrasound-guided fine-needle aspiration was performed. Treatment consisted of surgery when feasible followed by adjuvant postoperative radiotherapy (PORT) in the majority of cases (93%). Follow-up consisted of routine periodic outpatient controls with increasing intervals over time (2–6 month visits over a 10- to 20-year period). In accordance with the Dutch national guideline, the National Institute for Health and Care Excellence (in the United Kingdom) and National Comprehensive Cancer Network (in the United States) guidelines, additional imaging was performed on indication. There are no current guidelines suggesting periodic screening for distant metastases. We are aware that this current worldwide strategy with regard to imaging could potentially lead to late diagnosis of distant metastases. Treatment and follow-up strategies remained unchanged during this period. In 21 cases, thorough follow-up of distant disease by means of chest X-rays or CT scans of the chest and/or abdomen was available and these radiographs were reviewed by an expert thoracic/abdominal radiologist (R.R.) to determine the pattern of disease progression for untreated distant metastases. Scans were scored as “slowly” or “rapidly progressive disease,” respectively, according to the Response Evaluation Criteria In Solid Tumors guideline version 1.1 and associated with possible risk factors.[15] In each case of distant metastases, according to Response Evaluation Criteria In Solid Tumors, at least 2 target lesions per organ were identified and radiographs were reviewed for new lesions up to 1 year after initial diagnosis of distant metastases. In case of growth of target lesions below or above median growth, lesions were defined as slowly or rapidly progressive, respectively. CT scans of patients treated for distant metastases with chemotherapy were analyzed separately to measure response to treatment.

Statistical analysis was undertaken using the SPSS statistical software package version 20.0 (New York, NY). Distant disease-free survival (DDFS) was defined as the time from diagnosis until diagnosis of distant disease in which patients without distant metastases at last follow-up were right censored. Differences in DDFS between levels of possible prognosticators were analyzed by Kaplan-Meier curves and the log-rank test. For patients with distant metastases, we compared overall survival rates (defined as distant metastatic survival). A forward selection procedure (p-entry 0.05) was used to obtain a multivariate logistic regression model predicting 1-year distant metastatic survival because almost all patients with metastatic disease died during follow-up.

Results

One hundred five cases of ACC were identified, of which 44 patients were diagnosed with distant metastases during their follow-up with primary ACC of the head and neck. The demographic and tumor-related data for the whole population (n=105) are described in Table 1.

In 3 cases (T4N0 sinonasal, cribriform type; T4N2c base of tongue, solid type; and T3N2b submandibular gland, solid type) distant metastases were detected at presentation.

The remainder of cases was found during follow-up (ie, after surgery +/- PORT). Ninety-four percent of surgical cases were treated primarily with curative intent. In case of proven distant disease (mainly by chest Xray or CT), patients were informed accordingly and active surveillance was generally preferred. Palliative chemotherapy was introduced in patients who developed localized physical symptoms or in case of proven rapidly progressive distant disease. In 42 cases, localization of distant metastases was retrievable through chart review. They were found in the lungs (39/42; 93%), followed by the liver (12/42; 29%) and bone (12/42; 29%). Pulmonary metastases were most often seen without other organs affected and were always multiple at the time of diagnosis (23/39; 59%). Most distant metastases were located solely in the lungs, especially in case of tubular and cribriform ACC (23/42; 55%). Only 1 patient developed bone metastases without other organs affected and liver metastases were always found synchronously with lung and/or bone metastases. The distribution of organs affected is shown in Table 2.

Gender			
Male			54 (51%)
Female			51 (49%)
Age			19-87 y (mean 57.3 y)
Type of salivary gland			
Major			46 (44%)
	parotid	*27*	
	submandibular	*17*	
	sublingual	*2*	
Minor			59 (56%)
	oral cavity	*31*	
	oropharynx	*10*	
	other	*18*	
T status			
T1			23 (22%)
T2			34 (32%)
T3			13 (12%)
T4			35 (33%)
N status			
N0			94 (90%)
N+			11 (10%)
UICC stage			
I			23 (22%)
II			34 (32%)
III			9 (9%)
IV			39 (37%)
Histology			
Grade I			27 (26%)
Grade II			49 (47%)
Grade III			29 (27%)
Solid			
Yes			54 (51%)
No			38 (36%)
NR			13 (12%)
Perineural invasion			
Yes			74 (70%)
No			25 (24%)
NR			6 (6%)
Surgical Margins			
Clear			10 (11%)
Close			9 (11%)
Positive			68 (78%)
No Surgery			*18*

Postop RT	
Yes	81 (93%)
No	6 (7%)

Table 1. Clinicopathological data of 105 cases of ACC.

Organs affected in case of DM of ACC (42 cases*)	
Lung only	23 (55%)
Lung, liver	7 (17%)
Lung, bone	6 (14%)
Lung, bone, liver	3 (7%)
Bone, liver	2 (5%)
Bone only	1 (2%)
Liver only	0

Table 2. Distribution of metastases. *: 2 cases unknown.

The majority of distant metastases (91%) developed in the first 5 years after diagnosis of primary ACC, in which late onset distant metastases, up to 12 years after treatment, were also occasionally seen (2%), as shown in Figure 1.

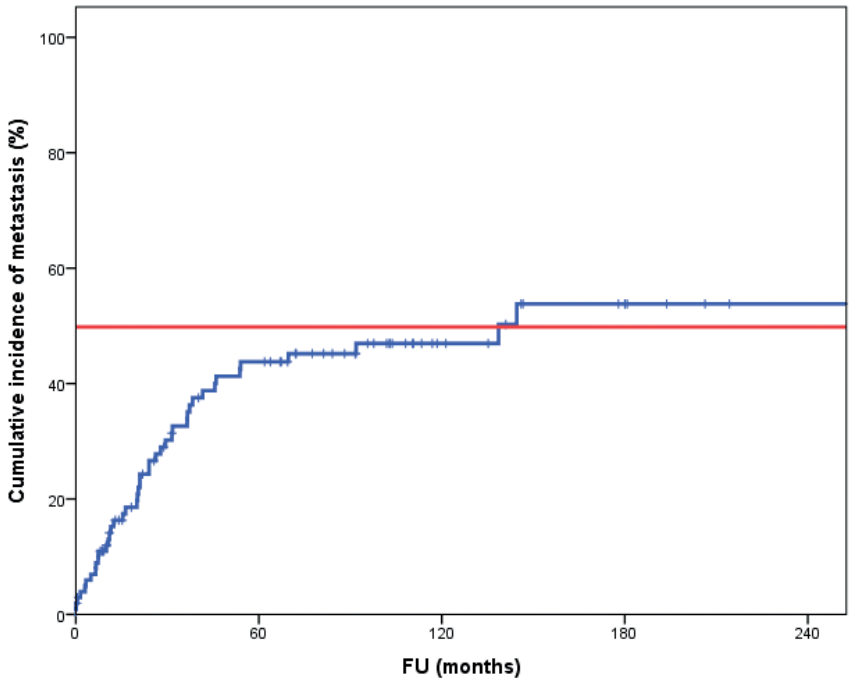

Figure 1. Cumulative incidence of distant metastases in adenoid cystic carcinoma. The horizontal line denotes the 50% level. Note the rapid increase in the first 5 years and incidence of metastases after even more than 12 years. FU, follow up.

Median survival after diagnosis of distant disease, defined as distant metastatic survival, was 13.8 months with a maximum of 98.5 months. Seventy-five percent of patients died within approximately 3 years. Table 3 shows the median distant metastatic survival of the current study in comparison with previous reports.[3–6]

Author	Median DMS (months)	DM localization	Range DMS (months)
Sur et al.[3] 1997	15	Overall[a]	NR
van der Wal et al.[4] 2002	25	lung	1-102
	13.5	lung+	1-75
Sung et al.[5] 2003	54	lung	1-149
	21	lung and bone	2-53
Gao et al.[6] 2013	36	Overall[a]	1-112
Current study	14	Overall[a]	1-98.5
	31	lung	1-98.5
	9	lung+	1-70

Table 3. DMS: Distant metastatic survival; NR: Not reported; lung+: pulmonary metastases with other organs affected. a: Overall: both lung and lung+.

Time to developing distant metastases (DDFS) was negatively influenced by advanced T classification (Figure 2), N1 classification, solid type ACC (any amount), and close/positive surgical margins. PNI and ENS were of no significant influence on DDFS (Table 4).

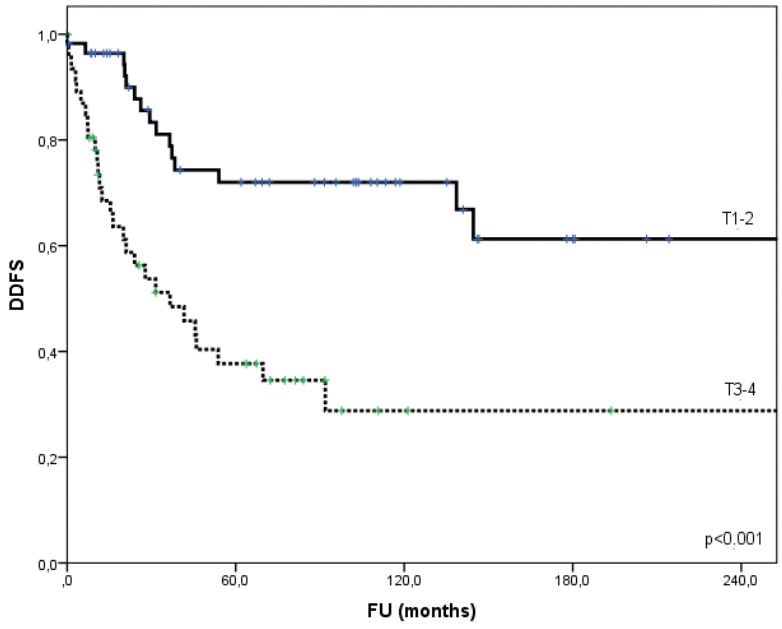

Figure 2. Distant disease free survival (DDFS) relative to T- classification. (T1-T2 vs. T3-T4; p< .001). FU, follow up.

Distant disease free survival (DDFS) (n=105)				
Parameter	**5- yr (%)**	**10- yr (%)**	**20- yr (%)**	**p- value**
T- classification				<.001
T1	94	94	94	
T2	56	56	35	
T3	56	56	56	
T4	31	13	0	
N- status				<.001
N0	60	56	49	
N+	23	23	0	
ENS				*0.31*
yes	0	0	0	
no	40	40	0	
Solid				<0.001
yes	40	40	24	
no	74	67	67	
Surgical margins				.020
negative	100	100	_	
close	75	75	75	
positive	50	42	38	
PNI				*.48*
yes	40	40	_	
no	56	52	46	

Table 4. Parameters analyzed for the whole cohort of ACC (n=105) with regard to distant disease free survival (DDFS). Abbreviations: ENS: Extranodal spread; PNI: Perineural invasion.

The overall distant metastatic rate was independent of a local recurrence (local recurrence +48% vs local recurrence -52%, respectively) and no difference was found in distant metastases propensity between minor (n = 26) and major (n=18) salivary gland ACC (DDFS; logrank; p = .732). In 40 of 44 cases with distant metastases (91%), growth pattern of the primary tumor was documented in the pathology database. In 28 of 40 cases (70%), the primary lesions of patients who developed metastases contained a solid component. In case of solid type ACC, 11 patients had liver metastases and 9 had bone metastases (synchronously with lung metastases except for 3 cases), whereas in the nonsolid type ACC group (12/40; 30%) 1 patient developed liver metastases and 1 patient had bone metastases (synchronously with lung metastases in both cases).

Possible prognosticators were analyzed through a Pearson chi-square test and/or a Fisher's exact test of which the results are shown in Table 5.

Risk factor (43 cases[a])			1- year DMS		p- value
			No. of cases alive	*No. of cases DOD*	
Surgical margins					.49
	Close		2	0	
	Positive		19	17	
	No surgery		2	3	
Histopathology					.026
	Cribriform		10	2	
	Tubular		5	2	
	Solid		2	6	
	N/A	16			
	Solid				.001
	yes		9	18	
	no		11	1	
	N/A	4			
	Perzin				.002
		I	7	0	
		II	12	7	
		III	4	12	
		N/A 1			
	Spiro				.003
		I	19	6	
		II	2	9	
		III	2	4	
		N/A 1			
PNI					.25
	yes		6	2	
	no		14	15	
	N/A	6			
T- classification					.21
	T1-2		10	5	
	T3-4		13	15	
N-status					.017
	N0		22	13	
	N+		1	7	
	ENS				.41
	yes		1	4	
	no		0	3	
DM localisation					.037
	Lung		17	6	
	Lung+		6	9	
	N/A 5				

Table 5. Possible risk factors analysed with regard to 1- year distant metastatic survival.

Abbreviations: DOD, dead of disease; N/A, not applicable; PNI, perineural invasion; ENS, extranodal spread; Lung+, lung plus bone and/or liver metastases.
*One case lost to follow up within 1 year.

There were no distant metastases in cases with an R0 resection and no significant differences in 1-year distant metastatic survival in patients with close or positive surgical margins. However, the cumulative incidence of distant metastases was higher in case of positive surgical margins relative to close surgical margins despite PORT. This was also seen with regard to solid type ACC versus nonsolid type ACC (Figure 3A and 3B) in which 1-year distant metastatic survival was significantly worse in solid type ACC than in nonsolid type cases.

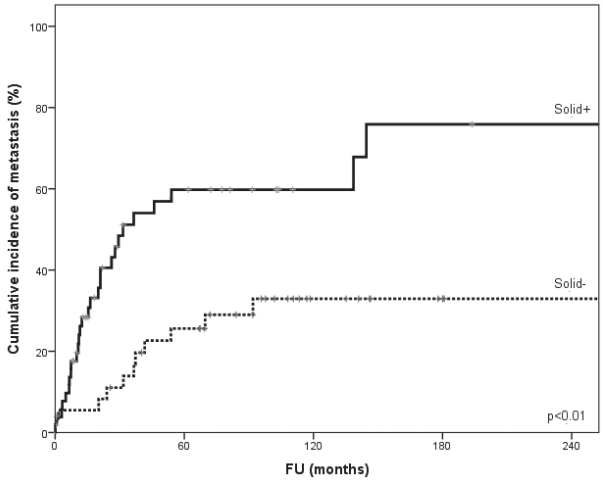

Figure 3A. Cumulative incidence of distant metastases with regard to histology (solid vs. nonsolid). Incidence of distant metastases is significantly higher in primary lesions with solid type tumour. (p<.001). FU, follow up.

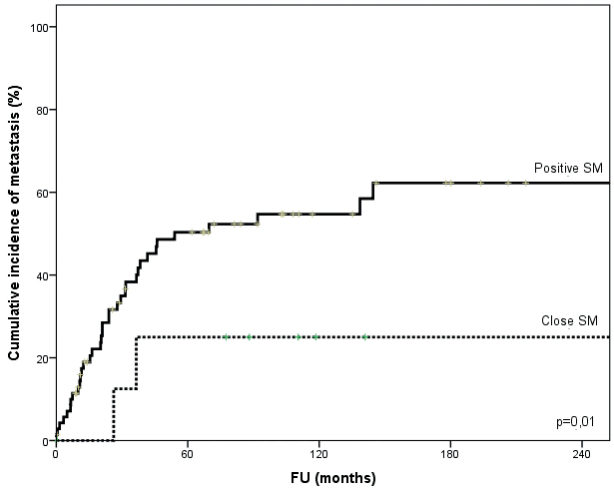

Figure 3B. Cumulative incidence of distant metastases with regard to surgical margins (SMs). Note that the incidence in case of positive margins is significantly higher. R0 resections not depicted (distant metastases n= 0; p< .001). FU, follow up.

A relative poor distant metastatic survival was also observed in cases of primarily diagnosed nodal disease (N+), although not significant. There were no cases of regional recurrence (Figure 4A and 4B).

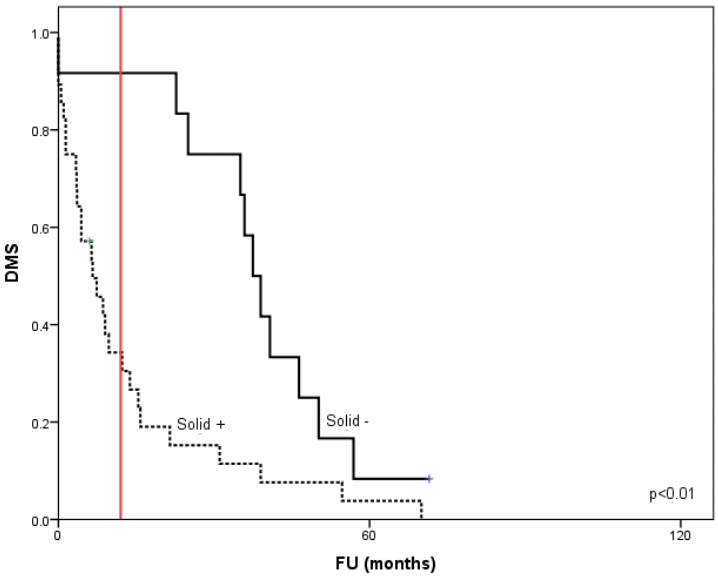

Figure 4A. Distant metastatic survival (DMS) relative to histology of the primary tumour (solid vs. nonsolid). The vertical line denotes 12 months. Note the rapidly progressive disease in case of solid type adenoid cystic carcinoma (ACC) (p< .01). FU, follow up.

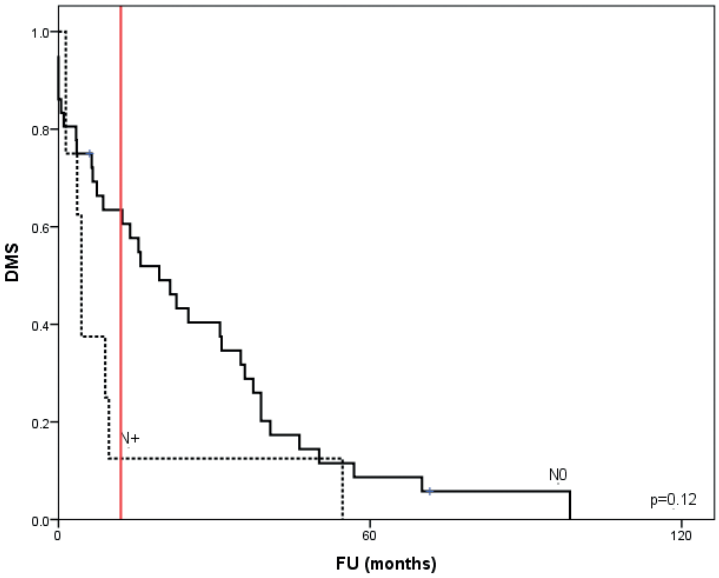

Figure 4B. Distant metastatic survival (DMS) relative to N classification (N0 vs N+). The vertical line denotes 12 months. Note the relative poor DMS in case of N+ disease. FU, follow up.

No cases of ENS, PNI, or advanced T classification were of influence on distant metastatic survival. In case of multiorgan distant metastasis (lung plus bone and/or liver; mostly in case of solid type ACC), survival was poorer than in lung metastases only, as depicted in Figure 5.

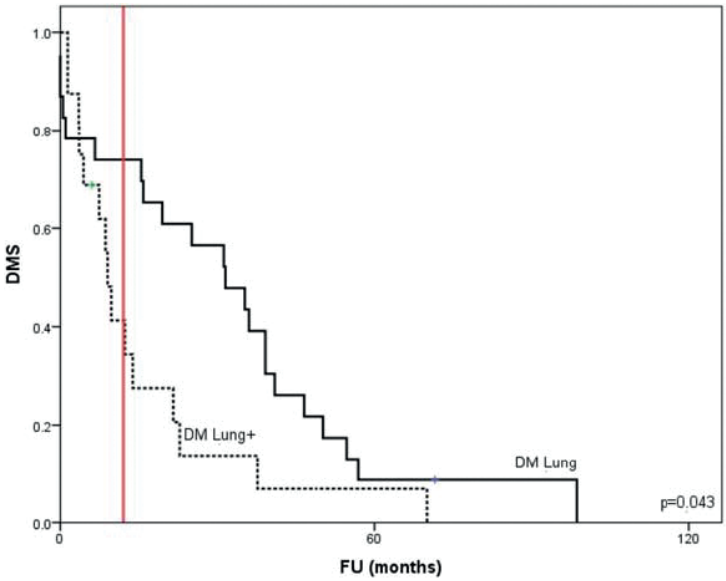

Figure 5. Distant metastatic survival (DMS) relative to organs affected with distant metastases. Note that in case of multiorgan disease (distant metastases [DM] lung+) metastatic disease is significantly more progressive. The vertical line denotes 12 months (p = .043). FU, follow-up.

On multivariate analysis, only solid growth pattern in ACC proves to be an independent negative prognosticator for distant metastatic survival, regardless of the amount of the solid component in the primary tumor. For histopathological revision, multiple slides per case were available (data not shown). With regard to review of radiographs (CT and X-ray), 21 cases of untreated distant metastases were eligible for analysis with at least 2 lesions per organ and sufficient (at least 2 measurements) follow-up. Median growth of determined target lesions in the lung was 1 mm per month (range, 0.3–7.5 mm), and for the liver was 2.5 mm per month (range, 1.9–4.0 mm). Fourteen of 21 cases (67%) developed new metastatic lesions at involved anatomic sites during follow-up. Growth of lung lesions above median (>1 mm per month) was designated as rapidly progressive disease. Twenty-nine percent of nonsolid type ACC showed rapidly progressive disease as opposed to 54% in the solid type ACC group. However, no significance could be confirmed because of the relative small amount of cases. Besides the association with solid type ACC, no association between the growth pattern of distant metastatic lesions and other prognosticators was found.

In the majority of cases treated for metastatic disease (multiple lung n = 3; multiple lung and liver n = 2; and multiple lung, liver, and bone n = 1), patients received cisplatin, doxorubicin, and

cyclophosphamide (CAP) up to 6 cycles with results ranging from progressive disease (n = 1) to stable disease (n = 3) to partial response (n = 2). Figure 6 shows an evident partial response after 1 month (2 cycles of CAP) in a patient with lung metastases.

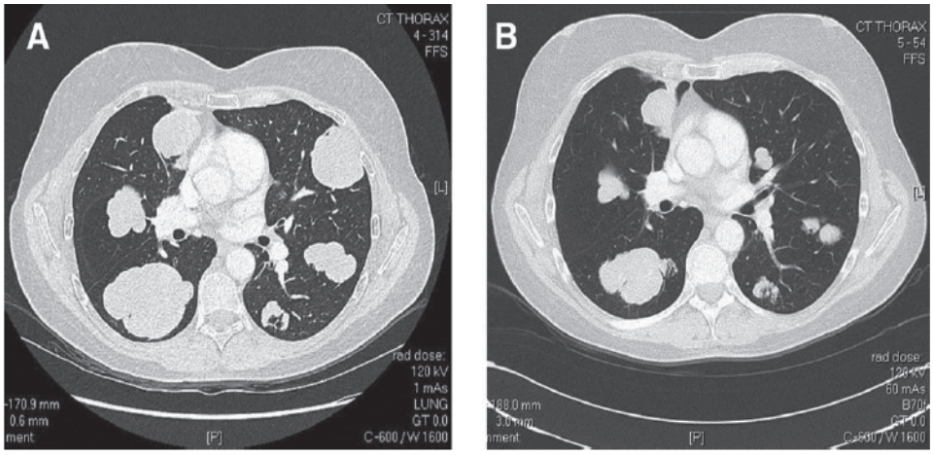

Figure 6. Axial chest CT before (A) and after (B) 2 cycles of palliative chemotherapy (cyclophosphamide [CAP]). Note the obvious decrease in diameter of lung metastases.

Another 2 patients with distant metastases (both multiple lung and liver metastases) were enrolled in a phase II gemcitabine multicenter trial (European Organization for Research and Treatment of Cancer 24982), of which 1 patient had stable disease and 1 patient showed progression.

Discussion

Distant metastases in ACC are often described as a relatively fatal occurrence and may even be considered an "indolent type" of metastatic disease. Several studies report survival for several years after diagnosis of metastatic disease and consequently patients are often informed in this manner. It is questionable whether this is a completely correct way of counseling patients.[4–6] Most previous studies report on risk factors for developing distant metastases rather than on survival with distant metastases. [16–18] Survival patterns for patients with metastases are important because they are understandably uncertain about individual patient's life expectancy. In contrast to other studies, this study has used the distant metastatic survival time because this is considered most indicative for prognosis.[5,18] In this study, the vast majority (91%) of distant metastases developed within the first 5 years after diagnosis, and time of survival after being diagnosed with distant metastases is actually relatively short (median survival of 13.8 months) compared to earlier reports,[5,19] with 75% of the population with distant metastases dying of their disease within approximately 3 years. Terhaard et al.[20] described a 1-year and 5-year survival after diagnosis of distant metastases of 68% and 32%, respectively, as compared to 54% and 7% in the present study. In some cases, the course of the

disease was relentless, showing rapidly progressive disease with multiple synchronous metastases in lungs, liver, and bone. Almost exclusively, this occurred when solid type ACC was present in the primary tumor, which is in accordance with previous reports.[18,21] Only those patients who had close or positive margins developed distant metastases, although clear surgical margins are generally considered difficult to achieve because of frequent PNI and anatomic localization. Although the importance of clear surgical margins has not been established in all previous reports,[22] the possible importance of wide margins, in this study, is demonstrated by the significantly better outcome in DDFS for close versus positive margins. These results should, however, be interpreted with caution because, on the other hand, we did not find a higher metastatic rate in case of locoregional failure. Wide field resection when feasible has been previously advocated by Sur et al.[3] and contradicts the suggestion by Umeda et al.[21] for conservative surgery with PORT. In the current analysis, we found no association among PNI, DDFS, and distant metastatic survival, respectively.

Others have actually reported association between PNI and development of distant metastases.[20,23] In a recent multicenter study by Amit et al.,[24] 495 cases of ACC were reviewed with regard to 3 categories of neural extension (perineural extension [PNE]; intraneural extension [INE]; and perineural inflammation). Survival was negatively influenced by INE but not by PNE. However, both PNE and INE did not seem to be prognosticators for developing distant metastases.[24] The review by Barrett and Speight[25] showed worse outcome in case of PNI but mainly in case of so-called named nerve involvement. No correlation was found for PNI and neck or distant metastases.[25] Advanced T classification is a negative prognosticator for developing distant metastases, as shown in Table 1 ($p < .001$). However, there is no significant difference in distant metastatic survival between early and advanced T classification (Table 2; $p = .34$), thus confirming again that the overriding prognostic factor is histopathology of the primary tumor. As expected, more distant metastases were found in patients with N+ disease, although this could also be associated with a solid type primary tumor because 90% of N+ cases was associated with solid type ACC (any amount). Although distant metastatic survival is not significantly poorer in N+ cases, a trend is observed and is likely explained by the biological behavior of metastatic disease, which is directly associated with the histology of the primary lesion (ie, solid type ACC; Figure 6A and 6B). The increased risk of nodal disease in solid type ACC has been previously reported by Myers and Ferris.[26] ENS was not a negative prognosticator in this series as opposed to the study by Bhayani et al.,[18] although their series included relatively few patients with nodal disease. A recent report by Liu et al.[27] showed a poorer metastatic-free survival in case of higher lymph node ratio and ENS in a relatively larger series of N+ cases of ACC (N+ $n = 47$; ENS $n = 18$). Larger numbers of patients are required, however, to determine the real prognostic influence of ENS in ACC. Some have shown a higher metastatic rate in minor as opposed to major salivary gland ACC.[10] However, others and we could not confirm this finding.[16] Spiro et al.[19] reported on higher incidence of distant metastases in case of locoregional failure. This was not found in our analysis in which the distant metastases rate was comparable in case of locoregional control and

failure (52% vs 48%). This supports the peculiar behavior of ACC with frequently developing distant metastases despite good clinical locoregional control, which suggests undetectable micrometastasis at the time of surgery.[20] However, too much is still unknown about the exact biology of ACC to consider this in planning treatment strategies, as suggested by Umeda et al.[21]

This study clearly shows that distant metastatic survival, regardless of other prognostic factors, is relatively short and on average 1 year. The vast majority of patients (75%) died of disease within approximately 3 years after diagnosis of distant metastases; only a small number of cases concur with the general assumption of distant metastatic ACC being an indolent type of disease. In case of multi- organ metastases, all patients died within 6 years of whom 50% within a year. In case of lung metastasis only, 50% died within 3 years and only 10% were still alive after 5 years. We furthermore confirmed that positive and close surgical margins, advanced T classification, nodal disease, and solid type ACC are influencing the development of distant metastases.[6,16,17] The influence of tumor grade has been questioned in the past, mainly because of difficulty applying the used grading systems.[20] The previously described faster tumor doubling time in case of solid type ACC is confirmed as the single negative prognosticator for distant metastatic survival seems to be solid type ACC regardless of the amount in this typically mixed type tumor.[19] The incidence of solid tumor components in the primary lesion (70%) in distant metastatic ACC is in accordance with the results of Bhayani et al.[18] who reported 73%. HGT is a previously described rare feature in ACC. It is important to describe these specific features in the pathology report because HGT in ACC has a high preponderance for nodal involvement and, therefore, neck dissection is advocated. Once definitive histology after primary surgery confirms HGT, one should consider adjuvant neck dissection or radiation of adjacent levels of the neck.[8,9] The quest for treatment targets and agents so far has been disappointing, as recently described in a review by Stenman et al.[28] on targeted therapies in salivary gland cancer. This showed no current effective treatment for recurrent or metastatic disease in case of ACC. In the present study, response rates with CAP regimen chemotherapy did not show encouraging outcomes and treatment was toxic. European Organization for Research and Treatment of Cancer 24982 phase II trial using gemcitabine was negative and the survival benefit of metastasectomy of the lung remains to be proven.[29,30] Two recent phase II studies with gefitinib (n= 18) and sorafenib (n= 23), respectively, did not prove to be effective or worthwhile exploring further.[31,32]

In conclusion, we found a relative poor survival in patients with distant metastatic ACC.

Acknowledgment

We would like to thank Professor Patrick J. Bradley for his expertise and meaningful contribution to this report.

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CHAPTER 5.

Mucoepidermoid carcinoma of the head and neck: CRTC1/3 MAML 2 translocation and its prognosticators

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Abstract

Purpose: Mucoepidermoid carcinoma (MEC) of the head and neck is a prevalent malignant salivary gland tumour with a reported good outcome. The aim of this study was to report the outcome in our centre.

Methods: A retrospective chart analysis with survival analyses was performed combined with fluorescence in situ hybridization (FISH) analysis to assess CRTC1/3 MAML 2 fusion gene presence.

Results: Sixty-four cases of MEC were identified. Median age at presentation was 51.4 years with a predominance for parotid gland involvement. Five, 10- and 20- year disease-free survival was 98%, 90% and 68%, respectively. Overall survival was 94%, 90% and 64%, respectively. Local recurrence was seen up to 14 years after primary diagnosis; distant metastases were diagnosed up to 17 years later. The overall recurrence rate was less than 20 per cent. CRTC1/3 MAML 2 fusion gene presence showed no survival benefit.

Conclusion: MEC of the head and neck has a favorable outcome with the exception of high-grade MEC. PNI and nodal involvement are not rare. CRTC1/3 MAML 2 fusion gene presence showed no survival benefit. The tendency for late onset of loco-regional and distant recurrence should not be underestimated.

Introduction

Mucoepidermoid carcinoma (MEC) is a glandular epithelial neoplasm characterized by mucous, intermediate and epidermoid cells, with sometimes columnar, clear cell and oncocytic features.[1] It is known as one of the most prevalent malignant salivary gland tumours of the head and neck. Besides adenoid cystic carcinoma (ACC) and acinic cell carcinoma (AciCC) it completes the top three most diagnosed salivary gland malignancies. Three histological grades are recognized (low, intermediate and high grade). Perineural invasion (PNI) is occasionally seen and lymph node metastases are considered rare. Besides the high-grade cases, patient with MEC have a reportedly excellent prognosis with associated long-term disease-free survival. Distant metastases (DM) are seldom encountered and the treatment of choice is surgery, followed by postoperative radiotherapy (PORT) when indicated. High-grade (HG) MEC, however, should be considered a distinct subtype within the group of MEC because of its propensity for nodal disease as well as DM.[2] Both major and minor glands are equally involved with a predominance for the parotid gland, the hard palate and buccal mucosa. The most important problem in grading of MEC is constituted by the intermediate category and the different systems used which may lead to under- or overgrading depending on the systems used with the direct consequence of under- orovertreating the patient.[2-4] Debate exists on which grading scheme to use (modified Healey, AFIP and Brandwein) and which treatment strategy to use.[5,6] Much like grading in other types of malignant salivary gland cancers, the application of these systems is time-consuming due to the point-based character and prone to inter- observer bias.[2] Nonetheless, grading and clinical stage are historically considered the main predictors of survival in MEC.[2,5-8]

Part of the MEC are characterized by a specific translocation of t(11;19)(q21;p13) leading to CRTC1/3 MAML 2 fusion gene. The presence of this fusion gene was originally reported mostly in low-grade tumours but more recently, it became apparent that also a considerable percentage of intermediate and high-grade tumours bear the translocation.[9-11] The presence of this translocation was initially considered to have a beneficial impact on outcome.[12,13] More recent research, however, suggests that there is no correlation between tumour status or survival and translocation status.[14] In this analysis, 64 cases of MEC diagnosed and treated at our institution over a 30-year period are reviewed with regard to prognosticators and outcome, including histological grading and translocation analysis.

Materials and methods

Medical charts of patients diagnosed with MEC from 1984 to 2013 were reviewed. Sixty-four cases of MEC were identified for further analysis. All patients were entirely treated and followed up at our institution. Clinical work up was standardised and consisted of physical examination, ultrasound guided fine-needle aspiration cytology (US-FNAC) or biopsy depending on localisation of the primary lesion and computer tomography (CT) or magnetic resonance (MR) imaging. A chest X- ray was routinely performed at first visit. Follow-up after treatment was done 2 monthly to 6 monthly for the first 5 ears followed by annual control visits over a total of 10- to 20-year period. Staging was done according to the TNM classification of the Union for International Cancer Control (UICC), eighth edition.[15] In all cases surgery with curative intent was feasible, followed by PORT in case of advanced stage disease or adverse features, e.g. perineural invasion (PNI), angio- invasion or unsatisfactory surgical margins. Variables analysed were age, gender, T- stage, N- status, extracapsular spread (ECS), surgical margins, PNI, tumour grade and PORT. For detection of the translocation in MEC samples, fluorescence in situ hybridization (FISH) analysis was carried out on 4 µm tissue sections according to the manufacturer's protocol, using ZytoLight R SPEC MAML2 Dual Color Break Apart Probe (ZytoVision Ltd, Bremerhaven, Germany) as described previously.[11] Due to lack of material or poor quality 45/64 tumours could be analysed for translocation status. The MAML2 Dual Color Break Apart Probe can detect rearrangements involving the MAML2 gene irrespective of the fusion partner (including the CRTC3-MAML2 fusion). The nuclei were counterstained with 4',6-diamidino-2-phenylindole (DAPI), diluted in Vectashield, and samples were evaluated by fluorescence microscopy (ZyGreen: excitation 503 nm, emission 528 nm; ZyOrange: excitation 547 nm, emission 572 nm). Cells without the t(11;19)(q21;p13) translocation show fused green and red signals, typically resulting in a yellow signal. Translocation- positive cells exhibit fused green and red, as well as separated red and green signals, or split signal (Fig. 1A, B).

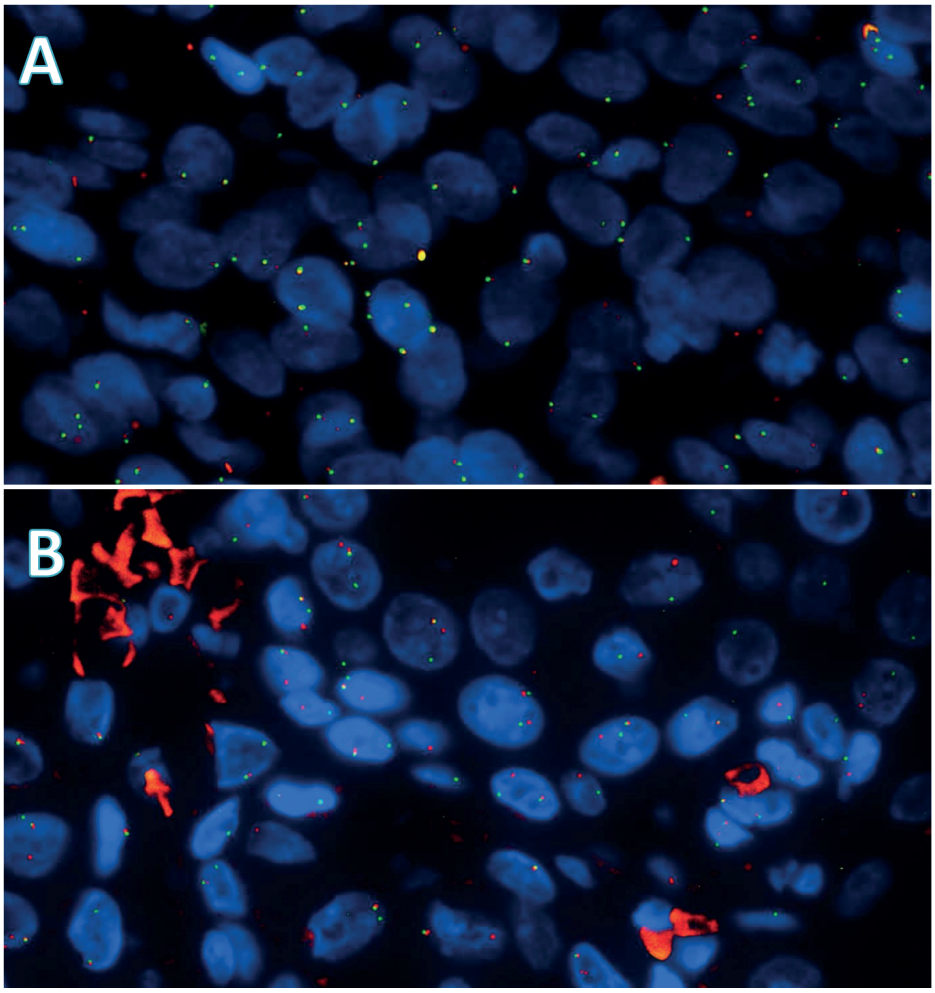

Figure 1AB. A. Example of FISH for tumor with a MAML2 translocation. The nuclei of most tumorcells (blue) contain a split signal (red and green dot).
B. Example of FISH for tumor without the translocation. All nuclei show an orange (green-red) unsplit signal.

A MEC sample was considered positive for the t(11;19) (q21;p13) translocation when the split signal was identified in at least 10 out of 100 cells. In all but one of 64 cases multiple slides were available for revision by an expert head and neck pathologist (EB). Grade was revised by the point-based AFIP system as suggested by the World Health Organization (WHO).[1] Survival analyses were done using SPSS statistical software version 22.0 (IBM, New York). Disease-specific survival (DSS) and overall survival (OS) were estimated through Kaplan–Meier curves. Multivariate analysis could not be reliably performed due to the small number of events in this typically indolent type of disease.

Results

The clinicopathological data are depicted in Table 1.

Clinicopathological data of 64 cases of MEC		N	%
Age			
Median	51.4		
Range	8- 87		
Gender			
Male		35	54
Female		29	46
Site			
Major			
	parotid	26	40
	submandibular	1	2
	sublingual	-	-
Minor			
	hard palate*	16	25
	oral cavity (non palate)	6	9
	oropharynx	9	14
	larynx	4	6
	other	2	3
T- stage			
T0		1	1
T1-2		52	81
T3-4		11	17
N-status			
N0		52	82
N+		12	18
	ECS	4	33
M- status			
M0		60	94
M1		4	6
UICC (8th edition) stage[16]			
I		33	52
II		12	18
III		7	11
IV		12	18
Surgical margins			
clear		30	46
close		24	37
positive		7	11
uncertain		3	5

Clinicopathological data of 64 cases of MEC	N	%
Grade (AFIP)		
low	38	60
intermediate	10	15
high	16	25
PNI		
yes	10	16
no	54	84
CRTC1/3- MAML 2 fusion gene		
positive	28	44
negative	13	20
N/A	23	36
PORT		
yes	43	66
no	21	33

Table 1. *: two cases with both hard and soft palate involvement; UICC: Union for International Cancer Control; PNI: Perineural invasion; PORT: postoperative radiation therapy. N/A : not assessed.

CRTC 1/3- MAML 2 fusion gene analysis was feasible in 42 cases. In 29/42 (69%) cases the translocation was present. Survival analyses showed no significant association nor was there a trend observed with the presence of the translocation. Fusion gene presence relative to tumour grades was 64%, 88% and 56%, respectively, for low, intermediate and high grade. Thirty-three cases of MEC staged N0 were available for translocation analysis showing presence in 24/33 (73%). For N + this was 4/9 (44%). Median age at presentation was 51.4 years (range 8- 87). Taking this median as a cut-off, it showed that patients aged 51 or more suffer a significantly worse DSS. It should be noted that advanced stage disease was more prominent in this group (≤ 50: 7% vs > 50: 42%). There is a trend for worse disease-free survival in older patients when analysed for early stage (T1–2) disease alone ($p = 0.051$). There was no clear gender predilection (54% male) and no difference in survival between males and females. Median follow-up was 102 months with a maximum of 258 months. The majority of MEC was located in the minor salivary glands (58%). All but one (submandibular gland) major gland tumours were located in the parotid gland; the hard palate (palate: $n = 19$: 15 hard, 2 soft, 2 combined) was the most affected site amongst the minor gland tumours (50%). 40% of tumours involved the parotid gland. Survival analysis showed no difference for minor versus major gland involvement. The vast majority (82%) of tumours were early stage (T1–2) tumours at the time of diagnosis. Nodal involvement was seen in 18% of cases of which four showed extracapsular spread (ECS) after surgical excision. N + disease was diagnosed in 11% of early stage tumours and in 42% of T3–4 tumours. The distribution of N- status was N1 ($n = 7$; 5 parotid, 1 oropharynx and 1 palate), N2b ($n = 3$; parotid, submandibular and oropharynx), N2c ($n = 1$; oropharynx midline) and N3 ($n = 1$; unknown primary). Relative to grade nodal disease was seen in 11%, 30% and 31% for low, intermediate and high-grade (HG) MEC, respectively. N + disease was negatively associated with DSS, OS (Fig. 2) and with developing distant disease as shown in Table 2.

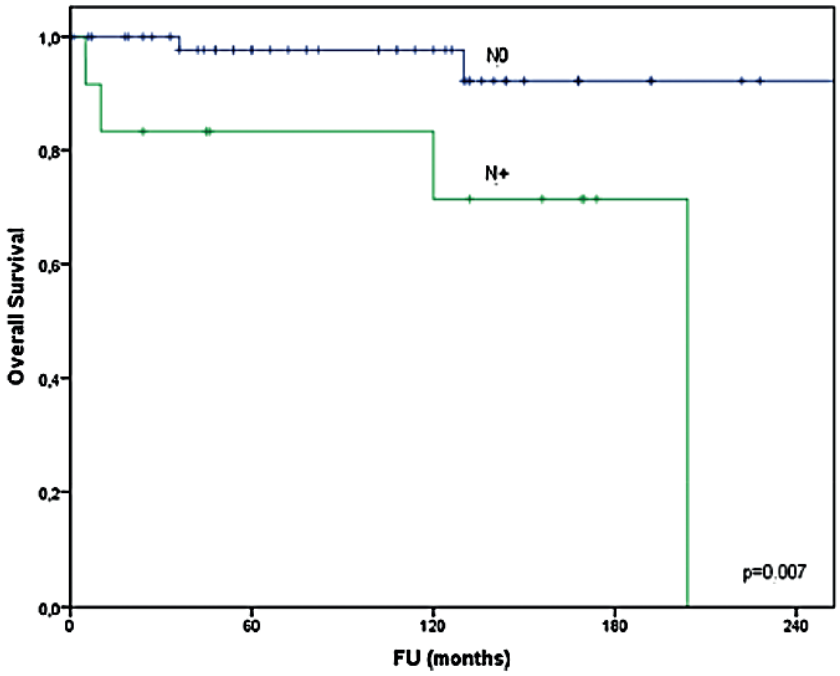

Figure 2. Overall survival relative to N- status.

5-, 10- and 20- year survival rates (%) in the current study (n=64)

	LCR	DSS	DFS	DDFS	OS
5y (%)	95	94	98	98	94
10y (%)	86	94	90	92	90
20y (%)	65	67	68	69	64
Age>50y (p- value)	**.023**	**.030**	.061	.06	**.017**
UICC Stage (Early vs advanced) (p- value)	.19	.075	.11	.28	**.026**
Grade (p- value)					
low vs intermediate (p- value)	.53	.69	.86	.71	.69
intermediate vs high (p- value)	.58	.51	.32	.86	.25
low-intermediate vs high (p- value)	.17	.069	.11	.31	**.011**
N+ (p- value)	.63	**.032**	.17	**.010**	**.007**
PNI (p- value)	.064	**.026**	**.027**	.16	**.047**
surgical margins (p- value)	.998	.33	.36	.095	.56
CRTC 1/3- MAML 2 fusion gene (p- value)	.55	.10	.094	.098	.29
PORT (p- value)	.83	.14	.99	.20	.11
major/minor (p- value)	.42	.90	.54	.58	.85

Table 2. LCR: local control rate; DSS: disease specific survival; DFS: disease free survival; DDFS: distant disease free survival; OS: overall survival; UICC: Union for International Cancer Control; N+: nodal involvement status; PNI: perineural invasion; PORT: Postoperative radiotherapy.

Distant disease was diagnosed in four (6%) cases, two of which were in the preoperative work up (both high grade). Two patients developed distant disease after a prior local recurrence (one low grade (translocation status negative); one intermediate (translocation status positive). In one case the interval between the local recurrence and diagnosis of DM was 6 years. Surgical margins were defined as clear (≥ 5 mm), close (1 > 5 mm) and positive (≤ 1 mm). Margins were clear in 46%, close in 31% and positive in 14% of cases with no association with T- status. Margins for parotid MEC were clear in 35% and close in 50% of cases and clear in soft/ hard palate in 63% with the remainder of cases showing only close margins. A close or positive margin status was not negatively associated with outcome. With regard to histological grade the incidence of lowgrade MEC was highest with 60%. The incidence of intermediate and HG MEC was 15% and 25%, respectively. HG MEC vs. low/ intermediate grade was negatively associated with OS: 5- and 10- year OS of 100% for low and intermediate grade versus 78% and 59% for high grade, respectively. $p = 0.011$; Fig. 3).

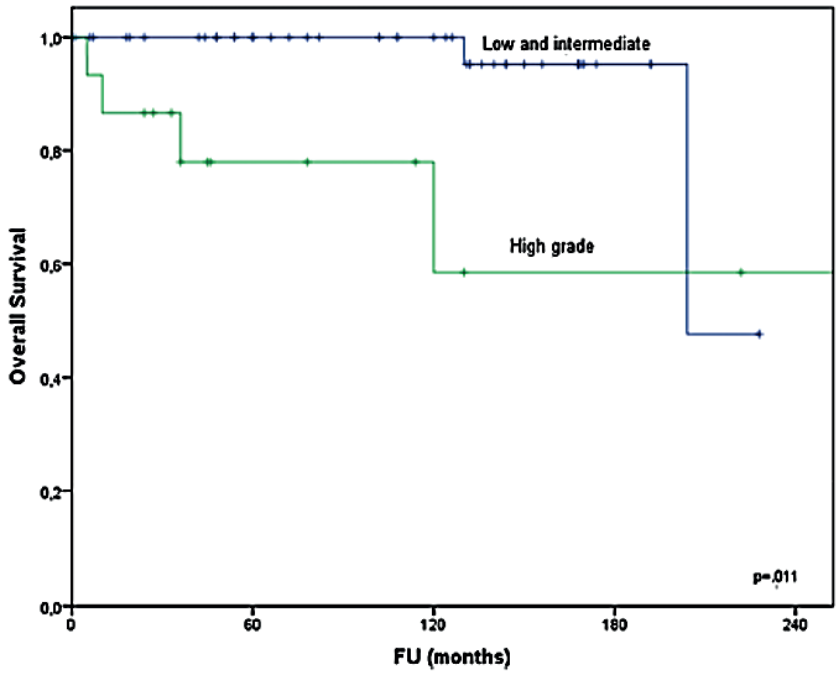

Figure 3. Overall survival relative to grade.

PNI (two points in the AFIP grading system) was diagnosed in 16% of cases and never in case of low-grade MEC. PNI was present in 44% of high-grade tumours and in 30% of intermediate-grade tumours. PNI was negatively associated with DSS (Fig. 4), DFS and OS. Sixty- three per cent of patients received PORT. Advanced stage tumours (T3–4), high-grade tumours and tumours with PNI all received PORT.

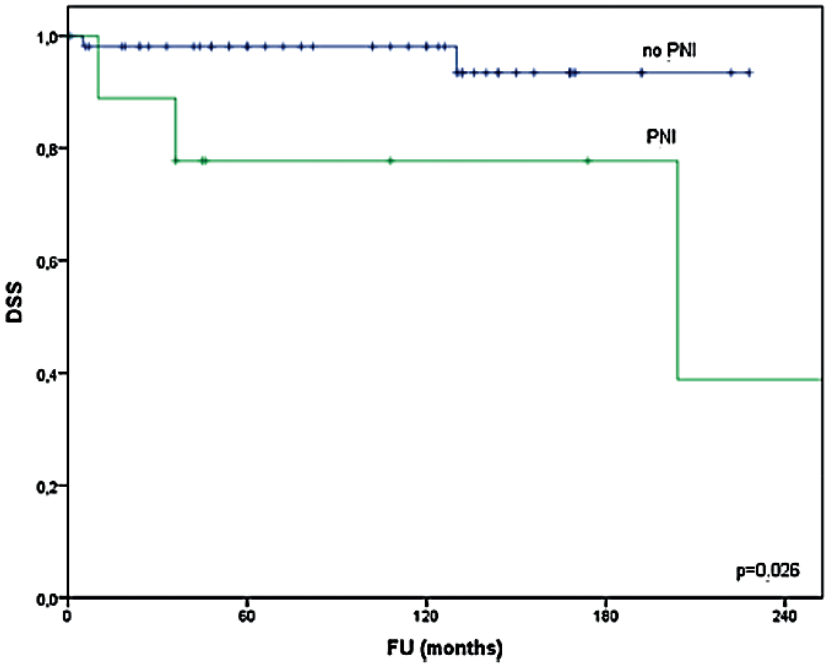

Figure 4. Disease specific survival relative to PNI.

In early-stage tumours (T1–2), low-grade tumours and tumours without PNI this was 58%, 47% and 61%, respectively. There was no superior local control or survival benefit in case of PORT. Local control rate was even worse in the group receiving PORT although no significant difference was found. For the total cohort analyzed, 5, 10- and 20- year DFS was 98%, 90% and 68%, respectively. For OS this was 94%, 90% and 64%, respectively. Local recurrence was seen up to 14 years after primary diagnosis where DM were diagnosed up to 17 years later. The overall recurrence rate in MEC was less than 20 per cent. (Fig. 5).

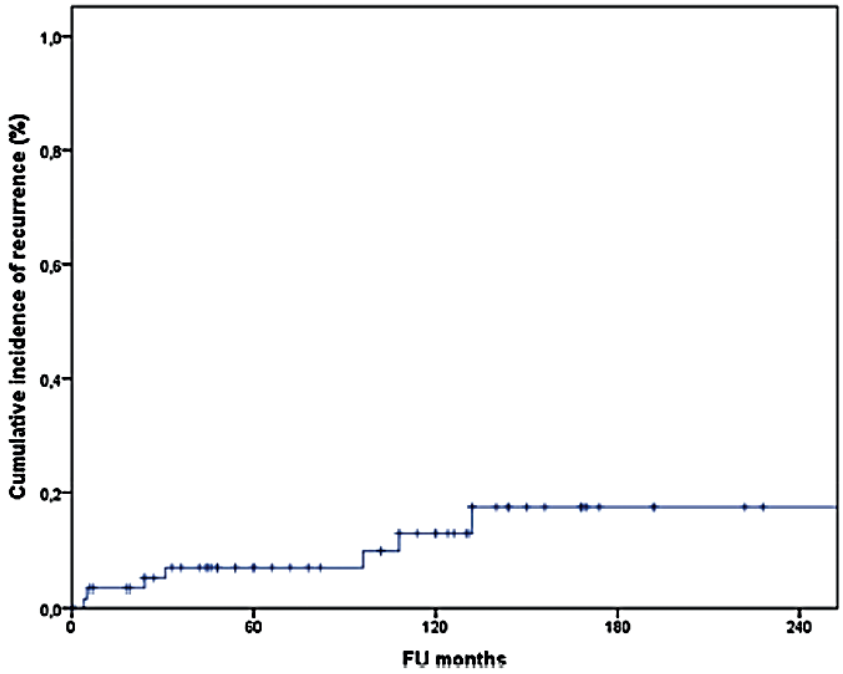

Figure 5. Cumulative incidence of recurrence*: In one case a local recurrence was diagnosed prior to distant disease (DM after 204 months). Therefore this late onset event is not shown in this graph. Less than 20% of patients develop recurrent disease.

Discussion

MEC of the head and neck is generally known as a disease with a favourable outcome. Ellis et al. describe a 3:2 female predilection which we could not confirm in the present study.[16] The most reported sites affected by MEC are the parotid gland and the hard palate, which is in accordance with our series.[17] Similar to our findings, early-stage tumours as well as low-grade tumours are predominantly diagnosed.[18]

Accuracy of fine-needle aspiration (FNA) is acceptable for HG MEC (MEC is identified as MEC; 87%) but less so for low-grade tumours (68%) where others suggest to perform core needle biopsy (CNB) which has a higher accuracy than FNA for detecting salivary gland malignancy in general.[19,20] The risk of seeding is almost negligible for both procedures.[21] Ample cytological experience with MEC ultimately leads to superior interpretation of FNA.[22] According to Kashiwagi et al. pre- operative MR imaging in case of suspicion of MEC may show different characteristics depending on grade.[23] With the current use of diffusion weighted imaging (DW MRI) the distinction between benign and malignant salivary gland lesions has dramatically improved.[24] In case of uncertain cytology or histology this may aid in preoperative planning. CT imaging is not suited for identifying PNI but may

aid in evaluating bony erosion or invasion.[25] There is little experience with 18-FDG PET- CT in MEC and previous reports mainly produce data on salivary carcinoma in general with small sample sizes for MEC.[26] In pulmonary MEC a correlation between high standardized uptake value (SUVmax) and HG MEC is suggested.[27] There is no debate regarding the treatment of MEC: surgery with or without PORT. One can discuss the necessity of (elective) neck dissection (END) or its extent as it has been described in a review by Moss et al..[28] They report on a relatively high incidence of occult nodal disease mainly in relation to high-grade tumours which should justify END in these patients fit for surgery. The problem, however, is that discriminating in grade on pre-operative histopathological/ cytological analysis is cumbersome due to the earlier mentioned problems with the grading systems applied.[2] Chen et al. found an incidence (Surveillance, Epidemiology and End Results; SEER) of 34%, 8.1% and 3.3% for high, intermediate and low-grade, respectively, of positive nodes in levels I–III. Based on this they suggest to perform END only in case of HG MEC.[29] In the current study the difference in incidence of nodal disease in intermediate and HG MEC was similar (30% and 31%, respectively). With an overall incidence of positive nodes of 18% in the current series and the possible risk of undergrading it might be a potential risk to refrain from END in all cases which are not HG MEC cases. Apart from this, the different grading systems used for MEC (AFIP, Brandwein and modified Healey) makes grading prone to down- and upgrading as is also discussed by Chen et al. and Seethala et al..[2,29] It is unclear which grading schemes were used in all individual cases from the SEER database but the use of multiple schemes might have influenced the incidence of nodal involvement relative to grade. A recent report by Qannam et al. describes the AFIP system (used in this study) as the most suitable.[30] The existence of these three grading systems will continue to contribute to inter-observer variability in the future. Ganly et al. have suggested to merely look for high mitotic rate and necrosis as these two features should predict a poorer outcome.[30-32] Positive or close margin status surprisingly did not show poorer outcomes than cases with clear margins. Achieving clear margins is difficult, mainly in the parotid (35%), oropharynx and oral cavity. We reached a 46% clear margin rate which seems reasonable in comparison to previous reports. McHugh et al., for example describe a 30% clear margin status in their case series of 125 patients.[17] An explanation for the relatively high percentage of close margins (50%) in the current study for MEC of the parotid gland is the proximity of the facial nerve and other surrounding anatomical structures in this area. Radiotherapy is historically employed as an adjuvant treatment in case of aggressive features (HG MEC), advanced stage disease, PNI, angio-invasion, extra- glandular growth and incomplete surgical margins. The National Comprehensive Cancer Network (NCCN) recommends PORT in early-stage (T1–2) disease in case of spillage, PNI and intermediate/ HG MEC.[17,31,33] In this cohort, 66% of patients received PORT, mainly in case of positive or close margins, PNI, high-grade disease, nodal involvement and advanced stage. This probably explains why the PORT- group has no better outcome in survival analyses compared to the no PORT- group; initial prognosis was worse due to adverse features necessitating PORT. Okomura et al. recently reported on possibly refraining from PORT in case of early-stage disease (T1–2) in

the presence of the translocation CRTC1/3- MAML2 fusion gene, even in case of intermediate or HG MEC. They reported 4/47 local recurrences which could be locally treated.[31] The results should be interpreted with caution due to the relatively small number of cases. The CRTC1/3- MAML 2 fusion gene translocation -CRTC1 first described as a candidate gene for induction of salivary gland tumours by Tonon et al. and CRTC3 by Fehr et al.[34,35]- was also analyzed in our group and was present in 69% of cases. This percentage is in accordance with the data published by Saade et al. who found 56% in their series and reviewed six more studies with an average of 62%.[36] Chenevert et al. found a 100% prevalence of the translocation in their series with a relative small sample size (n = 14).[37] Nevertheless, large differences are seen with regard to HG MEC ranging from 0 to 71%. Again, this is highly probably due to different grading systems used. Saade et al. further confirmed the unique correlation for the CRTC1/3- MAML 2 transcript with MEC which makes it a useful diagnostic feature. No survival benefit was found by Saade et al. in case of presence of the translocation.[36] This is in accordance with our findings. A recent study by Birkeland et al.—analyzing 90 cases of MEC for CRTC 1/3- MAML2 fusion gene— found similar results.[14] This contradicts the potential survival benefit described in previous series. It should be noted that these series were mostly relatively small warranting prospective multi centre studies for proper analysis.[12,36-38]

MEC of the head and neck has a favourable prognosis in general. HG MEC, however, should be considered a specific subtype with higher incidence of nodal and distant disease leading to poor overall survival. PNI and nodal involvement seem to be strong negative prognosticators and are relatively frequently encountered (15% and 18%, respectively). The mainstay of treatment is still surgery with PORT when indicated. To date, there are no effective adjuvant systemic treatments for MEC. There have been reports on partial responses from cisplatin, paclitaxel and gemcitabine, but these treatments have not been considered standard of treatment in the recurrent/ metastatic setting.[39] The CRTC1/3- MAML 2 fusion gene translocation might be a target for adjuvant systemic treatment in the future. Other genetic alterations, such as deletion in the CDKN2A/ p16 gene, might be worth exploring in this respect.[39-42] Treatment for patients in the recurrent/ metastatic phase should be optimized in the future. Treating physicians should be aware of the potential of MEC for late onset local and distant recurrence and the distinct and possible relentless course of HG MEC.

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CHAPTER 6.

Prognostic factors in Acinic Cell Carcinoma of the Head and Neck: The Amsterdam experience

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Abstract

Introduction : The aim was to analyse prognosticators in acinic cell carcinoma (AciCC) in two head and neck referral centers in Amsterdam, the Netherlands.

Materials and methods : Eighty- nine cases of AciCC treated between 1979 and 2016 were retrospectively reviewed. Five, - 10 -and 20- year estimates of survival were executed as well as univariate analysis of prognosticators.

Results : The majority of AciCC were T1-T2; 89%. Two percent had nodal disease (2%). The most affected organ was the parotid gland (85%) with a female preponderance (64%). Mean age was 52 years with most cases diagnosed in the fourth to sixth decade. The majority of patients received adjuvant radiotherapy. Elective neck dissection (END) in the N0 neck showed no metastases. High grade transformation (HGT) was found in 21% of cases. Median follow up was 101.9 months. Median time to recurrence was 26 months. Nine patients developed distant metastases (DM) of whom 6 had HGT-AciCC. Median survival with DM was 7 months. Five,- ten -and twenty- year estimates were 84%, 81% and 81% for recurrence free survival respectively. Negative clinical features were advanced stage disease and tumour size >2.6 cm. Negative histological features were a high mitotic rate, HGT, close and involved surgical margins and necrosis.

Conclusion : AciCC- HGT excluded- of the head and neck has an excellent prognosis and shows acceptable long term results. END can be considered as part of the standard treatment due to the relative high incidence of HGT- AciCC and low accuracy of cytology.

Introduction

Acinic Cell Carcinoma (AciCC)- also known as acinar cell carcinoma- of the salivary glands is a relatively rare tumour, representing 2 percent of salivary gland tumours, with a predominantly indolent course. In the Netherlands specifically, AciCCs represent 12.4- 17.4 % of salivary gland malignancies.[1] Historically, the first report of AciCC was in 1892 by Nasse describing it as a blue dot tumour.[2] Later Thackray and Lucas suggested the term "acinic cell tumour" before it was generally agreed to apply "carcinoma" instead of "tumour". This was due to efforts of head and neck- and oral pathologists to further unravel the oncologic pathogenesis of AciCC.[3-7] The majority of AciCCs originate in the parotid gland with a low incidence in the other major and the minor salivary glands.[7] In The Netherlands, approximately 15% of parotid malignancies are AciCCs which is in accordance with international reported incidence in literature.[8,9] There seems to be a predilection for Caucasians, females and advanced age.[10] Although the disease often has a protracted course, high grade transformation (HGT) -previously referred to as dedifferentiation- shows a significantly worse outcome.[11] HGT of AciCC is a rare phenomenon characterized by histologic progression of low-grade AciCC to high-grade adenocarcinoma or undifferentiated carcinoma with a higher propensity for loco- regional recurrence, lymph node- and distant metastasis (DM). It is generally associated with abundant cytoplasm, comedo-type necrosis and high mitotic activity.[11] The diagnosis mammary analogue secretory carcinoma (MASC) was introduced in 2010 and this tumour type was considered to have great similarity with AciCC. It derived its name from resemblance to secretory carcinoma of the breast with the identical ETV6-NTRK3 gene fusion. Its nomenclature has been changed to the current "secretory carcinoma". Despite the similarity to AciCC, secretory carcinoma has no gender predilection, is seen in younger patients, is more prevalent in the minor salivary glands and has minimal tendency towards HGT.[12-14] The recognition of secretory carcinoma has led to re-diagnosis of unjustly previously diagnosed AciCCs. The signature recurrent t(4;9)(q13;q31) translocation which leads to upregulation of Nuclear Receptor Subfamily 4 Group A Member 3 (NR4A3) has proven a meaningful tool in discriminating AciCC from secretory carcinoma. This seems especially true for cases with HGT.[15,16]

The mainstay of treatment for AciCC is surgery with or without postoperative radiotherapy (PORT). Overall, five-year survival is reportedly as high as 90% with a 20- year OS of over 50%.[17-20]

The roll of systemic treatment is limited to the recurrent- metastatic setting. Except for *HTN3-MSANTD3* fusion gene presence in a minority of AciCCs, no key target mutations or fusion genes have been identified for targeted treatment and reported response to platinum based treatments and combination treatment (e.g. cyclophosphamide, doxorubicin an cisplatin (CAP)) varies.[20,21] The Keynote phase 1b 028 study showed promising results for treatment with pembroluzimab for

salivary gland malignancies in general.[22] These results should be supported by the Keynote 158 study which is currently recruiting.[23,24]

Since previous institutional reports on AciCC generally describe a relatively limited number of cases of AciCC or reported on cases which were part of a group analysis of different types of malignant salivary gland tumours, we set out to analyse a series of AciCC treated in the two Amsterdam Head and Neck Centers: The Amsterdam University Medical Centres (Amsterdam UMC) and the Netherlands Cancer Institute (NKI). In this way, a large number of patients treated for AciCC could be collected .

Materials and Methods

All cases of AciCC treated at the Amsterdam UMC and NKI over a 37- year period (1979-2016) were identified and analyzed by means of retrospective chart analysis and revision of pathology. In the majority of cases multiple slides were available for histopathological review which was carried out by three expert head and neck pathologists (EB, LS and JvdW). In each case consensus was reached with regard to the features analyzed. Secretory carcinomas diagnosed after review of initially diagnosed AciCCs were excluded from the analysis. Diagnosis was primarily made on H&E staining. In case of doubt an immunohistochemical staining with pan-TRK was done. Initial diagnosis of adenocarcinomas not otherwise specified (NOS) and undifferentiated carcinomas of the salivary glands were not reviewed in this analysis. In theory, some of these cases would have been re-diagnosed as HGT- AciCC. AciCC with high grade features differs from the conventional low grade AciCC morphology. HGT-AciCC diagnosis was made based on high mitotic rate, especially with atypical mitoses, combined with necrosis, pleomorphism, angioinvasion and extraglandular growth which are less frequently seen in low grade AciCC.

Histopathological review was routinely performed on referral. All patients underwent a routine ENT examination combined with a chest X- ray. Ultrasound with fine needle aspiration cytology (US-FNAC) during the diagnostic work-up as well as a CT or MRI were performed in the majority of cases. Resection of the primary tumour was performed with elective neck dissection (END) in a selected group of parotid tumours (predominantly advanced T- stage or pre- surgical diagnosis of high grade features). Deep lobe resection was mainly performed in case of primary tumour involvement of the deep lobe or in case of proven lymph node metastases. Staging was done retrospectively according to the eighth edition of the TNM staging system of the Union for International Cancer Control (UICC).[23] PORT was indicated according to the following criteria: presence of advanced stage disease, adverse histopathological features (HGT, perineural invasion, extraglandular growth and angioinvasion) and close or positive surgical margins. Outpatient controls were routinely performed starting on a 3- monthly basis with 6- monthly visits in the long term.

Recorded outcome measures were loco- regional recurrence or DM, recurrence free survival (RFS), disease specific survival (DSS) and overall survival (OS) after completion of treatment. Factors analyzed in relation to these outcome measures were age, gender, site and size of tumour, histopathological features such as HGT, necrosis and mitotic rate, TNM-classification, stage, type of surgery for the primary, type of neck dissection (ND), surgical margins and PORT. These data were analyzed using a log rank test with Kaplan Meier curves and with univariate Cox regression analysis for determination of hazard ratios. Multivariate analysis could not be reliably performed due to a relative low number of events. SPSS© statistical software version 26 (IBM Corp., Armonk, NY) was used for statistical analysis.

Results

Eighty-nine patients with AciCC were identified, of whom 48 were treated in the Amsterdam UMC and 41 at the NKI. Fifty- seven patients were female (64%) and the median age at presentation was 53 (range 2-88). The majority of patients (60%) were aged over 50 at time of diagnosis. In 76 cases (85%) the tumour was located in the parotid gland. Other sites involved were the oropharynx (n=7), the oral cavity (n=4), the submandibular gland (n=1) and the sublingual gland (n=1). The clinicopathological data are shown in Table 1.

In 14 out of 89 (16%) cases, patients were previously (partly) treated elsewhere, mostly with local excision under the presumption of a benign tumour. A small number of cases was previously treated with curative intent elsewhere and then referred to our centers because of a recurrence.

At presentation, 77 out of 87 cases (89%) were diagnosed as T1-T2 and in 2 cases stage could not be retrieved. Median tumour size was 2.6 cm (range 0.7-8.5). At initial diagnosis, lymph node metastases were found in 2 cases: one patient had a small single lymph node metastasis (N1) and the other had a single metastasis in level II with clinical extracapsular spread (ECS) (N3b). Both were confirmed by ultrasound guided FNAC. There was one case of proven DM at first visit.

Five-, 10 and 20-year RFS was 84%, 81% and 81% respectively. For DSS and OS this was 90%, 88% and 88% and 85%, 79% and 60%, respectively (Table 2).

Clinicopathological data acinic cell carcinoma Amsterdam (n=89)

			%
Age		52.4y (2-88)	
Gender			
female		57	64
male		32	36
Site			
parotid		76	85
submandibular		1	1
sublingual		1	1
minor		11	12
Tumour size		2.6 (.7-8.5)	
T			
1		32	36
2		38	43
3		8	9
4		1	1
NA		9	10
cN			
cN0		82	92
cN+		2	2
NA		5	6
M			
M0 (at presentation)		88	99
M1 (at presentation)		1	1
Surgery			
parotidectomy		75	
Transoral resection		8	
segmental mandibulectomy		2	
maxillectomy		1	
ND only		1	
no surgery		2	
ND			
no		68	76
yes		21	24
SND		12	15
	L2	5	6
	L1-2	1	1
	L1-3	6	7
	L2-3	1	1
pN+		1*	8
(M)RND**		9	10
(r)pN+		9	100
Surgical margins			
	clear	46	53
	close	23	26
	positive	18	21
	NA	2	2

Clinicopathological data acinic cell carcinoma Amsterdam (n=89)			
			%
PORT			
	no	24	27
	yes	65	73
	60Gy	20	31
	66Gy	18	28
	other	27	42
Recurrence			
	no	74	83
	yes	15	17
DM			
	no	80	90
	yes	9	10

Table 1. Clinicopathological data of AciCC Amsterdam (n=89).*therapeutic selective neck dissection; ** therapeutic neck dissections for regional recurrence. NA; not applicable, ND; neck dissection, (M)RND; (modified) radical neck dissection, PORT; postoperative radiotherapy, DM; distant metastasis.

Tumours were stage I in 40 cases (45%), stage II in 35 cases (39%), stage III in 10 cases (11%), stage IVA in 3 cases (3%) and one case was stage IVC (1%). Figure 1 shows the KM estimate for RFS relative to stage. It depicts a relatively poor RFS in advanced stage disease (p< 0.001).

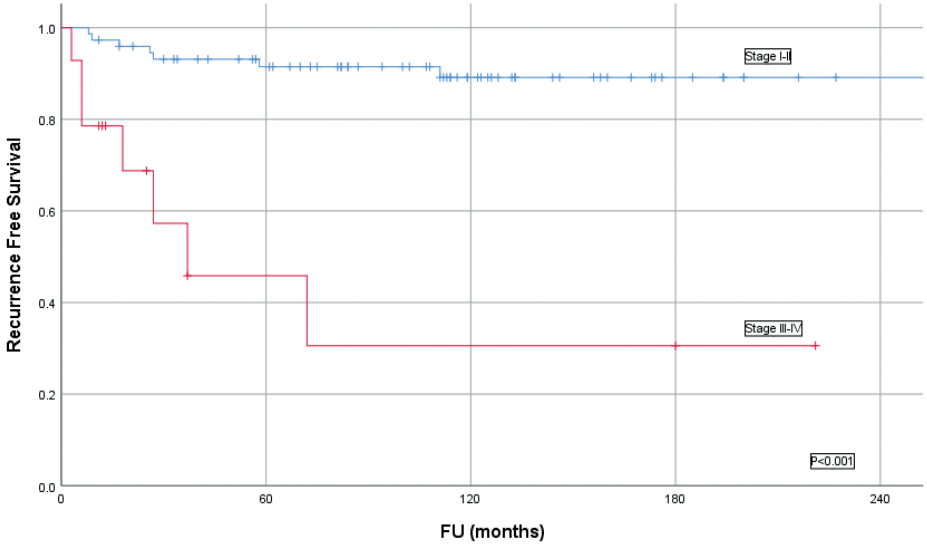

Figure 1. Recurrence free survival relative to stage (early vs advanced).

In 66 out of 89 cases FNAC was performed pre-operatively (74%). In 38 of these, AciCC was diagnosed or suspected (33 AciCC and 5 possible AciCC). This resulted in a sensitivity of FNAC for AciCC of 58% in this series. No core needle biopsies were done.

Five,- ten and 20 - year survival for AciCC and its prognosticators (n=89)

	RFS		DSS		OS	
5-y (%)	84		90		85	
10-y (%)	81		88		79	
20-y (%)	81		88		60	
	p- value	HR (95% CI)	p- value	HR (95%CI)	p- value	HR (95%CI)
Age <50>	0.137	2.4 (0.76 - 7.5)	0.433	1.7 (0.44 - 7.0)	0.007	4.6 (1.5 - 14.1)
Advanced vs. Early stage	<0.001	9.7 (3.3 - 28.3)	<0.001	13.7 (3.2 - 58.4)	<0.001	7.0 (2.8 - 17.8)
Tumour size >2.6cm	0.068	3.8 (0.90 - 16.1)	-**	-**	0.002	7.7 (2.1 - 28.0)
Surgical margins*	0.002	7.6 (1.7 - 34.3)	-**	-**	0.037	2.7 (1.1 - 6.7)
High mitotic rate	0.005	2.9 (1.4 - 6.1)	0.09	2.2 (0.88 - 5.4)	0.175	1.5 (0.83 - 2.8)
Necrosis	0.044	3.3 (1.03 - 10.3)	0.312	2.3 (0.47 - 10.9)	0.019	3.5 (1.2 - 9.8)
HGT	<0.001	2.9 (1.7 - 4.9)	0.001	3.2 (1.6 - 6.4)	0.002	2.0 (1.3 - 3.2)

Table 2. Five,-10- and 20- year survival for AciCC and analyzed prognosticators (n=89). RFS; recurrence free survival, DSS; disease specific survival, OS; overall survival, CI; confidence interval, HPF; high power field, HGT; high grade transformation, *; positive- close vs. clear margins, **; note: not estimated because of 100% survival in reference group.

All patients underwent surgery with curative intent in one of the two centers except for 2 cases; one patient had undergone surgery elsewhere and showed no signs of residual disease and one patient was diagnosed with distant disease at first visit. Of the 88 patients treated surgically, the vast majority (n=76) underwent parotidectomy: (partial) superficial (n=46); (sub)total (n=30). ND was performed in 21/88 cases (24%). Two cases had proven metastases prior to initial surgery for which a modified radical ND (MRND; e.g. level I-V ND with preservation of internal jugular vein, sternocleidomastoid muscle and spinal accessory nerve) and a selective ND of levels I-III were performed, respectively. In 9 cases a (M)RND was performed for regional recurrence after initial local resection. Six out of these nine (67%) (M)RNDs performed for regional recurrence were HGT- AciCC. The remaining 10 cases (3 HGT- AciCCs) of ND were elective NDs (END) of level II, II- III and I-III. No occult metastases were found in the END specimens. All ENDs were performed for AciCCs of the parotid gland. In one case a frozen section of an enlarged level II node was negative and further dissection was refrained.

Microscopic surgical margins achieved were clear (≥5mm) in 47/88 (53%), close (>1-<5mm) in 23/88 (26%) and positive (≤1mm) in 18/88 (20%). Relative to T- status, clear margin percentage reported for T1/T2 was 58% ,whereas for T3/T4 this was 20%. An involved or close margin status led to relatively poor RFS despite PORT, as shown in Figure 2 (P= 0.002).

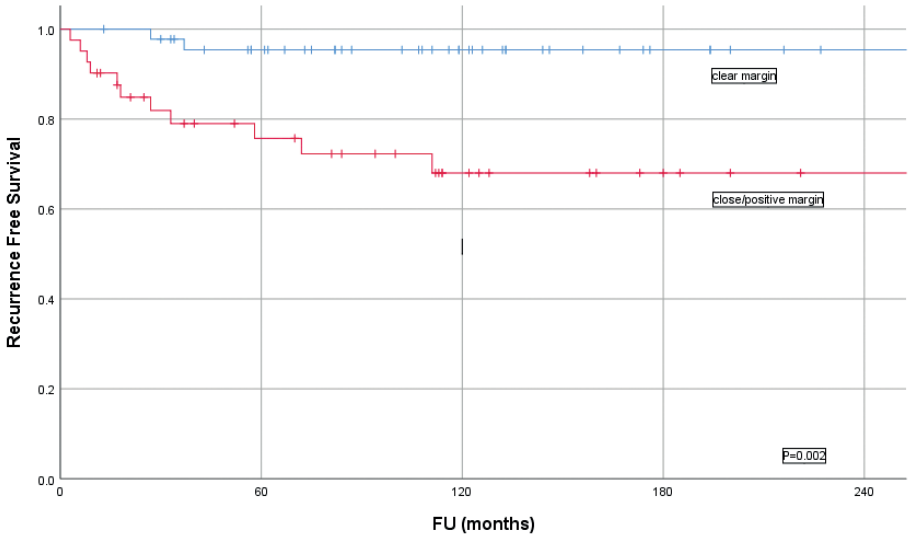

Figure 2. Recurrence free survival relative to surgical margin status(clear vs. close/positive).

Perineural invasion (PNI) was reported in 7/89 cases (8%). One case with PNI had clear surgical margins; 2 were close and 4 were positive. One case involved the soft palate, the other 6 were in the parotid gland.

HGT was reported in 19/89 cases (21%); figure 3AB.

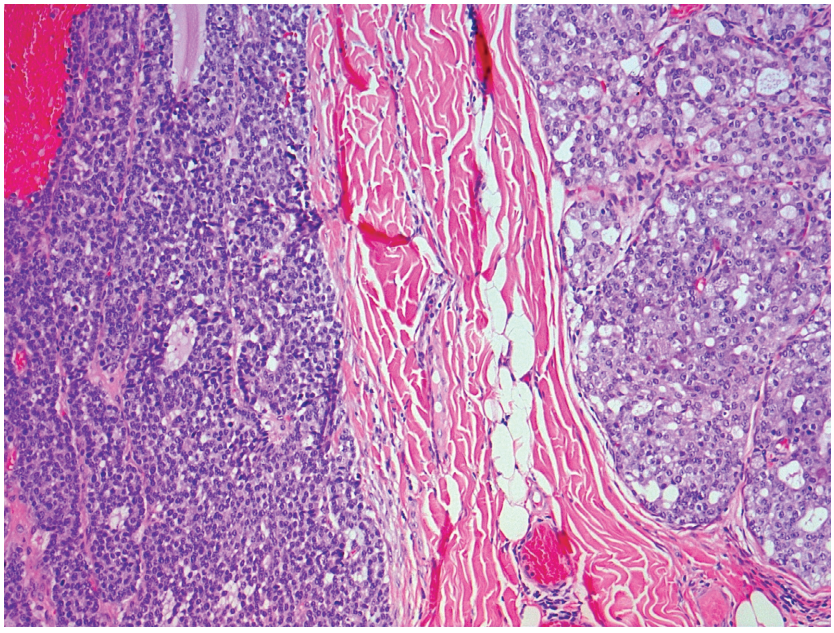

Figure 3A. Histopathological image of high grade transformation (HGT). The dedifferentiated component is seen on the left side of the image where the right shows "conventional" tumour with intercalated duct differentiation.

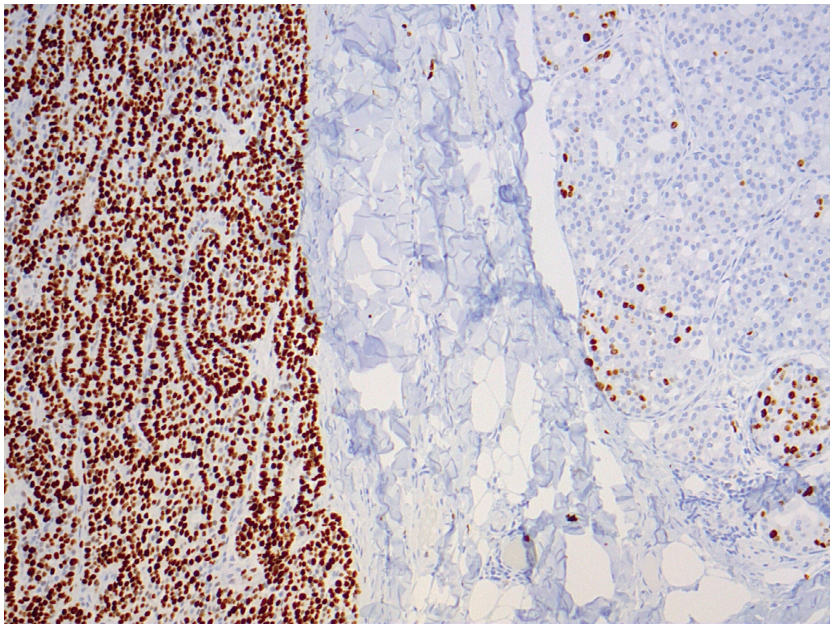

Figure 3B. MIB1 immunohistochemistry showing the high proliferative ratio in the HGT component.

All diagnoses of HGT-AciCC were after initial surgical treatment in one of the two centers and no cases of (recurrent) HGT were seen after initial diagnosis of conventional AciCC. Cases with HGT showed a poorer RFS, DSS and OS. (Table 2).

Comparable results for RFS were found in the presence of tumour necrosis or high mitotic rate which was defined by more than 2 mitosis per 10 high power fields (HPF). These last two features were not uniquely found in HGT-AciCC and were associated with poorer RFS. Eleven cases of HGT were found in patients aged >50 and 8 cases in patients <50 years (Pearson Chi- Square p= 0.865). The histopathological features analyzed relative to grade are shown in Table 3.

	Conventional AciCC (n= 70)	HGT- AciCC (n= 19)
PNI	4 (6%)	3 (16%)
angioinvasion	1 (1.4%)	4 (21%)
extraglandular growth	9 (13%)	16 (84%)
pleomorphism	7 (10%)	13 (68%)
necrosis	3 (4%)	8 (42%)
high mitotic rate	4 (6%)	17 (89%)
lymphoid stroma	24 (34%)	5 (26%)
atypical mitosis	0 (0%)	4 (21%)

Table 3. Histopathological features of AciCC (n=89). PNI; perineural invasion.

The HGT-AciCC cases showed remarkably worse outcomes as shown in the KM estimate for RFS relative to grade. (p<0.001; Figure 4)

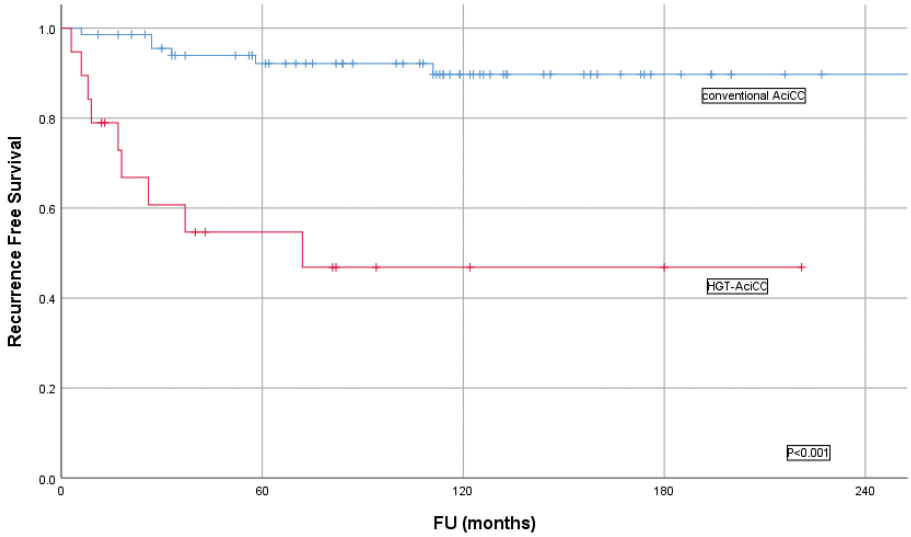

Figure 4. Recurrence free survival relative to grade (conventional vs. high grade transformation (HGT) AciCC).

Twenty-four cases of AciCC did not receive PORT (27%). These were all T1-T2 tumours (22 parotid, 2 soft palate) without negative characteristics (e.g. PNI, angio-invasion, HGT). Surgical margins of the non-irradiated patients were clear in 22/ 24 cases (92%). One case with a close margin was a cystic mass of 1.5 cm of the parotid with non-invasive features. In another case with a positive margin after RND for a local recurrence, PORT was refrained from because of a stage IV ovarian cancer with liver metastases diagnosed shortly after treatment of the AciCC.

Patients who received PORT all had advanced stage disease, close or positive surgical margins or adverse histopathological features. The majority of irradiated patients received a dose of 60-66 Gray (Gy) on the surgical bed. Of these, four patients needed postoperative re-irradiation due to recurrent disease.

Median follow up was 101.9 months (range 7- 405). At last follow-up 65 patients were alive with no evidence of disease. Three patients were alive with disease; 2 with distant disease and 1 with a local unresectable recurrence. All 3 had HGT tumours. During the follow-up period, 9 patients died of AciCC, 10 died of other causes and 2 died of unknown cause.

For the 15 patients with a recurrence, median time to recurrence was 26 months (range 3- 111). Five of these had a re-recurrence (3 with DM). Nine of these 15 patients had recurrent distant disease. In six of them, definitive histopathology showed HGT. In 4/9 HGT cases disease recurred within 9 months whereas the shortest time to recurrence for non- HGT- AciCC was 27 months. Seven patients were diagnosed with a local or regional recurrence. Figure 5 visualizes that the majority of recurrences developed within 40 months after treatment, but also shows that late recurrences do occur. Overall, DM occurred in 9 cases (10%). Median time to diagnosis of DM was 18 months (range 0-76 months) Median survival after diagnosis of DM was 7 months (range 1- 28).

Discussion

This reports shows that outcome in patients with AciCC in the studied population is acceptable. A relative high incidence (21%) of HGT in AciCC was found. Clinical nodal disease in the non- recurrent setting was seldom encountered and no occult lymph node metastases were found in performed ENDs. Patients with HGT- AciCC were at relative high risk for recurrent disease with a shorter RFS.

The high recurrence free survival rates as well as the low incidence of DM in this AciCC cohort confirms earlier reports of the relatively favourable prognosis of AciCC, with the exception of stage III/IV and HGT cases.[11,17,18] The majority of AciCCs is situated in the parotid gland which is in accordance with the literature.[5,10,17-20,26] In most cases, patients presented with early stage disease with a low incidence of clinically involved lymph nodes.

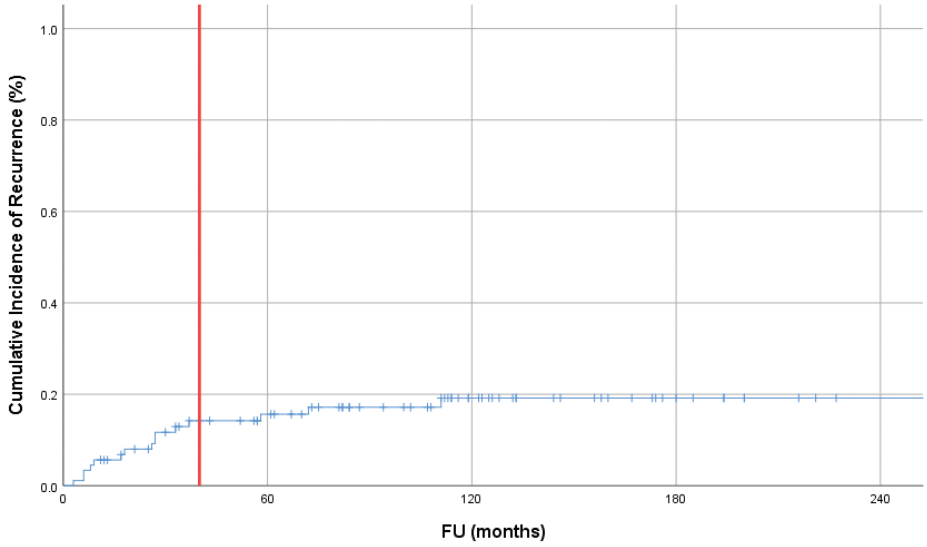

Figure 5. Cumulative incidence of recurrence in AciCC. Note that the majority of recurrence develop in the first 40 months post treatment (red vertical line denotes 40 months) and that total recurrence rate does not exceed 20 percent.

A gender predominance for females (male: female ratio 3:7) was found in the current study which is in accordance with most previous studies such as the one by Patel et al. in which the surveillance, epidemiology and end results (SEER) database was used analyzing 1129 cases of AciCC. [10,26,30] The age distribution in our series, with most patients in the 5th (n=15, 17 %), 6th (n=14, 16%) and 7th (n=13,15%) decade, is comparable with the SEER data (slight majority over 50- years of age) in which Gomez et al. found that 40% was over 50- years old. Neskey et al. found that over 60% of patients were over 45- years of age.[17,19] The median age of 52 years concurs with the reported median age (52y) by Hoffman et al. and that by the recent review by Kirschnick et al. (n= 422) who reported an average age of 47.51y.[30,31] Our cohort also included 7 pediatric patients, which illustrates the wide distribution in age groups. The distribution of HGT-AciCC cases (n=19; 21%) was equally distributed among age groups with diagnoses in patients in each age group. As reported in literature, the parotid gland is the most affected gland whereas the other major glands are seldom involved. Minor gland involvement is rare and reported as mostly seen in the buccal mucosa and lip.[32] In the Amsterdam series we found the soft palate to be the most involved in minor gland site for AciCC, despite the fact that AciCC is reported to be less predominant in the soft palate than other salivary gland carcinomas.[18]

The diagnosis of lymph node metastases at first consultation is very rare in AciCC. We only diagnosed 2 out of 89 cases (2%). The indolent biological behavior of at least low grade AciCC is in accordance with the clinical observation by Gomez et al. (8%) and Neskey et al. (9%).[17,19] A recent paper by Moon et al. confirmed the low incidence of lymph node metastases in AciCC (6.8%

in a SEER database study of 962 cases). It found a clear correlation of positive nodal status with advanced tumour stage and HGT.[33]

Tumour size showed to be a negative prognosticator as shown in Table 2. This is supported by the finding of Neskey et al. who found hazard ratios (HR) of 2.9 and 2.4 for OS and DFS in AciCCs larger than 3 cm respectively. HRs for OS and RFS in our series were both 7.7 (CI 2.1- 28.0) and 3.8 (CI 0.9-16.1), respectively for tumour size larger than 2.6 cm.[19] Surgery is historically the primary treatment modality for AciCC when feasible. Although the incidence of clinical nodal involvement in this series at first presentation was low, END of mainly levels II-III was often performed, mostly at the same time as the parotidectomy. No metastases were identified in these neck dissection specimens. In literature, there is no consensus as to when to perform END in the clinically N0 neck in AciCC. A recent retrospective analysis by Grasl et al. found that in END for AciCC the incidence of positive nodes was 4/27 (14.8%) which were situated in levels II, III and IV in case of a parotid gland primary tumour mainly without HGT.[27] This would suggest the necessity for END in AciCC, although the analyzed cohort was relatively small. Kaura et al. analyzed a series of parotid malignancies and concluded to at least perform END in high grade tumour types with invasive features such as salivary duct carcinoma and high grade AciCC.[28] The necessity of performing END in HGT-AciCC is supported by a recent paper by Yue et al..[29] These results would suggest to at least perform END in HGT- AciCC. The results in the current study did not confirm a high incidence of occult lymph node metastases (0/11) although the number of ENDs was relatively small. This complicates the interpretation of these results. It is clear that in case of confirmed nodal disease- often associated with HGT- a therapeutic ND is performed for at least levels II, III and IV.[17] In case of the clinically N0 neck, END is reportedly advised for large tumours preventing regional recurrence, or in case there is a preoperative suspicion of a high grade tumour based on clinical grounds or core needle biopsy.[19] In the current series only two patients had a clinically positive neck and underwent therapeutic ND. In case of regional recurrence ND was extended to the levels beyond II, III and IV. Since there was no occult disease in the END specimens sampled, the suggestion could be raised not to routinely perform END, supported by the reported rate of lymph node metastases of around 10%. Contrary, Grasl et al. advise to at least be vigilant for suspicious periparotid -and level II nodes during surgery and to proceed with ND in the consented patient when necessary. Based on their analysis, they advise to consider END in the N0 neck in AciCC with the footnote that hard evidence is lacking and multicenter prospective studies are needed to confirm the actual added value of END in AciCC.[27] However, with the incidence of 21% of HGT-AciCC in the current study and despite the negative ENDs performed (in mainly low grade AciCC), END in the N0 neck could be advised based on the relative high incidence of N+ disease in HGT-AciCC in previous literature, considering the pre-operative cytological uncertainty and the relative low morbidity of selective ND. Given the retrospective nature of the current study it was not exclusively possible to retrieve all reasons for deep lobe removal. The necessity of deep lobe resection in primary salivary gland malignancy is a

debated issue but should be performed (primary tumour in the deep lobe or tumour extension into the deep lobe) or considered in specific scenarios (proven positive intraparotid or cervical node; proven high grade tumour).[34]

Margin status seems to play an important role in survival in AciCC patients. As shown in Table 2 clear margins (≥5mm) are an evident positive prognosticator in all survival analyses ($p<0.05$) and the HR for RFS is 7.68 for positive/ close margins. Zenga et al. described 45 cases with a clear, close and positive margin in 44%, 40% and 16%, respectively. This is in line with our results of 53%, 26% and 20%. The HR reported by Zenga et al. is 3.72 for positive margin status for RFS.[35] The importance of obtaining an adequate surgical margin has also been previously described by Gomez et al. and Neskey et al. in their series as well as in earlier systematic reviews.[17-19]

PNI and angioinvasion are rare features in AciCC as is also shown in our cohort with an incidence of 8% and 6%, respectively. However, higher incidences have been described as by Gomez et al. (23% and 8.6%).[17] Despite this relative low incidence of both characteristics, their presence does have a negative impact on survival as it does in any other salivary gland carcinoma.[17,18,35] In the current study, mainly angioinvasion was a negative prognosticator (RFS, OS and DSS $p<0.05$).

HGT-AciCC is not that uncommon as we found 21% of cases to have high grade transformation. HGT- AciCC is recognized as an aggressive high grade tumour with a tendency for nodal involvement and DM. We found that HGT occurred both in patients under as well as over 50 years of age, in an equal distribution, which is in contradiction with the report by Skalova et al. in which a higher incidence in older patients was shown. Notably, the authors recommend adequately sampling of the entire surgical specimen since the presence of only small foci of HGT (5%) leads to a poorer prognosis and overlooking these transformed nests may lead to possible mismanagement in the adjuvant setting.[11] Gomez et al. reported on a proposed proliferative grading system - which is currently lacking for AciCC - which should be able to distinguish HGT in a proper manner by means of identifying high mitotic rate (>2 mitosis/10 HPF) and/or necrosis, pleomorphism as well as positive margins and/or extracapsular extension suggesting biological aggressive behavior. In their analysis 35% of cases were labeled as high grade tumours.[17] Ideally, a uniform grading system as suggested by the World Health Organization (WHO) for other salivary gland histologies would aid in more specific grading of AciCC to gain better insight in the prognosis.

In literature on AciCC there is a general consensus regarding PORT. Low grade and early stage tumours without adverse histopathological features are adequately treated with surgery alone when clear margins are achieved.[34-38] In case the facial nerve is uninvolved clinically or during surgery, it is preserved. If the tumour is in close proximity to the nerve and margins are involved, PORT should be sufficient to eradicate microscopic residual disease. In the current series, most

cases with close margins were irradiated whereas Zenga et al. reported that PORT can be refrained in such cases in the parotid gland. For parotid tumours, abutment of facial nerve branches is common and the perineurium might act as an anatomical barrier making PORT unnecessary.[39] In case of advanced stage disease as well as HGT and attributing adverse features as angioinvasion and PNI there is an agreement in literature that PORT is necessary.[32-35] The fact that there is a trend observed for poorer outcome in irradiated patients in the current study is probably due to the fact that initial prognosis was worse due to these adverse features necessitating PORT. Overall, the same rationale applies to AciCC as for other salivary gland carcinomas which means PORT should be omitted in case of early stage, low grade disease without adverse features and uninvolved surgical margins.[17-19, 34-40]

Although recurrent disease in AciCC is reportedly relatively rare, a 17% recurrence rate (15/88) in this study emphasizes that it is a circumstance to take into account. Specifically HGT- AciCC showed a preponderance for developing DM with a relative short RFS. This supports the accelerated and aggressive biology of this dedifferentiated tumour type. In case of a loco- regional recurrence, salvage surgery followed by PORT is the preferred treatment. With regard to distant recurrence, median survival with DM in this series was 7 months with a maximum of 28 months. Since late onset recurrent disease fits AciCC there is an incentive for long term surveillance of these patients. To date, the search for effective systemic treatment strategies in the metastatic and recurrent setting is ongoing. In general, systemic treatment with traditional platinum- based chemotherapy has shown limited effect. No druggable gene alterations have currently been identified in AciCC.[20]

Overall, patients with AciCC ,with the exception of HGT- AciCC, have an excellent prognosis after surgery with or without PORT with a low recurrence rate although late onset recurrence is not rare necessitating long term surveillance. The lack of treatment agents in the recurrent and metastatic setting underlines the importance of sufficient surgical treatment considering the relative high incidence of HGT-AciCC reported herein. This would encompass resection of the primary tumour with contemplation of performing an END- as an alternative to elective radiation of the neck- since pre- operative histopathological certainty is difficult to obtain. HGT- AciCC has a relatively high incidence of nodal involvement, poor prognosis with a high risk for recurrence and a short RFS.

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CHAPTER 7.1

General Discussion

GENERAL DISCUSSION

Malignant salivary gland tumours (MSGTs) of the head and neck are rare tumours with their own specific biology and clinical course. Even within this group the differences are striking. Due to the low incidence it has been historically difficult to unveil their characteristics. Many reports have been on MSGTs as a whole making interpretation of results almost impossible. Analysing combined data from different centers on specific tumour types increases the numbers but harbours the danger of bias due to possible differences in diagnostics and treatment. In this thesis, we set out to report on relatively large case series from one – and in one case two - head and neck referral center(s) with comparable regimens in Amsterdam with regard to the three most prevalent MSGTs: Adenoid cystic carcinoma (ACC), mucoepidermoid carcinoma (MEC) and acinic cell carcinoma (AciCC). This study design's most prominent feature was therefore to thoroughly analyze relatively large series of specific MSGTs diagnosed and treated identically with well recorded long term follow up.

Adenoid Cystic Carcinoma

ACC typically consists of cribriform, tubular and solid components.[1] The solid tumour type is considered a high grade tumour with accompanying clinical behaviour. ACC in general behaves as a high grade MSGT with a low incidence of cervical metastasis but with a high incidence of recurrence and distant disease.[1-8] These recurrences can develop very late after primary treatment which is specifically true for loco- regional recurrence. Obtaining clear surgical margins is difficult due to local anatomy and perineural invasion but has a significant positive impact on survival. Awareness of the high probability of involved or close surgical margins aids in proper counseling and surgical planning. Patients can be informed about the high chances of postoperative radiotherapy. The high recurrence rate in ACC both underlines the need for prolonged follow up of patients as well as the need for improved adjuvant systemic treatment. The chemotherapeutic regimens used today (cyclophosphamide, doxorubicin and cisplatin; CAP) have shown modest responses.[9-13] To date, genetic profiling has identified the signature translocation t(6;9)(q22-23;p23-24) leading tot *MYB- NFIB* fusion gene in ACC. Even without the translocation, MYB can be upregulated in ACC. Identification of overexpression of MYB aids in correctly diagnosing a MSGT as ACC. Several other genomic alterations in ACC have been identified in this typically chemoresistant tumour. These may provide the foundation for future therapeutic strategies in the recurrent and metastatic setting.[14-16] Multiple clinical trials regarding targeted therapies have not been successful but results of current trials are anxiously awaited.[17-22]

Since the traditional three- tiered grading systems for ACC have proven to lead to moderate reproducibility, the two- tiered grading system described in this thesis – presence or absence of a solid component- has been adopted in current literature.[1,2,23,24] The good reproducibility and low inter-observer variability of this scheme leads to proper identification of high grade tumours. Since

grade plays an important role in prognosis in ACC this simplification adds to proper stratification. This in turn leads to improved counselling of patients with ACC and a better prospect with regard to treatment outcome.

The high recurrence rate in ACC of the head and neck is a known feature in this type of salivary gland cancer. Typical negative prognosticators for distant disease (DM) specifically are advanced T- status as well as nodal involvement, the presence of solid type ACC and inadequate surgical margins.[25-30] In case of DMs, which mostly develop within the first 5 years post therapy, treatment options are limited. Although some patients survive for a relatively long time with DMs, this should be noted as exceptional. The correct way of counselling patients with distant metastatic ACC of the head and neck is to communicate a realistic scenario which is not surviving for years.[31] The limited added value of systemic treatment in the recurrent or metastatic setting should also be discussed thoroughly to manage expectations. In this manner, patients can decide on their treatment in dialogue with their physician which is even more important in this time of shared decision making. The recently introduced nomogram for survival in metastatic ACC could be a helpful tool in counseling patients.[32] The role of (lung) metastasectomy in ACC has not been abundantly analyzed but may provide survival benefit in selected cases. Furthermore, resected pulmonary lesions can be used for further unravelling of the biological response to systemic treatment.[33]

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma (MEC) is considered the most diagnosed MSGT. It is a glandular epithelial neoplasm with mucous, intermediate and epidermoid cells, incidentally accompanied by clear cell, columnar and oncocytic features.[34] In general, patients diagnosed with MEC have a good prognosis in terms of disease free survival with the exception of those diagnosed with high grade (HG) MEC.[35] The presence of the CRTC1/3 MAML2 fusion gene has originally been reported as a positive prognosticator in MEC. Where it was initially described to be predominantly present in low grade MEC, evidence for its presence in all grades has accumulated, including the current study. Although the translocation is highly specific for MEC, emphasizing its diagnostic value as such, its presence does not uniquely favor prognosis.[36-42] There have been reports on prognostic benefit of the presence of the translocation in HG MEC.[43] The absence of deletions inactivating the tumor suppressor gene CDKN2A has been reported to be a prerequisite for the prognostic benefit of the presence of the CRTC1/3 MAML2 fusion gene.[44] If it is a possible target for systemic treatment remains to be proven.[14]

With regard to surgical treatment, it is generally agreed to perform elective neck dissection for the N0 neck in high grade MEC.[45,46] However, both the use of different grading schemes (AFIP, Brandwein and modified Healey) as well as the difficulty of adequately identifying grade before surgery complicates matters. Based on the data in this study (similar high incidence of 31% and 30%

for high grade and intermediate grade respectively; mean 18%) there seems to be an incentive to perform END. The minimally added morbidity of for example level II-III END in parotid gland MEC supports this suggested regimen.[42]

The indications for postoperative radiation therapy (PORT) are much less debated. The general consensus is that PORT is indicated in case of presence of advanced stage disease, inadequate surgical margins and other adverse histopathological features (perineural invasion, angio- invasion, extraglandular growth and high grade disease). The observations in the current study underline the forenamed indicators for PORT.[42,47-50]

Although MEC in general has a low recurrence rate, awareness of both late onset recurrent disease as well as the specific aggressive behavior of HG MEC is paramount.

The lack of proven effective systemic treatment for MEC in the recurrent and metastatic setting has been and still is a key reason for further genomic sequencing in order to identify potential treatable targets.[14,51]

Acinic Cell Carcinoma

Acinic cell carcinoma (AciCC) is a malignant epithelial neoplasm of the salivary glands in which at least some of the neoplastic cells demonstrate serous acinar cell differentiation characterized by cytoplasmic zymogen secretory granules.[52] In more recent literature, the emphasis has been on high grade transformation (HGT) which is recognized as a specific entity within AciCC.[53-58] In the current two- center study, representing a relatively large number of cases, the incidence of HGT-AciCC proved to be high (21%). This confirms the importance of awareness of this dedifferentiated tumour type with its aggressive biology with accompanying high recurrence rates and relatively short recurrence free survival.[59] In general, patients with AciCC rarely present with clinical nodal disease. PNI and angioinvasion are both rare features in AciCC but are both negative prognosticators.[58,60,61]

Primary treatment is surgical with preservation of uninvolved named nerves (facial nerve). With regard to management of the N0 neck, there is agreement to perform END in case of advanced T- stage or proven HGT pretreatment.[62,63] However, since the presence of HGT is difficult to assess prior to surgery, there is reason for debate concerning performing END in the N0 neck. Since the incidence of occult nodal disease is relatively high in HGT- AciCC and considering the reported high incidence of HGT herein, END should be contemplated. This optimizes primary surgical treatment in a time where only PORT has proven to be an effective adjuvant treatment.[59]

PORT can be omitted in case of early stage disease without adverse histopathological features.[64-68]

Good long term survival in patients with AciCC is confirmed in this study with registered follow up of up to 20 years. The overall recurrence rate of 20% confirms its low grade features. However, the considerable group of patients suffering from HGT-AciCC deserves extra attention with regard to improvement of disease control beyond surgery and radiation.

Genomic sequencing in AciCC has revealed the genomic rearrangement [t(4;9)(q13;q31)] which enables upregulation of the transcription factor Nuclear Receptor Subfamily 4 Group A Member 3 (NR4A3). Specifically NR4A3 immunostaining (higher sensitivity and specificity than break apart FISH) proves to be useful in discriminating AciCC, even in HGT cases. To date however, no treatable targets have been identified through molecular profiling.[69,70]

In conclusion, this research has shown that ACC indeed has a high propensity for (late) recurrence and that achieving clear surgical margins is challenging due to local anatomy and frequent PNI. It has also proven that ACC with only the slightest presence of solid tumour component has a poor prognosis. This has led to an adopted new grading system with clear advantages over the earlier existing grading schemes. Additionally, the assumption of prolonged survival with DMs is rejected by showing a median survival with DMs of approximately 1 year.

Regarding MEC, this study has shown that the presence of CRTC1/3- MAML2 fusion gene does not always implicate a good prognosis. The high incidence of nodal involvement of up to 30% for high and intermediate grade cases justifies a low threshold towards END. HG MEC is prevalent (incidence of 25% in the current series) which should create awareness of not merely considering MEC as an indolent low grade MSGT.

Although AciCC is considered an indolent type of MSGT, the current focus on HGT in AciCC is more than justified. For patients suffering from this distinctive subtype, primary surgical treatment should be tailored and at least encompass (E)ND besides resection of the primary tumour. The need for further exploration of AciCC oncogenesis is paramount in order to identify potential treatment targets in this HGT subset with a high propensity for recurrent and metastatic disease.

CHAPTER 7.2

Summary

SUMMARY

This thesis describes clinico- and histopathological prognosticators as well as outcome in malignant salivary gland carcinomas of the head and neck with an emphasis on three predominant tumor types: Adenoid cystic carcinoma (ACC), mucoepidermoid carcinoma (MEC) and acinic cell carcinoma (AciCC). The results presented were gathered through retrospective analysis of patient data from the Amsterdam University Medical Centres (Amsterdam UMC) Vrije Universiteit Amsterdam. In the study regarding AciCC, patient data from both the Amsterdam UMC and the Netherlands Cancer Institute (NKI) were used.

Chapter 1 presents an overview of the current insights in the clinico- and histopathological characteristics and management of patients with a malignant salivary gland tumour (MSGT). The anatomy and physiology of the major salivary glands are described. The epidemiology and pathohistology of MSGTs with an emphasis on ACC, MEC and AciCC are discussed with special attention for the specific characteristics of this group including recent new insights in their molecular biology and changes in nomenclature. The current status of diagnostics and treatment is presented with among others the integrated use of the Milan System of Reporting Salivary Gland Cytology (MSRSGC) and the quest for improved adjuvant treatment.

In **chapter 2**, a relatively large single center series of 105 patients with adenoid cystic carcinoma (ACC) diagnosed and treated at the Amsterdam University Medical Centers, Vrije Universiteit Amsterdam in a period of 30 years, is retrospectively analysed with regard to outcome and possible prognosticators. All patients underwent surgery with postoperative radiation when indicated. The specific biological behavior of ACC is confirmed by its tendency for perineural invasion (PNI; 70%), relatively low incidence of nodal disease (10%) and distant as well as late local recurrence with a high overall recurrence rate of 77%. Mean age at presentation was 57.3 years and there was no gender predilection. Multivariate analysis showed several independent negative prognosticators for ACC of which advanced T- status was the strongest. Others included were N+ disease, grade III histology (Perzin grading system), close and positive surgical margins as well as older age. Interestingly enough, unsatisfactory margin status was significantly negatively correlated with disease free survival, disease specific survival and overall survival (OS) but not with local control. Five,- 10 and 20- year OS were 68%, 52% and 28%, respectively which is in accordance with the literature. Recurrent disease is common with mainly early onset distant disease (first 5 years post treatment) and late local recurrences (up to 20 years post treatment).Grade III ACC, consisting of a substantial part of solid type tumour should be regarded as a specific disease entity with a tendency for short term and relentless recurrence. This implies that almost all patients with ACC would benefit from improved adjuvant treatment once it becomes available.

In **chapter 3**, the routine grading systems for adenoid cystic carcinoma (ACC) are highlighted and their flaws are identified. Using different grading systems may lead to over- or undergrading and the cut off points used- >30 and >50% solid type component respectively- might lead to inter-observer variability. We therefore reviewed 81 cases by two experienced head and neck pathologists using both existing grading systems by Perzin and Spiro, respectively. Results were matched for an inter-observer agreement level. Cohen' s kappa scores were low (0.393 and 0.433 for Perzin and Spiro, respectively). As a third system, we merely scored the presence of a solid type tumour component regardless of its extent. This so called S+/- system showed a very high inter-observer agreement with a Kappa score of 0.990 which is excellent. This system was able to predict clinical outcome as good as the existing grading schemes. We therefore conclude that using the S+/- system has a high reproducibility and low inter-observer variability and should be considered a serious alternative for the traditional grading systems used.

In **chapter 4**, differences in patterns of survival in metastatic adenoid cystic carcinoma (ACC) are described. Historically, metastatic ACC has been described to have a relatively protracted course. We tested this hypothesis in a population of 105 patients, all diagnosed and treated at the Amsterdam University Medical Centres, Vrije Universiteit Amsterdam between 1979 and 2009. Incidence of distant metastasis (DM) in this population was 42% and 91% of DMs developed within 5 years post- diagnosis of ACC. Occasionally, DM were diagnosed up to 12 years post-diagnosis. Several tumour and disease characteristics were identified to be negatively associated with distant disease free survival (DDFS) such as advanced T classification, nodal involvement, solid tumour component (regardless of amount) and positive surgical margins. The organ most involved in distant disease was the lung, predominantly as single organ involvement (55%). Other organs affected were the liver and bone. These were predominantly sited in case of presence of solid type tumour; only 2 cases with synchronous metastatic disease were seen in the tumours without a solid component. With regard to survival with DM- distant metastatic survival (DMS)- solid type tumour presence was the only negative prognosticator in multivariate analysis. Patients with multi-organ involvement had a significantly poorer DMS than those with only lung metastasis. The median DMS with only lung metastasis was 31 months (range 1-98.5) and 9 months (range 1-70) in case of multi- organ DM. The overall DMS was 13.8 months (1-98.5). Overall, 75% of patients with metastatic ACC died within 3 years after diagnosis of distant disease. We therefore conclude that metastatic ACC is not always an indolent type of disease and that this warrants appropriate informing of patients.

In **chapter 5**, a population of 64 patients with mucoepidermoid carcinoma (MEC) of the head and neck is described, diagnosed and treated at the Amsterdam University Medical Centres, Vrije Universiteit Amsterdam in a 30-year period. This retrospective chart review was done to identify prognosticators. All patients underwent surgery with postoperative radiotherapy when indicated. Fluorescence in situ hybridization (FISH) was performed to identify the presence of the

t(11;19) (q21;p13) translocation which leads to CRTC1/3 MAML2 fusion gene. This translocation analysis was feasible in 42 cases of which 29 (69%) harboured the translocation. In contrast with earlier reports on survival benefit in patients carrying the translocation, we did not find this in this cohort. The parotid gland was the most affected major salivary gland in MEC and the palate was the most prevalent minor gland involved. The median age at diagnosis was 51.4 years with a slight predominance in males (54%). The accuracy of fine needle aspiration cytology for high grade (HG) MEC is acceptable with 87% but less so for low grade MEC (68%). Although elective neck dissection (END) is advised in HG MEC, currently used different grading systems (Armed Forces Institute of Pathology; AFIP, Brandwein and modified Healey) may lead to under- and overstaging potentially leading to undertreatment of the patient. With an incidence of 18% nodal disease- 11% in low grade, 30% and 31 % in intermediate and high grade respectively- in the current series it seems advisable to perform END in all cases of MEC. Perineural invasion (PNI) showed an incidence of 16% (0% in low grade and 44% and 30% in high and intermediate MEC respectively) . PNI, although absent in low grade MEC, seemed to be a negative prognosticator for disease specific survival (DSS) as well as for disease free survival (DFS) and overall survival (OS). Neck node involvement was negatively associated with DSS, distant disease free survival and OS. An involved or close surgical margin was not associated with poorer outcome. The decrease in long term DFS from 90% to 68% for 10- to 20- year DFS respectively emphasizes the risk of late recurrence and the need for long term follow up. To date there is no known successful systemic treatment available as adjuvant or in recurrent and metastatic setting.

Chapter 6 describes a two- center case series of 89 patients diagnosed and treated for acinic cell carcinoma (AciCC) of the head and neck at the Amsterdam University Medical Centers, Vrije Universiteit Amsterdam and the National Cancer Institute (NKI) in the period from 1979 to 2016. AciCC is historically recognized as a low grade tumour type with excellent long term survival. In the Amsterdam study an effort is made to identify possible prognosticators and to establish the role of high grade transformation (HGT) in AciCC of the head and neck. The vast majority of AciCC was early stage (T1-T2; 89%) and located in the parotid gland (85%) which is in line with previous reports. Mean age at diagnosis was 52 years. The male- female ratio was 3:7. All patients underwent surgery with curative intent followed by postoperative radiation (PORT)-73%- in case of advanced stage disease, close or positive surgical margins or adverse histopathological features. The presence of a close or positive margin led to a hazard ratio of 7.68 for recurrence. Fifteen out 89 patients suffered a recurrence (17%) of whom 9 developed distant disease with the majority (6/9) of these harbouring HGT-AciCC. Five,- 10 and 20- year recurrence free survival were 84%, 81% and 81%, respectively. The majority of these recurrence developed within 40 months after treatment. Median survival after diagnosis of DM was 7 months (range 1-28). Although perineural invasion and angioinvasion are rare features in AciCC- 8% and 6% in the current series- they prove to have a significant negative impact on outcome. Conventional AciCC when treated appropriate has an acceptable long term

survival with a low incidence of recurrence (<20%). The difficulty of correctly identifying HGT pretreatment means that adding elective neck dissection to resection of the primary tumour should be considered since the reported incidence of HGT-AciCC in this case series was 21%. The lack of systemic treatment options underlines the necessity for optimal primary surgical treatment.

CHAPTER 7.3

Future perspectives

FUTURE PERSPECTIVES

Although diagnostic and treatment modalities in MSGTs have been largely unchanged over the past decades there have been advances. With regard to diagnostics, the quality of imaging has dramatically improved. Besides the improvement in MR imaging overall, the introduction of diffusion weighted (DW) MR imaging has led to better distinction between benign and malignant salivary gland tumours.[71-73] The exception of a Warthin tumour tending to have a lower apparent diffusion coefficient (ADC) than an MSGT is noted. The combination of DW- MR imaging and perfusion MR imaging may aid in further distinction. Regardless of improved recognition of malignancy, imaging in general cannot specify different subtypes of MSGT.[71] The introduction of PET-CT -and 18F FDG PET-CT in head and neck cancer diagnostics specifically- has led to improved staging. Although 18F FDG PET-CT is not as optimal for MSGTs as for head and neck squamous cell carcinoma due to relatively low standardized uptake value (SUV) in some types, the relatively recent finding that ^{68}Ga PSMA PET-CT is useful in staging patients with ACC is hopeful.[74-78] Further development and improvements in the field of radiology and nuclear imaging will undoubtedly lead to superior imaging in the future.

The field of pathology is constantly moving due to new insights in tumour characteristics of MSGTs. The unraveling of tumour genetics is key in this respect and has led to identification of new tumour types. The World Health Organization (WHO) introduced a new overview on MSGTs in 2017.[79,80] The previously named mammary analogue secretory carcinoma (MASC)- a recognized entity since 2010- has been renamed as secretory carcinoma. In the period before 2010 these tumours were mostly unjustly diagnosed as AciCC. The polymorphous low grade adenocarcinoma is currently described as polymorphous adenocarcinoma (PA). There is no doubt that this landscape will shift in the years to come due to improved understanding of the MSGT- spectrum with advances made in genomic profiling.[14,16,81] A new WHO classification of MSGTs will be released in 2022.

Surgery will remain the mainstay of treatment in MSGTs. This means resection of the tumour often combined with (E)ND. Postoperative radiotherapy takes an important place due to often encountered adverse clinico-and histopathological features.[82,83] These radiation techniques have evolved over the last decades where standard of care is nowadays through intensity modulated radiotherapy (IMRT) sparing vital structures and decreasing toxicity where possible. Another exciting development is of course proton beam radiation which is currently readily available in the Netherlands. Intensity modulated proton therapy (IMPT) is gaining popularity in head and neck cancer care in general.[84] Specifically for unresectable ACC, there have been good results with carbon ion treatment with or without concurrent cisplatin.[85-87] Neutron beam radiation is another possibility but is scarce and accompanied by high toxicity.[88-90] Nevertheless, due to these exciting developments the result of optimal tumour response with minimal toxicity is closer than before.

The quest for successful systemic treatment has proven to be a long and hard journey. There have been reportedly acceptable results for concurrent chemoradiation in the adjuvant or primary setting (in case of inoperable disease) but in general responses are modest and short lived.[13,90-93] Since specific tumours like the salivary duct carcinoma (SDC) can be targeted due to presence of receptors like the androgen receptor (AR) and the Her2 receptor, systemic treatment has proven its value- androgen deprivation therapy (ADT), Her2 targeted therapy- mainly in the recurrent/metastatic setting but there have been recent reports on its added value in the adjuvant setting.[94-97] Nonetheless, possible treatment targets in other MSGTs have not been proven to respond as hoped for.[98-101] Again, meticulous biological profiling including identification of targets for immunotherapy will provide further insights in systemic treatment for MSGTs.[102] The fact that phase II studies and trials are currently ongoing and recruiting offers hope for the future. (NCT04209660; NCT03781986; NCT01969578; NCT05008237).

In conclusion, large improvements have been made in salivary gland cancer diagnostics and care. The biggest challenge ahead lies in optimization of treatment of patients with high grade MSGTs, specifically with regard to systemic treatment in the adjuvant and in the recurrent and metastatic setting.

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CHAPTER 8.1

Samenvatting

SAMENVATTING

Dit proefschrift beschrijft de klinische en histopathologische prognosticatoren evenals de behandeluitkomsten bij maligne speekselkliertumoren met de nadruk op drie predominante subtypen: Adenoid cysteus carcinoom (ACC), mucoepidermoid carcinoom (MEC) en acinuscelcarcinoom (AciCC). De beschreven resultaten zijn verkregen middels retrospectieve analyse van patientgegevens uit het Amsterdam UMC, Vrije Universiteit Amsterdam. Voor de studie over AciCC werd samengewerkt met het Antoni van Leeuwenhoek ziekenhuis/ NKI Amsterdam.

Hoofdstuk 1 schetst een overzicht van de huidige inzichten in de klinische en histopathologische kenmerken en behandeling van patiënten met een maligne speekselkliertumor. De anatomie en fysiologie van de grote speekselklieren worden beschreven. De epidemiologie en pathofysiologie van maligne speekselkliertumoren met de nadruk op ACC, MEC en AciCC worden besproken met speciale aandacht voor de specifieke karakteristieken van deze groep inclusief recente en nieuwe inzichten in de moleculaire biologie en veranderingen in de nomenclatuur. De huidige status van diagnostiek en behandeling wordt gepresenteerd met onder andere het geintegreerde gebruik van het Milan System of Reporting Salivary Gland Cytology (MSRSGC) en de zoektocht naar verbeterde adjuvante behandelingen.

In **hoofdstuk 2** wordt een relatief groot cohort van 105 patiënten beschreven met een adenoid cysteus carcinoom (ACC). Deze patiënten werden behandeld in het Amsterdam Universitair Medisch Centrum, locatie VUMC Amsterdam over een periode van 30 jaar. Er werd een retrospectieve studie gedaan naar behandeluitkomsten in relatie tot mogelijke prognosticatoren. Alle patienten ondergingen chirurgie met postoperatieve radiotherapie indien geindiceerd. De specifieke biologie van het ACC wordt bevestigd door het voorkomen van perineurale groei (70%), lage incidentie van lymfkliermetastasen (10%) en de hoge incidentie van zowel late locoregionale recidieven als afstandsmetastasen met een recidiefpercentage van 77%. Afstandsmetastasen ontstaan vooral in de eerste 5 jaar na diagnose en lokale recidieven kunnen zelfs na 20 jaar ontstaan. Multivariate analyse toonde verschillende onafhankelijke prognosticatoren voor ACC waarvan T- status de sterkste bleek. Anderen waren aanwezigheid van lymfkliermetastasen, graad III histologie (Perzin graderingssysteem), krappe positieve chirurgische marges evenals gevorderde leeftijd. Opvallend genoeg bleken niet afdoende marges niet significant gerelateerd aan lokale controle maar wel met ziekte vrije overleving, ziekte specifieke overleving en met overleving in het algemeen. Vijf,- tien -en twintig- jaars overleving waren respectievelijk 68%, 52% en 28% hetgeen in overeenstemming is met de literatuur. Graad III histologie, bestaande uit een substantieel deel van het solide type tumor dient beschouwd te worden als een specifieke entiteit met de eigenschap van snel en agressief recidiveren. Deze groep zou in het bijzonder gebaat zijn bij verbeterde aanvullende behandeling die nog onvoldoende is geïdentificeerd.

In **hoofdstuk 3** worden de gebruikelijke graderingssystemen voor adenoid cysteus carcinoom (ACC) belicht en hun zwakheden worden beschreven. Het gebruik van verschillende graderingssystemen kan leiden tot over- en ondergradering en de gebruikte afkappunten- >30% en >50% solide tumor component- kunnen leiden tot inter-observer variabiliteit. Derhalve werden 81 casus van ACC her beoordeeld door twee ervaren hoofd-hals pathologen door gebruik te maken van de bestaande graderingssystemen volgens respectievelijk Perzin en Spiro. De resultaten werden vergeleken met betrekking tot inter-observer overeenstemming. De Cohen kappa scores waren respectievelijk 0.393 en 0.433 hetgeen beschouwd dient te worden als laag. Middels een derde graderingssysteem werd slechts de aanwezigheid van een solide tumor component vastgelegd. Dit zogenaamde S+/- systeem toonde een erg lage inter-observer variabiliteit met een kappa score van 0.990 hetgeen uitstekend wordt beschouwd. Dit systeem bleek in staat om de uitkomst even goed te voorspellen als de bestaande systemen. Derhalve concluderen wij dat het S+/- systeem zowel een hoge reproduceerbaarheid als een lage inter-observer variabiliteit heeft en overwogen moet worden als een serieus alternatief voor de gebruikte traditionele graderingssystemen.

In **hoofdstuk 4** worden de verschillen in overlevingspatronen bij het gemetastaseerde adenoid cysteus carcinoom (ACC) beschreven. Historisch wordt gemetastaseerd ACC beschreven met een langdurig ziektebeloop. Deze hypothese werd getest op een populatie van 105 patiënten, allen gediagnosticeerd en behandeld in het Amsterdam Universitair Medisch Centrum, locatie VUmc van 1979 tot 2009. De incidentie van afstandsmetastasen in deze populatie was 42% waarbij 91% van de afstandsmetastasen ontstonden binnen 5 jaar na de diagnose. Verschillende tumor- en ziektekarakteristieken werden geïdentificeerd als negatief geassocieerd met afstandsmetastasen-ziekte vrije overleving zoals een hoog T- stadium, lymfekliermetastasen, solide tumor (ongeacht aandeel) en positieve chirurgische marges. Afstandsmetastasen kwamen het meest voor in de longen en meestal ook alleen daar (55%). Andere aangedane organen waren de lever en de botten. Laatstgenoemden waren vooral aangedaan in geval van aanwezigheid van het solide tumor type. Slechts twee gevallen met synchrone metastasen werden gezien in de groep zonder solide tumor aanwezig. Met betrekking tot overleving met afstandsmetastasen bleek de aanwezigheid van het solide tumor type de enige onafhankelijke negatieve voorspeller. Patiënten met meerdere aangedane organen hadden een significant slechtere overleving dan die met enkel longmetastasen. De mediane overleving met metastasen waarbij enkel de longen waren aangedaan bedroeg 31 maanden (range 1-98.5) en 9 maanden (range 1-70) in geval van multi-orgaan pathologie. Voor het gehele cohort bedroeg de mediane overleving met metastasen 13.8 maanden (range 1-98.5). Vijfenzeventig procent van de patiënten met afstandsmetastasen overleed binnen 3 jaar. We concluderen derhalve dat het op afstand gemetastaseerde ACC niet altijd gepaard gaat met een relatief lange overleving en dat hier bewustwording voor moet zijn om zodoende patiënten op een juiste manier te informeren.

In **hoofdstuk 5** wordt een populatie beschreven van 64 patiënten met een mucoepidermoid carcinoom (MEC) van het hoofd-halsgebied welke gediagnosticeerd en behandeld zijn in het Amsterdam Universitair Medisch Centrum, locatie VUmc over een periode van 30 jaar. Deze retrospectieve analyse werd gedaan om prognosticatoren te identificeren. Daarnaast werd een fluorescentie in situ hybridisatie (FISH) uitgevoerd om de aanwezigheid van de t(11;19)(q21;p13) translocatie aan te tonen welke leidt tot het CRTC1/3 MAML2 fusie gen. Deze translocatie analyse was uitvoerbaar voor 42 gevallen waarvan in 29 gevallen (69%) de translocatie aanwezig was. In tegenstelling tot eerdere rapportages aangaande een overlevingswinst voor patiënten met de translocatie konden wij dat in dit cohort niet aantonen. De parotis was de meest aangedane speekselklier waarbij dit het palatum was voor de kleine speekselklieren. Er was geen onderscheid in voorkomen bij mannen en vrouwen en de mediane leeftijd bij diagnose was 51.4 jaar. De sensitiviteit van cytologie voor identificatie van een hooggradig MEC is acceptabel met 87% maar minder voor laaggradig MEC (68%). Hoewel een electieve halsklierdissectie wordt geadviseerd voor hooggradig MEC kunnen de huidig gebruikte graderingsssytemen (Armed Forces Institute of Pathology; AFIP, Brandwein en modified Healey) zorgen voor een onderschatting welke kan leiden tot onderbehandeling. Met een incidentie van 18% voor lymfekliermetastasen in de huidige studie- 11% bij laaggradig MEC en respectievelijk 30% en 31% bij intermediair en hooggradig MEC- lijkt het aan te bevelen een electieve halsklierdissectie te verrichten in alle gevallen van MEC. Perineurale groei is niet zeldzaam met een incidentie van 16% in deze studie (0% bij laaggradig en respectievelijk 44% en 30% bij hooggradig en intermediair). Perineurale groei, hoewel afwezig bij laaggradig MEC, bleek een negatieve prognosticator voor ziekte specifieke overleving, ziektevrije overleving en overleving in het algemeen. Aanwezigheid van lymfekliermetastasen was negatief geassocieerd met ziekte specifieke overleving, afstandsmetastasen- ziektevrije overleving en overleving in het algemeen. Een krappe of positieve chirurgische marge was niet geassocieerd met een slechtere overleving. Lange termijn ziekte vrije overleving is acceptabel maar de afname van 90% naar 68% van 10- naar 20- jaars overleving benadrukt het risico van late recidieven en de noodzaak tot langdurige controle van patiënten. Resumerend lijkt de aanwezigheid van het CRTC1/3 MAML2 fusie gen geen gunstige invloed te hebben op het ziektebeloop van MEC. MEC heeft een goede prognose met een recidief percentage van minder dan 20%. Hooggradig MEC is een specifieke entiteit met een relatief hoge incidentie van lymfekliermetastasen en afstandsmetastasen. Er zijn momenteel geen gekende succesvolle systemische behandelingen in de adjuvante, recidief of gemetastaseerde setting.

Hoofdstuk 6 beschrijft een populatie uit 2 centra van 89 patiënten, gediagnosticeerd met en behandeld voor een acinaircelcarcinoom (AciCC) in het Amsterdam Universitair Medisch Centrum, locatie VUmc en het Nederlands Kanker Instituut- Antoni van Leeuwenhoek (NKI-AvL). AciCC wordt beschouwd als een laaggradige tumor met uitstekende lange termijn overleving. In deze Amsterdam studie wordt gepoogd prognosticatoren te identificeren evenals de rol vast te stellen

van hooggradige transformatie (HGT) bij AciCC van het hoofd-halsgebied. De grote meerderheid van de tumoren waren vroeg stadium tumoren (T1-T2; 89%) en voornamelijk gelokaliseerd in de parotis (85%) hetgeen overeenkomt met bestaande literatuur. De gemiddelde leeftijd bij diagnose was 52 jaar met een voorkeur voor het vrouwelijk geslacht (67%). Alle patiënten ondergingen chirurgie met curatieve intentie gevolgd door postoperatieve radiotherapie (73%) in geval van hoog stadium, krappe of positieve chirurgische marges en negatieve histopathologische kenmerken. De aanwezigheid van een krappe of positieve marge leidde tot een relatief risico van 7.68 met betrekking tot recidiefkans. Vijftien van de 89 patiënten kregen een recidief (17%) van wie 9 afstandsmetastasen ontwikkelden. In 6 van de 9 gevallen bleek sprake van HGT-AciCC. Vijf,- tien- en 20- jaars recidiefvrije overleving waren respectievelijk 84%, 81% en 81%. De meerderheid van deze recidieven ontwikkelden zich in de eerste 40 maanden na behandeling. De mediane overleving na de diagnose van afstandsmetastasen was 7 maanden (range 1-28). Hoewel perineurale groei en angioinvasie zeldzame kenmerken zijn bij AciCC- 8% en 6% in de huidige studie- hebben zij wel een significante negatieve invloed op de uitkomst van behandeling. Het conventionele ACiCC heeft een acceptabele lange termijn overleving bij adequate behandeling met een lage recidiefkans (<20%). Het probleem om voor de behandeling accuraat HGT vast te stellen leidt ertoe een afdoende chirurgische behandeling inclusief selectieve halsklierdissectie toe te passen gezien de relatief hoge incidentie van HGT in deze studie (21%). Het ontbreken van systemische behandeling onderstreept de noodzaak voor een optimale primaire behandeling.

CHAPTER 8.2

List of publications

LIST OF PUBLICATIONS

Articles

1. **van Weert S**, Valstar MH, Lissenberg- Witte BI, Vergeer MR, Bloemena E, Smit L, van der Wal J, Smeele LE, Leemans CR. Prognostic factors in Acinic cell carcinoma of the head and neck: The Amsterdam Experience. Oral Oncol. 2021 Dec 29;125:105698. doi: 10.1016/j.oraloncology.2021.105698. PMID: 34973520.
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CHAPTER 8.3

Curriculum Vitae

CURRICULUM VITAE

Stijn van Weert werd geboren op 8 april 1977 in Boxtel. Hij doorliep het Gymnasium aan het Jacob Roelandslyceum in Boxtel van 1989 tot 1995. Aansluitend volgde hij de studie geneeskunde aan de Rijksuniversiteit Limburg (thans Universiteit Maastricht) van 1995 tot 2001. Na het afronden van zijn co- schappen volgde een periode van 10 maanden (2002) als assistent- geneeskundige niet in opleiding (AGNIO) aan de afdeling Keel-, neus -en oorheelkunde en hoofd- halschirurgie van het VU medisch centrum (VUmc; thans Amsterdam UMC) (Prof. Dr. C.R. Leemans) om erna te starten met de opleiding tot KNO- arts (2002) in het academisch ziekenhuis Maastricht (thans Maastricht UMC+) onder Prof. Dr. J.J. Manni en Prof. Dr. B. Kremer. Een deel van de opleiding vond respectievelijk plaats in het Catharina Ziekenhuis in Eindhoven (Dr. F.C.P.M. Adriaansen) en in het toenmalig Atrium Medisch centrum in Heerlen (thans Zuyderland Medisch centrum) onder supervisie van Dr. T.D. Zijlker. De opleiding werd afgerond in december 2007.

Vanaf januari 2008 startte hij met zijn fellowship hoofd- halschirurgie aan het VUmc onder supervisie van Prof. Dr. C.R. Leemans en rondde dit af in januari 2010. Hij bleef hierna als staflid en later chef de clinique verbonden aan de afdeling en maakte in deze periode een begin aan dit proefschrift. Sinds augustus 2020 is hij als KNO- arts/ hoofd- halsoncoloog werkzaam in het Maastricht UMC+.

Stijn is getrouwd met Marit van Weert- Steggerda. Zij hebben samen twee kinderen: Casper (2009) en Jasmijn (2010).

CHAPTER 8.4

Dankwoord

DANKWOORD

Een proefschrift als dit kan niet tot stand komen zonder de patiënten die geraakt zijn door de diagnose speekselklierkanker. Velen van hen heb ik met mijn collega's behandeld en vervolgd en doe dat nog steeds met veel passie. Ik ben hen zeer erkentelijk voor het vertrouwen en de mogelijkheid met hun inbreng de zorg op dit vlak weer wat verder te kunnen brengen ondanks het feit dat er nog een wereld te winnen is.

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Collega's van de afdeling radiotherapie en in het bijzonder Derek Rietveld en Dr. Marije Vergeer als co- auteurs: Daar waar radiotherapie deel uitmaakte van het onderzoek- vrijwel altijd- waren jullie bereid kritisch mee te kijken en jullie feedback te geven. Daarnaast is jullie bijdrage als sterke afdeling binnen de hoofd- halszorg onmisbaar en van hoog niveau. Het was een plezier met jullie te werken.

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