



MUCOEPIDERMOID CARCINOMA: COMPARATIVE STUDY BETWEEN OLD AND NEW GRADING SYSTEMS

THESIS

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ABSTRACT

Background

Mucoepidermoid carcinoma is the most common malignant salivary gland tumor. Histopathologic grade of this tumor is the most important predictor of prognosis that has a great impact on treatment protocols. Tumor behavior is worse with aggressive outcome in high grade than in low-grade mucoepidermoid carcinoma, leading to a need for more intensive treatment.

Methods

A retrospective clinical study and prospective review of histopathologic grading were done using the three most popular grading systems of 60 patients with mucoepidermoid carcinoma diagnosed at Surgical Pathology Department, National Cancer Institute (NCI) from 2005 to 2010.

Results

Recurrence rate was strongly correlated with high tumor grade ($P = 0.003$, 0.03 and 0.005 according to AFIP, Brandwein and Modified Healy grading systems). Male gender was significantly correlated with the tumor high grade ($P = 0.01$). Lymph node status was significantly correlated with overall survival ($P = 0.026$). Using Brandwein grading system showed that as histologic grade increased from low & intermediate to high, disease free survival ($P = 0.029$) was significantly decreased. The Kaplan-Meier estimated 1-year, 3-year and 5-year overall survival were 65.2%, 55.5% and 41.0%; respectively.

Conclusions

Outcomes of the cases with intermediate-grade mucoepidermoid carcinoma are less clear and can be categorized as low or high grade according to the used grading system. However, Brandwein grading system may have a better predictive value than the previously used Modified Healey and AFIP systems as it identifies very well the low grade cases. Further tools, such as immunostaining for Ki-67 in conjunction with tumor grade may predict the tumor prognosis accurately.

Keywords

Mucoepidermoid carcinoma- Grading – Prognosis – Survival analysis.

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Mucoepidermoid carcinoma is defined as a malignant glandular epithelial neoplasm characterized by mucous, intermediate and epidermoid cells, with columnar, clear cell and oncocytoid features (*Eveson et al., 2005*).

Mucoepidermoid carcinoma is the most frequently diagnosed malignancy in salivary gland. Among the major salivary gland, the parotid is the most commonly involved (*Boahene et al., 2004*). It comprises approximately 10–15% of all salivary gland neoplasms and about 30% of salivary malignancies (*Rapidis et al., 2006*).

Mucoepidermoid carcinoma is the histologic subtype of salivary gland tumors for which grading is the most prognostically and therapeutically relevant factor (*Seethala, 2011*).

Morphologic features of mucoepidermoid carcinoma have been incorporated into many different grading systems which were correlated with prognosis and therefore play an important role in treatment decisions (*Nance et al., 2008*).

Many grading schemes were proposed depending on subjective evaluation of relative proportions of the different cell components, degree of cellular atypia, mitotic frequency, presence of necrosis and invasiveness (*Thompson, 2006*). However there is still controversy around grading of mucoepidermoid carcinoma, and there is no uniformly accepted grading system (*Chenevert et al., 2011*).

The three most popular grading systems are the modified Healey grading system, proposed by *Batsakis and Luna, 1990*, the AFIP grading system, proposed by *Auclair et al., 1992* and Brandwein system, proposed by *Brandwein et al., 2001*.

Retrospective study of mucoepidermoid carcinoma (MEC) cases diagnosed at Surgical Pathology Department, National Cancer Institute (NCI), Cairo University during the period (January 2005 to June 2010).

Grading of all available cases according to the three most popular grading systems; modified Healey grading system, AFIP grading system and Brandwein grading system.

Correlation of histopathologic grade (according to the three grading systems) with age, gender, stage, state of surgical margins, recurrence and overall survival.

Mucoepidermoid carcinoma

Definition

Mucoepidermoid carcinoma is defined by World Health Organization (WHO) as a malignant glandular epithelial neoplasm characterized by mucous, intermediate, epidermoid cells with columnar and oncocytoid features (*Eveson et al., 2005*).

Histogenesis

The primary function of the salivary glands is to moisten the mucous membranes of the upper aero-digestive tract. These glands are located in the submucosa throughout the oral cavity, pharynx, and upper airways (*Madrigal et al., 2007*).

Both the major and minor salivary glands all over the body are composed of acinar and duct systems (*Mills, 2010*). Salivary glands may be of the serous, mucous, or mixed sero-mucous type (*Rapidis et al., 2006*). Myoepithelial cells surround each acinus. The intricate duct system is composed of intercalated, striated, and interlobular ducts (*Mills, 2010*).

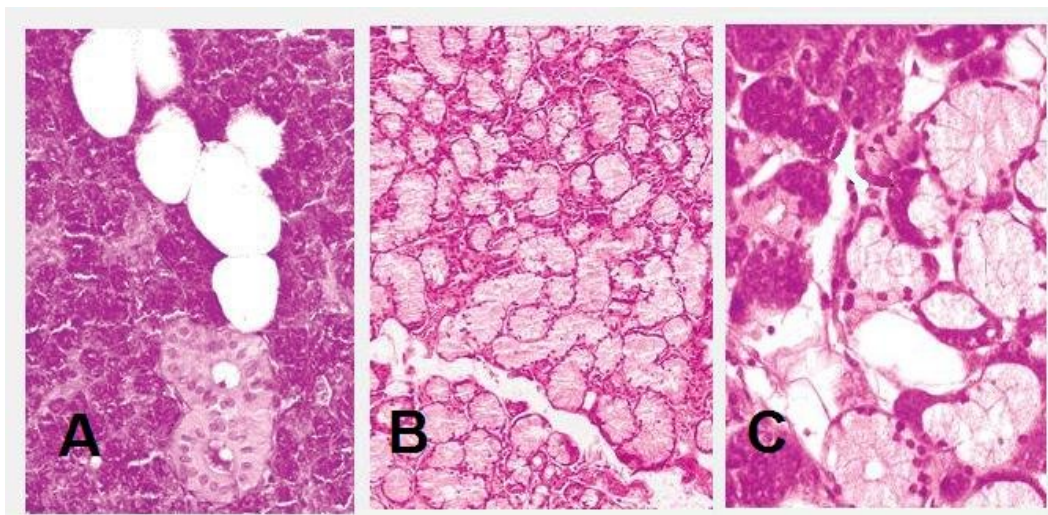


Figure (1): Types of salivary glands. (A) Serous. (B) Mucous. (C) Mixed sero-mucinous (*Ellis and Auclair, 2009*).

Salivary gland duct is composed of several cell types (mucous secreting, basaloid, intermediate, and epidermoid, representing the histo-genetical origin of mucoepidermoid carcinoma (*Rapidis et al., 2006*).

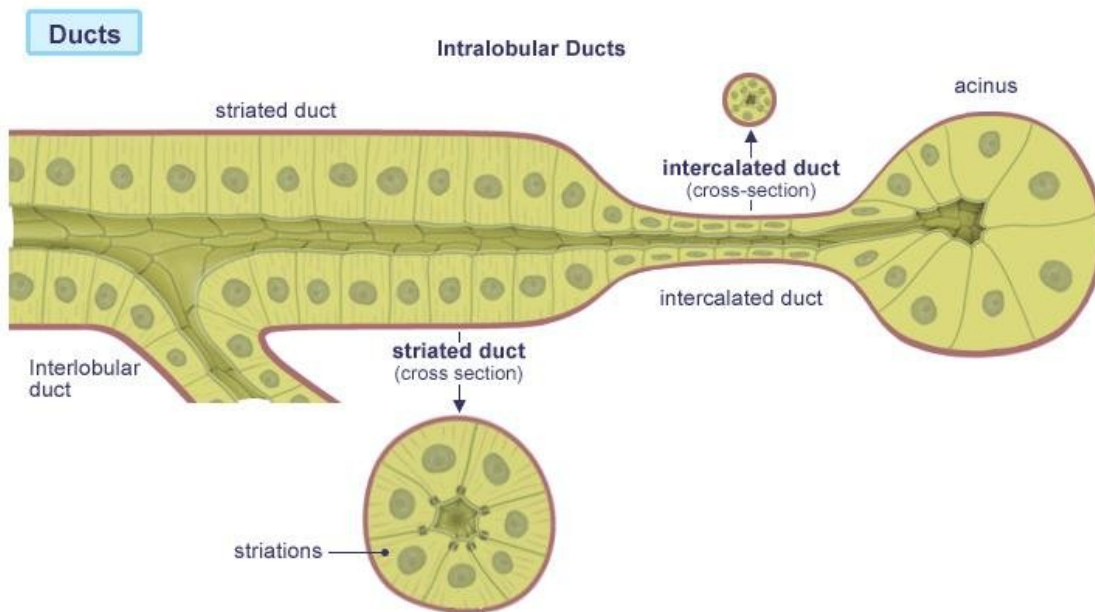


Figure (2): Types of salivary gland ducts (*McKee, 2011*).

Oncocytic metaplasia in salivary glands is a common finding with aging. They are rare before 50 years of age, increase in frequency with advancing years, and become constant after 70 years (*Mills, 2010*).

Mucoepidermoid carcinoma occurs at various sites, mainly salivary glands and to less extent in other sites such as larynx, lung, esophagus, anus, cervix, breast and skin (*Yasuda et al., 2006*).

The presence of salivary tissue in sites other than major salivary glands or the above mentioned sites having minor submucosal salivary glands is considered heterotopia. It may be classified as intra-nodal and extra-nodal. Heterotopic salivary gland tissue has been identified in a wide variety of anatomic sites (Figure 3), including the external and middle ear, the mastoid region, the thyroglossal duct, the thyroid capsule, and even the parathyroid glands.

Cervical lymph nodes are the most common sites for the benign salivary gland inclusions. Intramandibular salivary gland tissue may appear on the lingual surface of the bone within surface indentations, most often situated in the angle of the mandible. These heterotopic salivary rests explain the rare occurrence of salivary tumors arising within the mandibular bone (*Mills, 2010*).

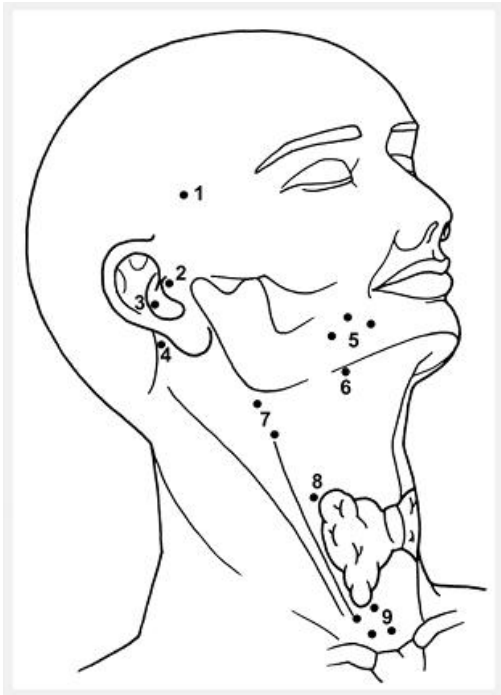


Figure (3): Extranodal salivary heterotopias. Pituitary gland (1), middle ear (2), external auditory canal (3), cerebellopontine angle (4), mandible (5), oropharynx (6), cervical superior (7), thyroid capsule (8), and lower anterolateral neck (9) (*Madrigal et al., 2007*).

Salivary mucoepidermoid carcinoma is thought to arise from pluripotent reserve cells of the excretory ducts of salivary gland that have the potential to differentiate into squamous, columnar, and mucous cells (*Rahbar et al., 2006 and Ozawa et al., 2008*).

Breast, oral cavity, and major salivary glands are derived from the embryonal ectoderm and their basic tubule-alveolar structures probably explaining the similar morphologic features of tumors arising in these different sites (*Camelo-Piragua et al., 2009*).

Initially, mucoepidermoid carcinoma was recognized as only occurring in the salivary glands but later some appreciated that they occurred in the trachea and bronchi as well, where it arises from the minor salivary gland tissue of the proximal tracheo-bronchial tree (*Yang et al., 2004*). Smoking habit is not associated closely with the risk of developing this tumor (*Huang et al., 2009*).

Mucoepidermoid carcinoma may also arise from submucosal glands along the gastrointestinal tract. Esophageal mucoepidermoid carcinoma is rare and it may be an association with small cell carcinoma (poorly differentiated neuro-endocrine carcinoma) (*Werner et al., 2000*). Mucoepidermoid carcinoma represents a rare variant of intra-hepatic cholangio-carcinoma (*Nakanuma et al., 2000*).

Primary thyroid mucoepidermoid carcinoma is very rare and its origin has not been fully understood (*Teijeiro et al., 2004*). Two histologically distinctive types of mucoepidermoid carcinoma occur in the thyroid gland. The first type is a non-follicular-derived tumor of probable origin from ultimobranchial body rests/solid cell nests, which occurs in the setting of chronic thyroiditis (*Baloch et al., 2000*). Solid cell nests are irregular structures of about 1 mm in maximal diameter, usually found in the thyroid lateral lobes and are composed of non-keratinizing squamous cells and ductal structures lined by ciliated columnar epithelium (*Jung and Kang, 2010*). The ultimobranchial body is an out-pocketing of the fourth pharyngeal pouch that fuses with the thyroid diverticulum, giving rise to calcitonin-producing C-cells (*Kusakabe et al., 2006*). The second type is similar to salivary gland mucoepidermoid carcinoma (*Baloch et al., 2000*) and it is thought to originate from follicular epithelium or as a metaplastic variant of papillary carcinoma where a component of conventional papillary carcinoma may be identified (*Jung and Kan, 2010*).

Thymic mucoepidermoid carcinoma has been postulated by some authors to originate from pluripotent epithelial stem cells of endodermal origin (*Wick et al., 2004*).

Cutaneous involvement by mucoepidermoid carcinoma as a primary origin is extremely rare. Thus, in cases when the skin is affected it is important to rule out the possibility of metastases from a distant mucoepidermoid carcinoma (*Lo'pez et al., 2010*). In the skin, primary mucoepidermoid carcinoma is considered a synonym of hidradenocarcinoma which is the malignant counterpart of hidradenoma. Most neoplasms have apocrine differentiation, but some show eccrine features (*Requena et al., 2006*).

Orbital tissues affected with mucoepidermoid carcinoma include the lacrimal sac, lacrimal gland, and the conjunctiva (*Robinson et al., 2006*).

Epidemiology

Incidence

In most countries mucoepidermoid carcinoma is the most common primary major and minor salivary gland malignancy and it represents less than 0.5% of all malignancies and less than 5% of malignant head and neck tumors (*Williams and El-Naggar 2010*). Mucoepidermoid carcinoma accounts for 12-29 % of all salivary gland tumors (*Thompson, 2006*). It comes after pleomorphic adenoma and adenoid cystic carcinoma (*Ellis and Auclair, 2009*).

Just greater than half of mucoepidermoid carcinomas (about 60%) arise in major salivary glands, usually parotid gland, about 20% originate from the minor glands of the palate, and another 19% occur, in decreasing order of frequency, in the buccal mucosa, retromolar region, tongue and upper and lower lips. They occur much more frequently in the lower lip than the upper lip (*Williams and El-Naggar, 2010*).

According to a recent population based study in the United States including diagnosed cases of carcinomas of the major salivary glands between 1992-2006 in the Surveillance, Epidemiology and End Results Program (SEER), the age-adjusted incidence rate (IR) of mucoepidermoid carcinoma among males was 3.23 while among females it was 2.67. Mucoepidermoid carcinoma shows equal distribution in different races. No significant changes in incidence of mucoepidermoid carcinoma were noted over the 15-year time period of study (*Boukheris et al., 2009*).

The Armed Forces Institute of Pathology (AFIP) reported that mucoepidermoid carcinoma is the most common major salivary gland tumor, followed by acinic cell carcinoma, adenoid cystic carcinoma, adenocarcinoma-NOS, polymorphic low grade adenocarcinoma and carcinoma ex-pleomorphic adenoma. This distribution was different from that observed in the SEER population (*Boukheris et al., 2009*).

In a European study including all salivary gland tumors from 1974 to 2005 mucoepidermoid carcinoma was the frequently diagnosed tumor, accounting for 11.5% of malignant and 32.7% of all salivary gland tumors. Mucoepidermoid carcinoma was the most common malignant diagnosis in major and minor salivary glands (*Jones et al., 2008*). A similar distribution has been found in studies from the United States (*Sadeghi et al., 1993*) and Japan (*Takahashi et al., 1990*).