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ORIGINAL ARTICLE

Mucoepidermoid carcinoma of minor salivary glands: a clinical study of 16 cases and review of the literature

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OBJECTIVE: Mucoepidermoid carcinoma (MEC) is the most common malignant tumor of salivary glands with a widely diverse biologic behavior that is correlated with the histological grade of the tumor. The purpose of this study was to evaluate the clinical outcomes of MEC of minor salivary glands in a group of 16 patients, who were treated in our clinic, and to discuss the management of this carcinoma.

MATERIALS AND METHODS: Between 1985 and 2000, 16 patients with MEC of minor salivary glands were treated in the Clinic of Oral and Maxillofacial Surgery of the 'G. Papanikolaou' General Hospital, in Thessaloniki. The age range was 16–65 years. The distribution of the primary sites was: hard plate (one), soft palate (two), hard and soft palate (three), hard and soft palate with spread in paranasal sinus and nasal cavity (one), buccal mucosa (three), hard palate, alveolar process and buccal mucosa (two), and retromolar triangle (our). The tumors were clinically staged according to the tumor nodes metastase (TNM) system (Seifert, 1991). All patients were treated radically with surgery. The surgery was combined with radiotherapy in nine patients. Radiotherapy was delivered using Co-60. Doses ranged from 50 to 60 Gy and the duration of the therapy ranged from 25 to 35 days. Immunohistochemical assay of the expression of the Ki-67 antigen was performed on a subset of 15 cases.

RESULTS: The mean follow-up range was 4–14 years. From the 16 patients with MECs 10 (62.5%) were alive and five (35.6%) had died from the disease. Four patients were free of the disease for more than 5 years (range 8–14), five patients were free of the disease for 5 years and one patient was free of the disease for 4 years. One patient lived more than 10 years and died from another cause. Local recurrence developed in one patient 10 years after the initial treatment. Lymph node metastases occurred in one patient within the first year after the initial surgical treatment. Distant metastases (two in bones and one in lungs) occurred in three patients within 2 years after completing the treatment. The Pearson chi-square statistical analysis was used for comparing the Ki-67 values in correlation with histological grade of the tumors. The Ki-67 expression was only 1% in low-grade MECs, while in intermediate-grade tumors it was estimated between 3 and 4%. The high-grade tumors had increased expression (10%) of tumor cells.

CONCLUSION: Complete surgical excision is the treatment of choice for MECs. Adequate excision is important in all grades of tumors. Prognosis of MECs is a function of the histological grade, adequacy of excision and clinical staging. The immunohistochemical study of Ki-67 expression may provide additional prognostic information for this tumor.

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Keywords: minor salivary glands; mucoepidermoid carcinoma; Ki-67 expression

Introduction

Mucoepidermoid carcinoma (MEC) is the most common malignant tumor of the salivary glands (12–29%), while for many authors it also represents the most common type of malignancy for minor oral salivary glands (Spiro *et al*, 1978; Brandwein *et al*, 2001). When MEC arises in minor salivary glands it can be located on the palate, in the retromolar area, the floor of the mouth, the buccal mucosa, the lips and the tongue. Rarely it can arise as primary jaw tumor or as a laryngeal, lacrimal, nasal, paranasal, tracheal or pulmonary tumor (Brookstone and Huvos, 1992; Wedell *et al*, 1997; Noda *et al*, 1998; Brandwein *et al*, 2001). The greatest incidence occurs between the third and sixth decade of life, but it may occur at any age. It is the most common malignant salivary gland tumor to arise in children and adolescents of <20 years of age and it

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has a slight predilection for women (Castro *et al*, 1972; Krolls *et al*, 1972; Seifert *et al*, 1986; Ellis and Auclair, 1996; Hicks and Flaitz, 2000; Brandwein *et al*, 2001; Caccamese and Ord, 2002).

Previously this tumor was considered benign and had been called 'mucoepidermoid tumor'. The first report on 'mucoepidermoid tumors' was by Stewart *et al* (1945). They divided these tumors into 'relatively favorable' and 'highly unfavorable'. However, 8 years later Foote and Frazell (1953) revealed that some patients with 'relatively favorable' tumors included in the previous citation, developed distant metastases. So they suggested establishing a third or intermediate-grade lesion, which resembled more with the low than with the high-grade tumors in microscopic features. Since that time many authors have favored the classification of MECs into low, intermediate and high grade, based on the relative proportion of cell types (Jakobsson *et al*, 1968; Eversole, 1970; Eversole *et al*, 1972; Evans, 1984; Auclair *et al*, 1992). From time to time other authors suggested various grading criteria that include the degree of tumor invasion, anaplasia, pattern of invasion, degree of maturation of the various cellular components, mitotic rates, presence or absence of necrosis, neural or vascular invasion and proportion of tumor composed of cystic spaces relative to solid growth (Spiro *et al*, 1978; Nascimento *et al*, 1986; Seifert, 1991; Goode *et al*, 1998; Brandwein *et al*, 2001).

Low-grade tumors commonly develop a nesting pattern with multiple well-circumscribed squamous nests containing numerous clear cells. Many low-grade tumors, especially in the minor salivary glands, contain a prominent mucin-secreting component composed of columnar cells lining cystic spaces (Waldron *et al*, 1988; Brandwein *et al*, 2000). Intermediate-grade tumors are less cystic and show a greater tendency to form large, more irregular nests or sheets of squamous cells and often have a more prominent intermediate cell population. High-grade tumors are predominantly solid, with greater degrees of atypia, similar to squamous cell carcinoma (Brandwein *et al*, 2001).

Over the past two decades clinicopathological studies supported that predictors of morbidity and mortality of MEC of salivary glands are related to tumor size, histopathological grade, clinical stage of disease, perineural and vascular involvement, and lymph node and distant metastases. In our days it has been possible to investigate other biological parameters, which recognize the proliferative nature of the tumor, as DNA, flow cytometric analysis (DNA index, proliferative fraction), proliferating cell nuclear antigen (PCNA) and Ki-67 proliferation antigen (Batsakis and Luna, 1990; Batsakis, 1994; Hicks *et al*, 1995; el-Naggar *et al*, 1997; Hicks and Flaitz, 2000).

The purpose of this study is to evaluate the clinical outcomes of MEC of minor salivary glands in a group of 16 patients and to discuss the management of this carcinoma. In addition, the study of Ki-67 expression demonstrated the difference in immunoreactivity between low- and high-grade MECs.

Material and methods

A total of 16 patients were diagnosed with MEC of minor salivary glands and treated in our clinic at the 'G. Papanikolaou' General Hospital in Thessaloniki during the period 1985–2000. The female to male ratio was 9:7. The age range was 16–65 years. The location of the tumor was hard palate (one), soft palate (two), hard and soft palate (three), hard and soft palate with spread in paranasal sinus and nasal cavity (one), hard palate, alveolar process and buccal mucosa (two), buccal mucosa (three) and retromolar triangle (four) (Table 1). The tumors were clinically staged according to the TNM system. Diagnostic imaging of the primary lesion included plain films or CT and MRI tomographies (Figures 1 and 2).

All the patients were primarily treated with surgery. Preoperative biopsy was performed to establish the tumor's histopathological grade and the treatment planning. In seven cases local excision of the primary tumor achieved via an intra-oral approach, and the defect was closed by local flaps or buccal fat while in nine cases radical excision was performed by extra-oral approach. Primary tumor excision was combined with neck node dissection (supraomohyoid or radical neck

Table 1 Tumor sites

Tumor site	*Number of cases*
Hard palate	1
Soft palate	2
Hard and soft palate	3
Hard and soft palate with spread in paranasal sinus and nasal cavity	1
Buccal mucosa	3
Hard palate, alveolar process and buccal mucosa	2
Retromolar region	4
Total	16

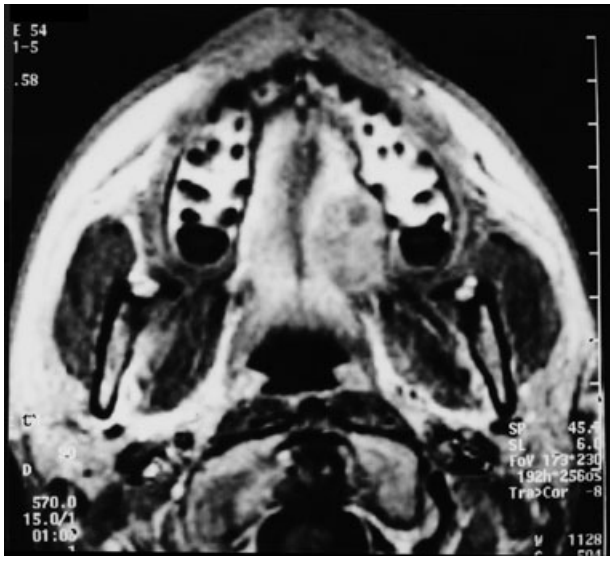

Figure 1 MRI scan of MEC of the palate

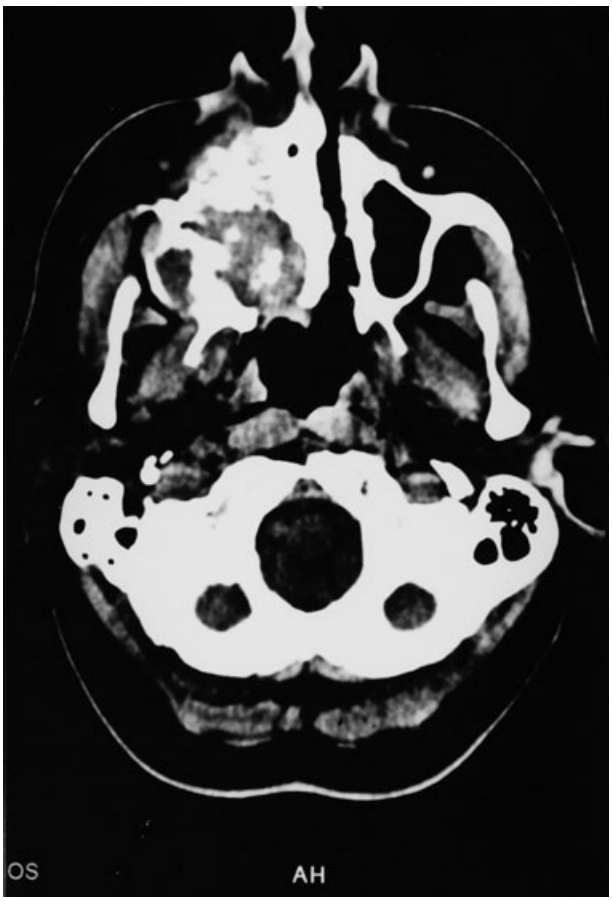

Figure 2 CT scan of MEC of the palate with spread in the paranasal sinus and nasal cavity

dissection) in four patients, who from the clinical and radiographic examination, revealed positive lymph nodes. Nine patients were treated with surgery alone, while seven patients underwent surgery with adjuvant radiotherapy. For the patients treated by maxillectomy (total or partial) the defect was packed with iodoform gauge to heal by second intention or closed by the temporalis muscle. Marginal mandibular resection was performed in those cases when the lesion was located in the retromolar region, and the preoperative radiographic examination had revealed invasion of jaw periosteum (Table 2).

The interval between surgery and the start of radiation therapy was 30–35 days. The radiotherapy was delivered using Co-60. Doses ranged from 50 to 60 Gy and the duration of therapy ranged from 25 to 35 days.

The surgical margins were defined as negative when the pathological specimens showed margins of normal tissue more than 5 mm from the tumor margin. MECs were histologically graded as low (mucous cells-cystic pattern), intermediate (mucous and intermediate cells) or high (squamous cells-solid pattern). Other suggested grading criteria had included the degree of maturation of various cellular components, mitotic rates, presence or absence necrosis, neural invasion and bony invasion

Table 2 Methods of surgical treatment

Methods	*Number of cases*
Topical excision (intra-oral approach) (T_1–$T_2N_0M_0$)	7
Maxillectomy (Weber–Ferguson approach) (T_3–$T_4N_0M_0$)	3
Maxillectomy and supraomoyoid dissection (T_3–$T_4N_1M_0$)	2
Radical excision and marginal mandibular resection (T_3–$T_4N_0M_0$)	2
Radical excision and marginal mandibular resection with radical neck dissection (T_3–$T_4N_1M_0$)	2
Total	16

as they are proposed by WHO (Seifert, 1991). Only two of the tumors were high-grade (Figure 3), with four being intermediate-grade (Figure 4) and the remaining 10 being low-grade (Figure 5).

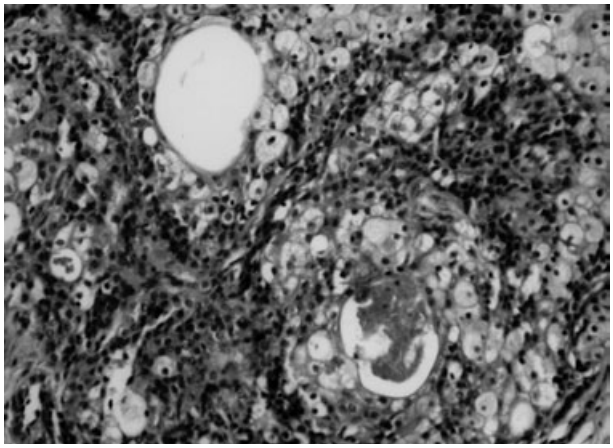

Figure 3 High-grade MEC showed more solid pattern with atypia (hematoxylin and eosin; original magnification ×250)

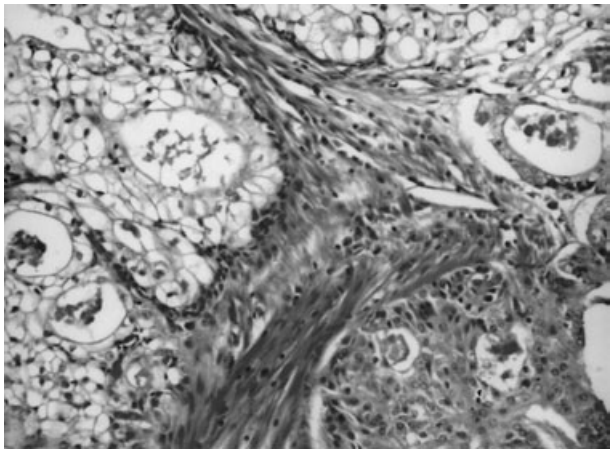

Figure 4 Intermediate-grade MEC composed of equal proportions of mucous and intermediate cells (hematoxylin and eosin; original magnification ×250)

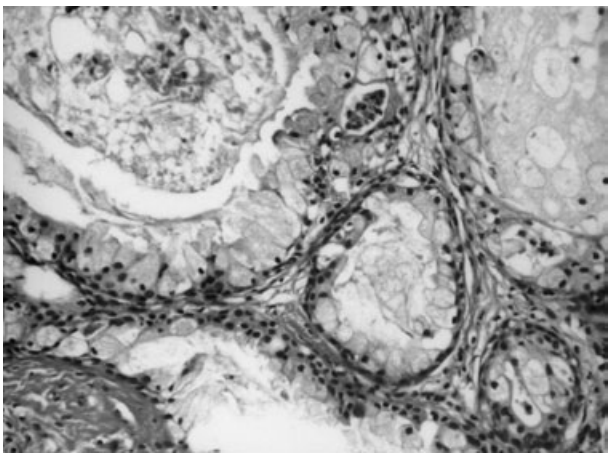

Figure 5 Low-grade MEC composed of mucous cells lining cystic spaces (hematoxylin and eosin; original magnification ×250)

Immunohistochemical stain with monoclonal antibody Ki-67 was performed on a subset of 15 cases in paraffin-embedded sections. Two 4 μm-thick sections from a representative tissue block were collected for each case. One section was stained with hematoxylin–eosin to confirm the diagnosis. The other section for immunohistochemistry was de-waxed and re-hydrated, and treated in a microwave oven for 15 min at 700 W in 10 mm l^{-1} citrate buffer (pH 6.0). Endogenous peroxidase was blocked with 1% hydrogen peroxide in methanol (10 min), following incubation with primary antibody (1:20, Dako, Copenhagen, Denmark). Section was incubated for 30 min with biotinylated secondary antibody rabbit anti-mouse antibody (Dako) at 1:200 concentrations. Visualization was achieved using commercial ABC (Vector, Burlingame, USA) 30 min and DAB reagents (Dako, 5 min) with Mayer's hematoxylin as a counterstain. Sections from a reactive lymph node were used as positive controls and areas with normal salivary gland tissue exhibiting very low proliferate activity were used as negative controls. In addition, normal staining of basal cells in adjacent epithelium was included as an internal positive control when present. The ratio of Ki-67 positive cells was expressed as the percentage of at least 1000 cells counted randomly at 400× magnification. Stained nuclei were regarded as positive irrespective of staining intensity. The evaluation was performed by one of the authors (F.I.) who had no knowledge of the clinical outcome.

Results

The mean follow-up range was 4–14 years. From the 16 patients with MEC, 10 (62.5%) were alive and five (35.6%) had died from the disease. One patient lived more than 10 years and died from another cause. Four patients were free of the disease for more than 5 years (ranging from 8 to 14), five patients were free of the disease for 5 years and one patient was free of the disease for 4 years (Table 3). Local recurrence developed in one patient 10 years after the initial treatment (low-grade). Lymph node metastases occurred in one patient within the first year after the initial surgical treatment (high-grade). Distant metastases (two in bones and one in lungs) occurred in three patients within 2 years after completing the treatment (two intermediate-grade and one high-grade) (Table 4).

Table 3 Results

Time	*Number of cases*
Free of the disease more than 5 years (two low-grade and two intermediate-grade)	4
Free of the disease 5 years (low-grade)	5
Free of the disease 4 years (low-grade)	1
Death from the disease less than 5 years (two high-grade and two intermediate-grade)	4
Death from the disease more than 10 years (low-grade)	1
One patient lived more than 10 years and died from another cause (low-grade)	1
Total	16

Table 4 Treatment failure

Type of failure	*Number of cases*
Local recurrence: 10 years after the treatment (low-grade)	1
Lymph node metastases: 1 year after the treatment (high-grade)	1
Distant metastases: in bones, 2 years after the initial treatment (intermediate-grade)	2
Distant metastases: in lungs, 2 years after the initial treatment (high-grade)	1
Total	5

The Pearson chi-square statistical analysis was used for comparing the Ki-67 values in correlation with histological grade of MECs. The expression of Ki-67 was only 1% in low-grade tumors, while in intermediate-grade tumors it was estimated between 3 and 4% (Figure 6). The high-grade tumors had increased expression (10%) of tumor cells (Table 5).

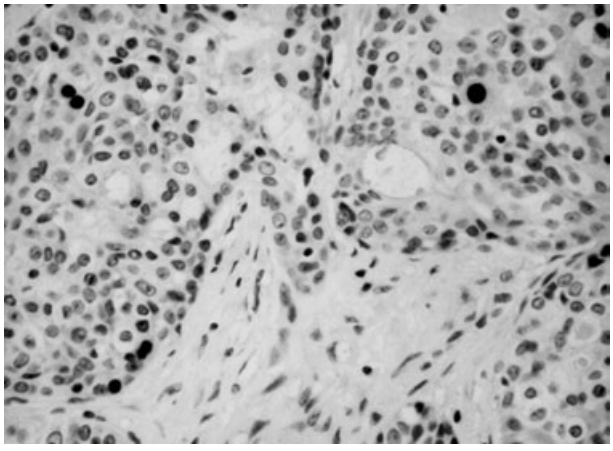

Figure 6 Immunohistochemical staining for Ki-67 in MEC (intermediate-grade) with 3% positive cells (original magnification ×250)

Table 5 Ki-67 expression in correlation with histological grade of MECs and the prognosis

Ki 67	*Dead, 00*	*Live, 00*	*Total*
1,00	Low grade: 1	Low grade: 8	9
4,00	Intermediate grade: 2	Intermediate grade: 2	4
10,00	High grade: 2	High grade: 0	2
Total	5	10	15

Discussion

In the literature the histopathological grading criteria of MEC remain controversial. It is suggested that they are related to the proportion of cell types, the degree of maturation of cellular components, the pattern of invasion and proportion of tumor composed of cystic space relative to solid growth. The low-grade tumors are usually <4 cm in diameter, circumscribed but non-encapsulated, and predominantly cystic. More than 50% of the tumor cells are well-differentiated epidermoid and mucus-producing cells. There are few mitoses (<3 mitoses/10 HPF) and minimal nuclear polymorphism. The high-grade tumors are usually larger than 4 cm, with ill-defined margins, being solid rather than cystic, with areas of hemorrhage and necrosis. These neoplasms show numerous mitoses (>4 mitoses/10 HPF) and pronounced nuclear polymorphism. Less than 10% of the tumor cells consist of mucus-producing cells, which often are not readily identified without special stains (Seifert, 1991; Auclair *et al*, 1992; Goode *et al*, 1998).

Auclair *et al* (1992) studied the grading criteria of MECs presenting 143 cases of MECs of minor salivary glands. The clinical features suggesting aggressive behavior were short duration, presence of clinical symptoms and location of tumor in the tongue and the floor of the mouth. The histopathological features that indicated high-grade behavior were an intra-cystic component of $<20\%$ ($+2$ point value), four of more mitotic figures per 10 high power fields ($+3$ point value), neural invasion ($+2$ point value), necrosis ($+3$ point value), and cellular anaplasia ($+4$ point value). Tumors with a point score of 0–4 were considered low-grade and none of 122 patients with this score died of the disease. Point scores of 7 or above indicated highly aggressive behavior and six of 10 patients with these high scores died of the disease. Scores 5–6 were considered intermediate between low-grade and high-grade score, because only one of 13 patients with these scores died of the disease.

Brandwein *et al* (2001) in their clinicopathological study of 80 MECs proposed a grading schema with 'characteristic features' (cell component, cellular composition) and 'defining features' (necrosis, perineural spread, vascular invasion, bony invasion, mitoses). They believe that the defining features are those that dictate the grade of these tumors. Grade 1 tumors (low-grade) lack the defining features of Grade 3 (high-grade) tumors (necrosis, perineural spread, vascular invasion, bony invasion, >4 mitoses/10 HPF, high-grade nuclear pleomorphism). Each of these features was assigned a point value, as in Goody's study, and the total sum of points determined the tumor's grade. Brandwein *et al* characterize as high-grade the tumors with a point score of 4 or more, while Goode *et al* characterize as high-grade the tumors with a point score of 7 or more. So that Brandwein *et al* have the suspicions that the Goody's criteria have a tendency to downgrade MECs.

Studies of Ki-67 and PCNA expression demonstrate the difference in immunoreactivity for these proliferation markers between low- and high-grade MECs. Clinicopathological studies have shown increased Ki-67 and PCNA immunoreactivity in MECs and other malignant salivary gland tumors when compared with benign salivary gland tumors and normal salivary gland tissue. Distinct differences in the number of nucleolar organizer regions have also been shown between low- and high-grade MECs. Relatively few tumor cells show PCNA or Ki-67 immunoreactivity in low-grade MECs. Intermediate-grade MECs have a moderate increase in PCNA and Ki-67 immunoreactivity over that found in low-grade tumors. The proportion of proliferating tumor cells, as are revealed by PCNA and Ki-67 immunoreactivity, progressively increased from low to intermediate to high-grade tumors (Hicks and Flaitz, 2000; Okabe *et al*, 2001; Foschini *et al*, 2002).

Radical surgery is the treatment of choice for all high-grade MECs, or low/intermediate-grade tumors that are large and involve the bone (Caccamese and Ord, 2002). Adequate excision is important in all grades of tumor with much higher recurrence rates reported with positive surgical margins (in order of 50% for low- and intermediate-grade tumors and slightly $>80\%$ for high-grade tumors) (Healey *et al*, 1970). Olsen *et al* (1981) used partial maxillectomy regardless of the size or grade of the tumor for adult patients. However, cure rates of 100% were reported in adults with low- and intermediate-grade MECs utilizing local and wide local excision, respectively, with bone removal only when erosion was present. It is believed that radical surgery is contraindicated in small, localized tumors with low- to intermediate-grade histological appearance (Eversole *et al*, 1972).

Radiation therapy is used with surgery although this carcinoma seems to be radioresistant. Radiation therapy should be added in high-grade tumors and for patients with unclear surgical margins or for patients with positive lymph nodes (Brandwein *et al*, 2001). Tran *et al* (1986) reported that in patients with positive surgical margins postoperative radiotherapy improved local control from 50 to 71%. North *et al* (1990) noted that, in patients receiving surgery alone, 26% failed locally, compared with 4% of those receiving radiotherapy as well. Hosokawa *et al* (1999) demonstrated acceptable local control and survival with surgery followed by radiation (>55 Gy) in patients with questionable or positive surgical margins. We believe, and agree with many authors, that MECs of minor salivary glands with low to intermediate grade should be treated with wide local excision intraorally, if it can be achieved, with clear surgical and histological margins. Radical

surgery with resection of bone (maxillectomy or marginal mandibular resection) is indicated when tumor invasion is diagnosed and for all high-grade tumors. This surgical protocol is used for the patients with MECs in our clinic. It is generally accepted that, for high-grade MECs, radiotherapy combined with surgery should achieve local control of the disease and good survival rates. We combined the radical surgery with radiotherapy for seven cases of our patients namely: two cases of high-grade MECs, four cases with positive lymph nodes that the radical excision was combined with supraomohyoid or radical neck dissection, and one case with a large tumor located in the hard and soft palate and extended in paranasal sinus and nasal cavity. It is useful, for MECs of minor salivary glands, the histopathological stage of the tumor to be associated with the clinical findings (rapid or slow development, with symptoms or asymptomatic, the location of the tumor, in the palate, in the floor of the mouth, the clinical staging T_1–T_4) before treatment decisions (Nascimento *et al*, 1986; Auclair *et al*, 1992; Guzzo *et al*, 2002).

Prognosis of MECs is a function of the histological grade, adequacy of excision and clinical staging. Low-grade tumors have a 5-year survival rate of 90–100%, with the exception of the submandibular gland MECs. The studies from the Armed Forces Institute of Pathology (AFIP, Goode *et al*, 1998) indicated that 5% of major gland and 2.5% of minor gland low-grade MECs metastasized to regional lymph nodes or resulted in death. Brandwein *et al* (2001) believe that Goode *et al* (1998) have a tendency to downgrade MECs and query if this 'downgrading' may have contributed to these statistics. Intermediate- and high-grade tumors have a greater tendency to infiltrate, recur and metastasize with reported 5-, 10- and 15-year cure rates of 49, 42 and 33%, respectively (Krolls *et al*, 1972; Brandwein *et al*, 2001; Guzzo *et al*, 2002; Monoo *et al*, 2003). Plambeck *et al* (1996) reported 5- and 10-year survival rates of 91.6 and 89.5%, respectively, regardless of tumor grade. Most of the high-grade MECs show their malignant behavior within the first 5 years after surgery, in contrast with the continuous increase in survival rate over a 20-year period seen with ACC and acinic cell carcinoma (Brandwein *et al*, 2001). From the patients of our study, four died within the first 2 years (two cases of high-grade and two cases of intermediate-grade) (Table 4).

A correlation has been found between prognosis and the following parameters: age (better in younger patients), sex (better in females), extraglandular extension, vascular invasion, mitotic rate, cell proliferation (as measured by Ki-67 antigen) (O'Brien *et al*, 1986; Tran *et al*, 1986). Histopathological features that correlated with poor outcome were cystic component $<20\%$, four or more mitotic figures per 10 high-power fields, neural involvement, necrosis and anaplasia (Brandwein *et al*, 2001). High Ki-67 expression is significantly correlated with increased histological grade, especially necrosis, cell anaplasia and mitotic index (Goode *et al*, 1998; Hicks and Flaitz, 2000; Okabe *et al*, 2001; Foschini *et al*, 2002).

Our immunohistochemical findings in correlation with prognosis agree with these of most authors. A common finding is no expression or minimum expression (1%) of Ki-67 in low-grade MECs with progressive increase from intermediate-grade (4%) to high-grade (10%) tumors (Hicks and Flaitz, 2000; Brandwein *et al*, 2001; Okabe *et al*, 2001; Monoo *et al*, 2003). Two patients of our study with high-grade MEC had increased expression (10%) of Ki-67 and died within the first 2 years after the treatment (lymph node metastases and metastases in lungs) (Table 4).

Conclusions

Low- and intermediate-grade MECs of salivary glands tend to have a favorable outcome when compared with high-grade MECs that have a greater tendency to recur and to metastasize.

Treatment outcome of these tumors is influenced by clinical stage and histological tumor grade. Radical surgery is used for all high-grade MECs or low/intermediate-grade tumors that are large and involve the bone. In patients with positive surgical margins or for high-grade tumors radiotherapy could be combined with surgery.

Proliferative markers (Ki-67) demonstrate the histological grade of MECs and provide additional prognostic information regarding the expected biological behavior, recurrence, metastatic potential and overall survival.

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