MUCOEPIDERMOID CARCINOMA OF THE ORAL CAVITY

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There is presently no uniformly accepted grading system for mucoepidermoid carcinoma, largely due to a lack of consensus as to what criteria should be used to formulate histological grades. The present study was undertaken to determine the relationship between histological grade, clinical stage and survival in these neoplasms. Clinical and histological data from 34 patients with mucoepidermoid carcinoma were reviewed. Mucoepidermoid carcinoma was most common in the parotid gland (44.1%), while 25% of patients had tumors in the minor salivary glands. Low, intermediate, and high-grade neoplasms accounted for 61.7%, 26.5%, and 11.8% of tumors, respectively. There was a general trend towards increasing clinical aggressiveness with increasing histological grade. Similarly, postoperative tumor recurrences were marginally more common in high-grade than in low-grade mucoepidermoid carcinomas. However, both of these findings were statistically insignificant, mainly due to small sample size, late clinical presentation, poor clinical follow-up, incomplete management and incomplete records. These factors explain the relatively low survival figures in the present study, as compared to higher survival figures in white patients with mucoepidermoid carcinoma. (*J Natl Med Assoc.* 2001;93:178–184.)

Key words: mucoepidermoid carcinoma ◆ neoplasm

Histological grading of malignancies is one of several variables considered useful in the assessment of biologic aggressiveness, as well as monitoring response to therapy and prognosis.[1] That there is no uniformly accepted grading system for mucoepidermoid carcinoma, despite half a century of trying, is a testimony to a lack of consensus as to what features should be used to formulate the grades, and the imperfect separation of histological grades as an independent prognostic variable from size of the primary neoplasm and its clinical stage.[1]

It has been pointed out that identification of mucoepidermoid carcinoma is usually easy, but histological sub-classification is a difficult and controversial problem.[2]

Foote and Frazell concluded that all mucoepidermoid tumors were malignant, albeit in degree, and classified them as low, intermediate and high-grade tumors.[3] Jakobson et al. determined grade primarily from presence or absence of invasive growth.[4] Spiro et al. classified mucoepidermoid carcinoma as low, intermediate or high-grade, with 5-year survival rates of 92%, 83% and 24%, respectively.[5]

An update of our experience of mucoepidermoid carcinoma in Ibadan is desirable, with emphasis on histological sub-classification of these neoplasms, since this may have important implications

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on prognosis. The aim of the present study was therefore to determine if the histological grading of mucoepidermoid carcinoma influences survival, and the relationship between histological grade, clinical stage and survival in our patients with this neoplasm.

MATERIALS AND METHODS

All benign and malignant salivary gland neoplasms histologically diagnosed during the period 1975 to 1995 were extracted from the files of the Oral Pathology Department and Cancer Registry of the University College Hospital, Ibadan.

The hematoxylin-eosin-stained sections of these cases were retrieved from the archives of the departments of Oral Pathology and Histopathology of this hospital. The cases were histologically reviewed and re-classified according to the World Health Organization (WHO) classification of salivary gland tumors.[6] In all, slides from 310 patients were retrieved and examined. Of these, 243 fulfilled the histological criteria for the histodiagnosis and typing of true salivary gland neoplasms.

The archival paraffin blocks of 40 cases originally diagnosed as mucoepidermoid carcinoma were retrieved. New 5-μm sections were cut, and stained with Ehrlich's hematoxylin-eosin, Southgate's mucicarmine and Alcian blue methods. Six cases originally classified as mucoepidermoid carcinoma, but not showing either positive mucicarmine or Alcian blue reactions, were deleted from this group and reclassified as squamous cell carcinoma of salivary gland origin.

The 34 patients diagnosed as having mucoepidermoid carcinoma were subclassified according to Spiro et al.'s criteria[5] as low-grade, intermediate or high-grade, based on histological criteria as follows:

A. Low-grade mucoepidermoid carcinoma: These neoplasms displayed well developed glandular or microcystic structures lined by a single layer of mucus secreting columnar cells. Occasional borders of papillary infolding formed by intermediate type cells or epidermoid cells or focal inflammatory reaction with foreign body giant cells were sometimes observed.
B. Intermediate-grade mucoepidermoid carcinoma: These neoplasms consisted of solid areas of epidermoid (squamous) cell or intermediate (basaloid type) elements with predominance of intermediate cells. Papillary cystic structures and infoldings showing epidermoid or basal cells occurred quite frequently.
C. High-grade mucoepidermoid carcinoma: In this subgroup of neoplasms, there was an increased tendency for intermediate basal and epidermoid cells to appear in solid nests or cords. Variation in size and shape of neoplastic cells, prominent nucleoli and abundant mitotic figures were easily recognised. Glandular and cystic structures were only occasionally seen.

The clinical case records of affected patients were retrieved and clinical information including age at diagnosis, gender, site, and primary therapy were extracted. Information on clinical follow up, including whether the patient was alive or dead at the time of last clinical contact, was obtained where available. Presence or absence of tumor recurrence, and interval between therapy and recurrence and type of treatment given for recurrence(s) was also noted. For dead patients, interval between time of first diagnosis and death was noted.

These survival indices were correlated with the histological grade of mucoepidermoid carcinoma in order to determine whether there was any relationship between these parameters and survival.

Patients were staged using the TNM clinical staging of salivary gland tumors of the American Joint Committee on Cancer Staging.[7]

The data obtained were tabulated and statistically analysed using chi-square testing where applicable. Levels of significance were set at $p < 0.05$.

RESULTS

Subjects

There were 21 men (61.8%) and 13 women (38.2%), resulting in a male-to-female ratio of 1.6:1. The peak age of occurrence was in the sixth decade of life (Fig. 1). The mean age of occurrence was 44.5 years.

Anatomic Location

Of the 34 tumors selected, major salivary glands were involved in 24 (70.6%) patients (15 parotid, 6 submandibular and 3 sublingual) and minor glands in 10 patients (29.4%). Among the intraoral minor glands, the most common site was the palate (5 patients), other sites being the antrum (2 patients),

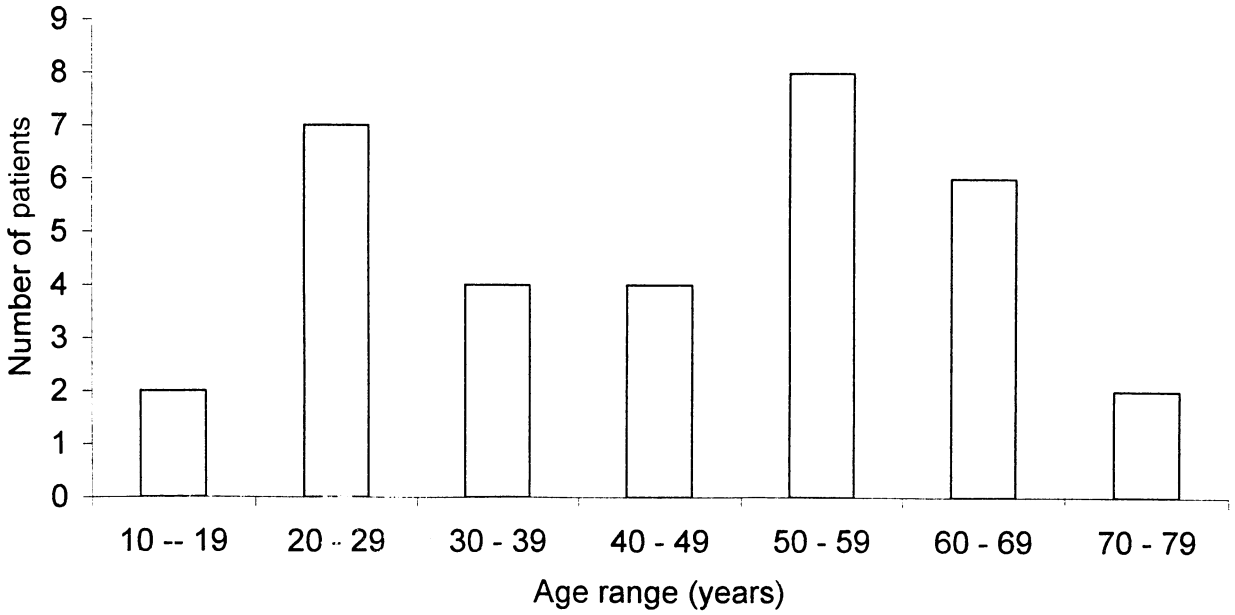

Figure 1. Age distribution of patients with oral mucoepidermoid carcinoma.

other minor glands (1 patient), while 2 patients had tumors at unknown sites.

Histological Grading

Overall, four patients had high-grade mucoepidermoid carcinoma (11.8%), nine had intermediate-grade (26.5%) and 21 had low-grade (61.7%) (Fig. 2). Figures 3 and 4 show photomicrographic representation of intermediate and low-grade mucoepidermoid carcinomas.

Symptomology

Table 1 shows the clinical features of patients with mucoepidermoid carcinoma. The most common clinical manifestation was localized swelling which was painful in 24 (70.6%) patients and painless in 9 (29.4%). Figure 5 shows a clinical photograph of a 45-year-old patient with mucoepidermoid carcinoma of the parotid gland. There was no obvious correlation between clinical symptoms and signs and histological grade in this study.

Postoperative Survival

The 5- and 10-year survival rates for low-grade mucoepidermoid carcinoma were 28.6% and 10.5%, 33.3% and 0% for intermediate-grade, and 25% and 0%, respectively, for high-grade (Table 2). The overall 5- and 10-year survival rates for mucoepidermoid carcinoma were 29.4% and 5.9%, respectively. There was no statistically significant difference in the survival of patients with low versus intermediate ($p = 0.15$), low versus high ($p = 0.09$), or intermediate versus high-grade neoplasms ($p = 0.38$).

Clinical Staging

The only stage I neoplasm (T2N0M0) was seen in a low-grade mucoepidermoid carcinoma, and stages II (T3N0M0) and III (T2N1M0 and T4bN0M0) carcinomas were confined to low and intermediate-grade neoplasms (Table 3). There were 17 stage IV carcinomas and 1 unclassifiable (T3NXM0) carcinoma. However, this trend was not statistically significant ($\chi^2 = 1.21$, df = 1, $p = 0.3$).

Distant metastasis occurred in 2 (5.9%) of 34 patients. One was in an adult male of unknown age with antral high-grade mucoepidermoid carcinoma, who had pulmonary metastasis. The second was a 28-year-old woman with submandibular low-grade mucoepidermoid carcinoma with metastasis to the orbit. The survival periods of these patients until last follow-up were 2 and 10 years, respectively.

Tumor Recurrence

Overall, postoperative tumor recurrence occurred in 9 (26.5%) patients. Of these, 2 of 4 (50%)

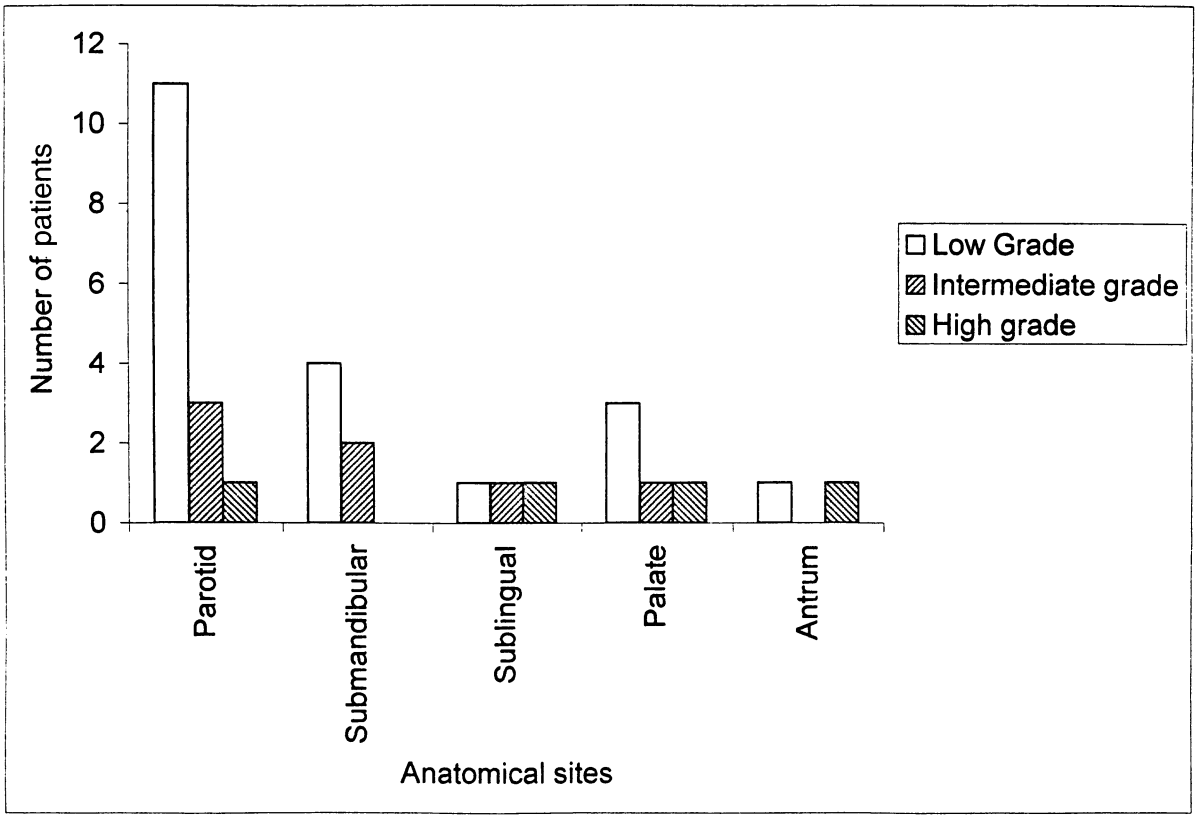

Figure 2. Histogram showing distribution of histological grades of oral mucoepidermoid carcinoma according to anatomical sites.

recurrences were high-grade, 2 of 9 (22.2%) intermediate-grade and 5 of 21 (23.8%) low-grade neoplasms. However, correlation of tumor recurrence to histological grade was not statistically significant ($\chi^2 = 1.29$, df = 2, $p = 0.7$).

Of these patients with recurrent disease, 1 of the 2 high-grade, 1 of the 2 intermediate-grade and 2 of the 5 low-grade recurrences were uncontrolled by surgery, chemotherapy or radiotherapy.

The median intervals for tumor recurrence were 3 months (range = 2 to 9 months) for high-grade, 8 months (range = 4 months to 1 year) for intermediate-grade and 2 years (range = 6 months to 7 years) for low-grade mucoepidermoid carcinomas.

DISCUSSION

The peak age of occurrence of mucoepidermoid carcinoma was in the sixth decade of life, with a mean of 44.5 years. This finding is in contrast with a previous study by Adekeye and Robertson[8] who reported a low mean age of 25.3 years but concurs with other reports.[9,10]

Our findings concur with those of others that the major salivary glands account for 75% of cases of mucoepidermoid carcinoma in white patients—the majority occurring in the parotid—and minor salivary glands for 25% of patients, of which the majority occurred in the palate.[10,11]

In the present study, 61.7%, 26.5% and 11.8% of mucoepidermoid carcinomas were of low, intermediate or high-grade respectively. Spiro et al.[5] and Accetta et al.[10] found that 41.4% and 31.8%, respectively, of neoplasms were low-grade, 38.4% and 45.4% were intermediate-grade and 20.2% and 22.8% were high-grade. Thus, the incidence of low-grade mucoepidermoid carcinoma appears to be higher in the present study than in those two caucasian studies. However, Evans,[11] using a two-grade system, reported low and high-grade neoplasms to have an incidence of 71% and 29%, respectively, which is similar to our findings.

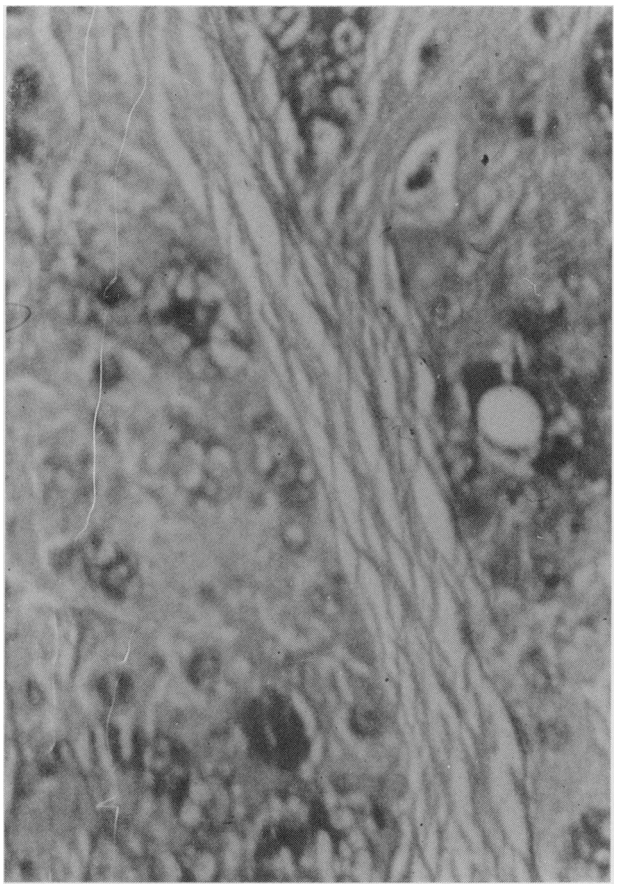

Figure 3. Photomicrograph showing intermediate-grade mucoepidermoid carcinoma (Alcian blue, 200×).

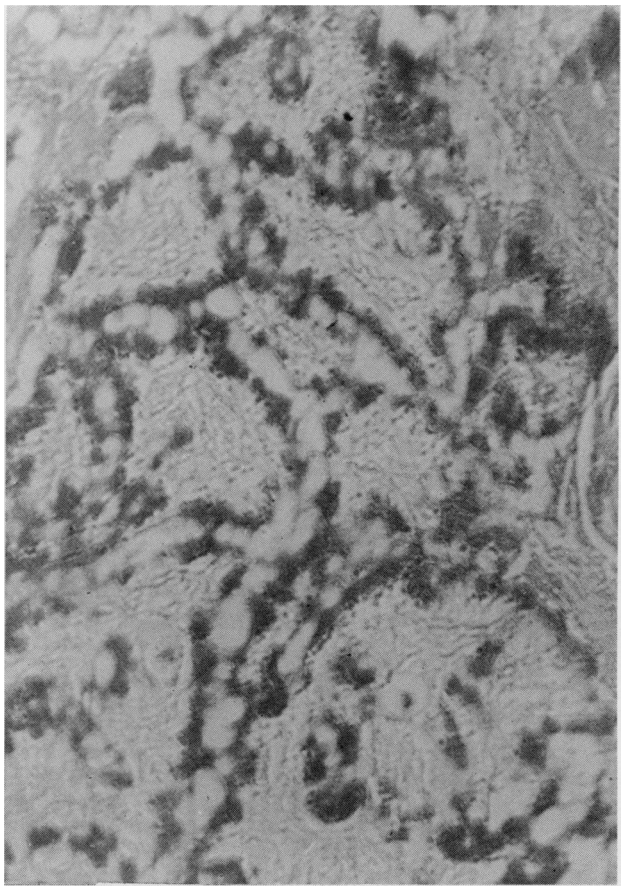

Figure 4. Photomicrograph showing low-grade mucoepidermoid carcinoma (Alcian blue, 200×).

Again, probably because of the small number of cases in the present study, the duration of symptoms and clinical outcome of patients with mucoepidermoid carcinoma in the present study was not related to histological grade. Thus, although the 5- and 10-year survival rates for low-grade mucoepidermoid carcinoma were 31.5% and 10.5%, for intermediate-grade 33.3% and 0%, and for high-grade 25% and 0% respectively, these figures were not significant. Nevertheless, other studies have demonstrated that poorly differentiated mucoepidermoid carcinomas tend to pursue an aggressive course, as compared to most well differentiated intermediate mucoepidermoid carcinomas, which usually pursue a relatively indolent course.[10]

In contrast to our poor survival figures, others have observed that the 5-year survival for low-, intermediate-, and high-grade mucoepidermoid carcinoma were 95%, 80–90% and 25–30%, respectively.[2] The low survival figures in our study, as compared to the high white figures can be explained based on late clinical presentation because of either financial reasons or prior consultation with traditional medicine men. In support of this hypothesis, only one of our patients presented with stage I disease progression but the majority of patients were in stage IV. However, Spiro et al. found that 43.8% of clinically staged patients were in stage I, indicating earlier clinical presentation.[5]

Tumor metastases occurred in 2 (5.9%) of our patients, which is lower than the figure of 15% recorded by Spiro et al.[5] However, several patients in our study were lost to clinical follow-up, which may explain this apparent discrepancy.

There was no significant relationship between clinical stage and histological grade, probably because of the low numbers of cases in the present study. However, the only stage I neoplasm we observed was low-grade, and stages II and III carcinomas were confined to low and intermediate-grade

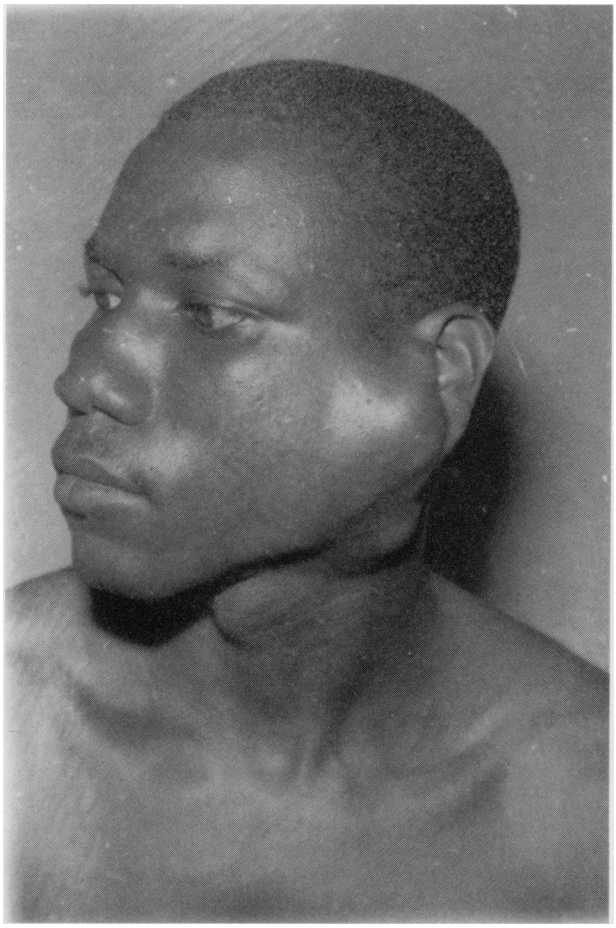

Figure 5. A profile view of a 45-year-old man with mucoepidermoid carcinoma of parotid gland.

neoplasms. Spiro et al. also observed a similar relationship between histological grade and clinical stage.[5] Sixty-four percent of their patients with stage I tumors were low-grade neoplasms, whereas 91% of clinically advanced cases had intermediate and high-grade neoplasms.

Table 1. Symptomology

Parameter	Tumor Grade				
	Low	Intermediate	High	Total	%
Painful swelling	14	7	3	24	70.6
Painless swelling	7	2	—	9	29.4
Ulceration	13	4	4	21	61.8
Fixation of lymph nodes	9	2	3	14	41.2
Toothache and mobility	4	4	3	11	32.2
Bleeding	5	3	3	11	32.4

Table 2. Duration of Symptoms

Duration	Grade			Total	%
	Low	Intermediate	High		
<1 year	4 (died)	6 (2 died)	1 (1 died)	11	32.4
1–3 years	7 (2 died)	—	2 (1 died)	9	29.4
4–5 years	2	—	—	2	5.9
5–10 years	4	3	1	8	23.5
>10 years	2 (1 died)	—	—	2	5.9

In our study, postoperative tumor recurrence occurred in 26.5% of patients. This is similar to the findings of Spiro et al., who observed a tumor recurrence rate of 26%.[5] Postoperative tumor recurrence could not be significantly related to histological grade, although being relatively more common

Table 3. Tumor Staging and Grading

Stage	Grade			Total	%
	I	II	III		
Tumor size					
T1 (<2 cm)	—	—	—	—	—
T2 (2–4 cm)	2	1	—	3	8.8
T3 (4–6 cm)	3	2	1	6	17.6
T4 (>6 cm)	9	3	2	14	41.2
TX	7	3	1	11	32.4
Extension (skin, soft tissue, bone, lingual and facial nerves)	15	4	3	22	64.7
Nodes					
N0 (No nodes)	5	4	1	10	29.4
N1 (regional nodes)	16	5	3	24	70.5
Distant Metastases					
M0 (None)	20	9	3	32	94.1
M1 (Metastases)	1	—	1	2	5.9
Stage					
I	1	—	—	1	2.9
II	1	1	—	2	5.9
III	2	1	—	3	8.8
IV	10	4	3	17	50
Not staged	7	3	1	11	32.4
Total	21	9	4	34	100

in high-grade and less common in low-grade neoplasms. However, Seifert et al. note that local recurrence occurs in 6% of low-grade, 20% of intermediate-grade and 80% of high-grade neoplasms, which tends to agree with our findings.[2]

Most tumor recurrences in mucoepidermoid carcinoma occur within 1 year of treatment, as observed in the present study.[5] Recurrences tend to occur more rapidly in high than in low-grade neoplasms.

CONCLUSION

Our findings suggest that mucoepidermoid carcinoma generally show a tendency to increased clinical aggressiveness with increasing histological grade. Thus, although the 5- and 10-year survival rates for mucoepidermoid carcinoma in our study were relatively higher for low-grade than for high-grade neoplasms, the figures obtained were not statistically significant. Similarly, postoperative tumor recurrences were marginally more common in high-grade than in low-grade tumors. Other investigators have been able to demonstrate significant correlation between increasing histological grade and clinical aggressiveness of mucoepidermoid carcinomas, which also concurs with our findings.

REFERENCES

1. Batsakis JG, Luna MA. Histopathologic grading of salivary gland neoplasms: I—mucoepidermoid carcinomas. *Ann Otol Rhinol Laryngol.* 1990;99:835–838.

2. Seifert G, Brocheriou C, Cardesa A, Eveson JW. WHO international histological classification of tumors—tentative histological classification of salivary gland tumors. *Path Res Pract.* 1990;186:555–581.

3. Foote FW, Frazell EL. Tumors of major salivary glands. *Cancer.* 1953;6:1065–1133.

4. Jakobson PA, Blanok C, Eneroth CM. Mucoepidermoid carcinoma of the parotid gland. *Cancer.* 1968;22:111–124.

5. Spiro RH, Huvos AG, Berk R, Strong EW. Mucoepidermoid carcinoma of salivary gland origin. A clinicopathologic study of 367 cases. *Am J Surg.* 1978;136:461–8.

6. Thackray AC, Sobin LH. *Histological Typing of Salivary Gland Tumors.* International Histological Classification of Tumors, No 7. Geneva: World Health Organisation; 1972.

7. American Joint Committee on Cancer. *Manual for staging of cancer.* Philadelphia: JB Lippincott Company; 1993;49–52.

8. Adekeye EO, Robertson JM. Salivary gland tumors in Northern Nigeria. *Tropical Doctor.* 1979;9:168–174.

9. Arotiba GT. Salivary gland neoplasms—a review of cases seen in LUTH. Dissertation for the Fellowship of the West African Postgraduate Medical College in Dental Surgery; 1991.

10. Accetta PA, Gray GF, Hunter M, Rosenfeld L. Mucoepidermoid carcinoma of salivary glands. *Arch Pathol Lab Med.* 1984; 108:321–325.

11. Evans HL. Mucoepidermoid carcinoma of the salivary glands. A study of 69 cases with special attention to histologic grading. *Am J Clin Pathol.* 1984;81:696–701.