Original Article

Salivary Adenoid Cystic Carcinoma: A Clinicohistologic Study in a Nigerian Tertiary Institution

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Abstract

Background: Adenoid cystic carcinoma (ADCC) is a slow-growing salivary gland tumor with high recurrence and mortality rates. Histologic variants present variable aggression. This has not been investigated in Nigeria. This study aimed to investigate association of histologic variants with clinical aggression in Nigerian cases.**Patients and Methods:** Fifty-nine ADCC from 363 salivary gland tumors were selected from the departmental oral biopsy archives. Clinical data were retrieved, and hematoxylin and eosin sections were reviewed for confirmation and categorization into solid, cribriform, and tubular (modified Perzin, Spiro and van Weert systems). Estimated mean tumor growth rates (EMTGRs) were computed and matched with histologic variants. Statistical analysis was Chi-square, Kruskal–Wallis, and Mann–Whitney's test. *P* value was ≤0.05. Statistical package was SPSS. **Results:** Age ranged between 7 and 83 years (mean 49.2 ± 16.8 years). About 75.1% occurred in the 4th–6th decade ($P = 0.02$). Most common histologic variant was predominantly cribriform no solid (PCNS) pattern (40.7%). In major salivary glands, there was association between histologic variant and EMTGR ($P = 0.025$). PCNS had the highest EMTGR (0.840) followed by predominantly solid (PS) (EMTGR, 0.744). These were significantly higher than predominantly tubular no solid (PTNS) (EMTGR, 0.442) and predominantly tubular 30% solid (EMTGR, 0.115). In minor glands, there was also association between histologic variants and EMTGR ($P = 0.017$). However, the highest EMTGR (0.509) occurred in PTNS followed by PCNS (0.428). These were significantly higher than PS (0.259) with the least EMTGR. **Conclusion:** Trend of clinical aggression of histological variants based on EMTGR of ADCC varies depending on the type of salivary gland (major vs. minor).

Keywords: Adenoid cystic carcinoma, analysis, estimated growth rate, histologic variants

Introduction

Adenoid cystic carcinoma (ADCC) is a slow-growing high-grade malignant epithelial neoplasm, which has been shown to display three histologic variants, namely solid, cribriform, and tubular.[1,2] A particular tumor is classified based on the most predominant pattern seen microscopically. The histological classification scheme for ADCC has been shown to be important for clinical and prognostic correlation.[1] The present study aims to classify histologically cases of ADCC using Perzin, Spiro, and van Weert criteria[3-5] with slight modifications. Furthermore, the relationship between histopathological variant and the biologic behavior of the tumor will be investigated.

Patients and Methods

All clinical data and histological materials of cases histologically diagnosed as ADCC that occurred within the salivary glands and were managed at Lagos University Teaching Hospital from January 1970 to December 2016 were retrieved from the biopsy records of Department of Oral and Maxillofacial Pathology/Biology. Cases with complete information were selected for inclusion in the study, and parameters studied included sociodemographic and the clinicohistologic data.

Paraffin-embedded tissue blocks were retrieved, sectioned in at 4 μ thickness and stained with hematoxylin and eosin. Diagnosis was confirmed on the freshly stained

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slides, subsequently evaluated and categorized. Categories were based on a modified version of Perzin *et al*., Spiro *et al*., and van Weert *et al*. grading systems into the following specific histologic variants. Type I: predominantly solid (PS), Type II: predominantly cribriform and 30% solid, Type III: predominantly cribriform no solid (PCNS), Type IV: predominantly tubular and 30% solid, and Type V: predominantly tubular no solid (PTNS).[3-5]

Evaluation of histological sections was done by more than one consultant investigator who had been calibrated, and only reconciled values were recorded.

Clinical aggression of ADCC was speculated based on estimated tumor growth rate for each tumor which was computed from the largest diameter of a tumor and duration at presentation (tumor growth rate = largest diameter of tumor at presentation in centimeters/duration of tumor in months).[6,7] For each histological variant, a mean of the estimated tumor growth rate was computed and named estimated mean tumor growth rates (EMTGR). The EMTGR for each histologic variant was then compared with those of other histologic variants. Furthermore, EMTGR for histological variants were compared within minor salivary glands as well as within major salivary glands.

Methods of statistical analysis include nonparametric tests consisting of Kruskal–Wallis and Mann–Whitney's tests. Level of significance was set at $P \leq 0.05$. Data obtained were analyzed using the statistical package software (SPSS) for windows version 21.0 (SPSS Inc., Chicago, IL, USA).

Ethical approval

Ethical approval was granted in writing by the Ethics Committee of Lagos University Teaching Hospital, Lagos, Nigeria.

Results

ADCC constituted 59 (16.3%) cases of a total of 363 salivary gland tumors (both benign and malignant) diagnosed at our center.

From the total of 59 cases of ADCC studied, 31 (52.5%) cases occurred within the minor glands, of which the palate was the most affected ($n = 26$, 44.1%) while 28 (47.5%) cases occurred in the major salivary glands from which 21 (35.6%) cases occurred in the parotid glands [Figure 1]. The age of patients ranged from 7 to 83 years, with a mean age of 49.2 ± 16.8 years. The mean age in males (54.3 ± 20.5 years) was almost a decade higher than that for females (45.4 ± 12.5 years) and was statistically significant ($P = 0.044$) [Table 1].

There were 25 (42.2%) males and 34 (57.6%) females, with a male-to-female ratio of 1:1.4 [Table 1]. The PCNS [$n = 24$: 40.7%; Figure 2] and the PS [$n = 18$: 30.5%; Figure 3] were the two most common histologic variants [Table 2]. The mean estimated tumor growth rate for all tumors (EMTGR) was 0.530 ± 0.684 cm/month.

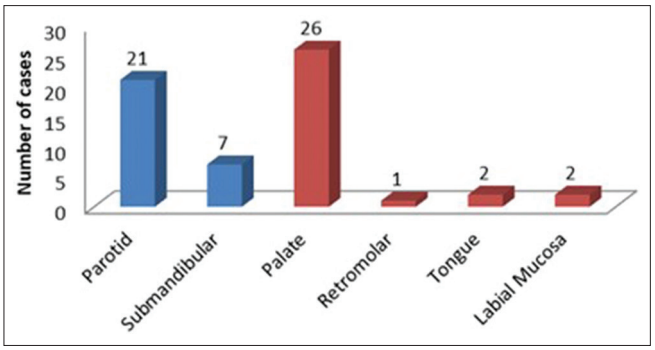

Figure 1: Histogram showing site distribution of adenoid cystic carcinoma in major and minor glands

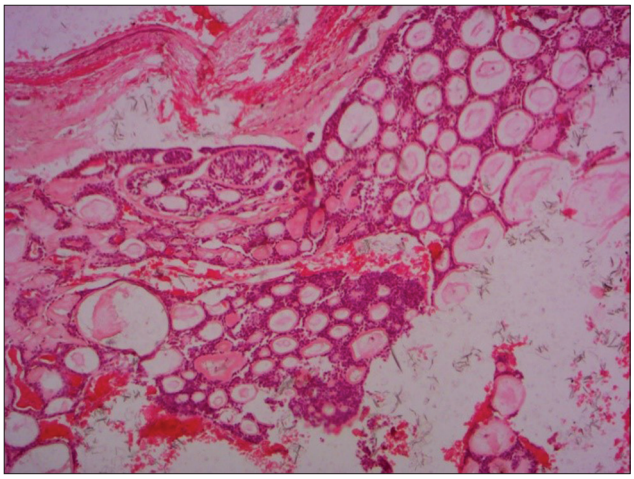

Figure 2: Photomicrograph of predominantly cribriform no solid histologic variants of adenoid cystic carcinoma (H and E; ×100)

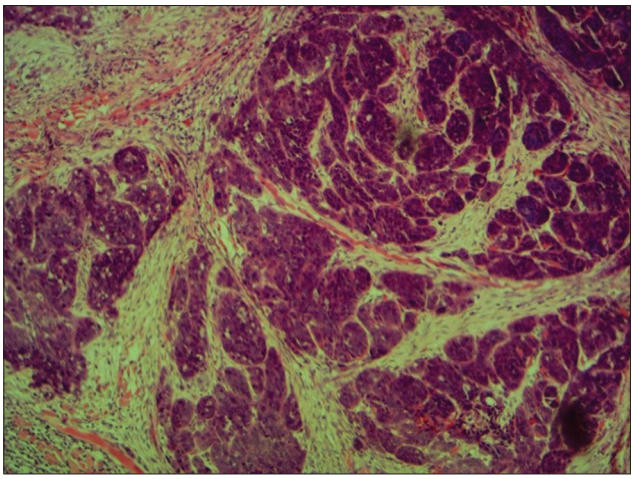

Figure 3: Photomicrograph of predominantly solid histologic variant of adenoid cystic carcinoma (H and E; ×400)

Major glands

Lesions in the major glands were slightly more common in males than females (ratio of 1.15:1) and occurred at a modal age group of 31–60 years and a mean age of 52.8 ± 17.8 years [Table 3]. The parotid gland (n = 21: 75%) was the most commonly affected major salivary gland [Figure 1]. PCNS

Table 1: General sociodemographic characteristics of the patients

Variable	Frequency (%)
Age of patients (years)	
1-30	5 (8.5)
31-60	37 (62.7)
61-90	17 (28.8)
Total	59 (100.0)
Mean age (years)	49.2±16.8
Males	54.3±20.5
Females	45.4±12.5
P	0.044*
Gender of patients	
Male	25 (42.4)
Female	34 (57.6)
Total	59 (100.0)

*P value is statistically significant at $P \leq 0.05$

Table 2: General distribution of histologic variants of adenoid cystic carcinoma

Histologic variants	Frequency (%)
PS	18 (30.5)
PC30%S	1 (1.7)
PCNS	24 (40.7)
PT30%S	3 (5.1)
PTNS	13 (22.0)
Total	59 (100)

PS: Predominantly solid, PC30%S: Predominantly cribriform and 30% solid, PCNS: Predominantly cribriform no solid, PT30%S: Predominantly tubular and 30% solid, PTNS: Predominantly tubular no solid

and PS ($n = 20$: 71.4%) were the two most common histologic variants in major salivary glands [Table 4].

The EMTGR for ADCC observed in the parotid gland (0.690 ± 0.780 cm/month) was significantly higher than EMTGR observed in submandibular gland (0.570 ± 0.890 cm/month) [Table 5]. In the major salivary gland, further observation showed a significant association between the histologic variants and the EMTGR ($P = 0.025$). The nature of this association is that the PCNS (EMTGR = 0.840 ± 1.100 cm/month) and the PS (EMTGR = 0.740 ± 0.770 cm/month) were each observed to have a higher EMTGR than the PTNS [Figure 4] (EMTGR = 0.440 ± 0.410 cm/month) and PS with 30% solid (EMTGR = 0.120 ± 0.150 cm/month) [Table 6].

Minor glands

In respect of the minor glands, ADCC was more common in females than males (ratio of 2.1:1) and occurred at a modal age group of 31–60 years with a mean of 45.9 ± 15.5 years [Table 3], with the palate (83.9%) being the most commonly affected site [Figure 1]. The PCNS and PS together ($n = 18$: 58.0%) were the two most common histologic variants [Table 4].

There was a significant association between age group of individuals and EMTGR of the tumor ($P = 0.030$) [Table 7]. The nature of this association is such that patients in younger age group (1–30 years) tended to have a higher EMTGR (1.120 ± 0.890 cm/month) compared to patients in the older age group 31–60 years (EMTGR = 0.321 ± 0.426 cm/month) and age group 61–90 years (EMTGR = 0.257 ± 0.378) [Table 7].

Furthermore, there was an association between gender of the individuals and the EMTGR of ADCC in minor

Table 3: Sociodemographic characteristics of adenoid cystic carcinoma in major and minor salivary glands

Variable	Frequency (%)
Major glands	
Age of patients (years)	
1-30	1 (3.6)
31-60	16 (57.1)
61-90	11 (39.3)
Total	28 (100.0)
Mean age (years)	52.8±17.8
Gender of patients	
Male	15 (53.6)
Female	13 (46.4)
Total	28 (100.0)
Minor glands	
Age of patients (years)	
1-30	4 (12.9)
31-60	21 (67.7)
61-90	6 (19.4)
Total	31 (100.0)
Mean age (years)	45.9±15.5
Gender of patients	
Male	10 (32.3)
Female	21 (67.7)
Total	31 (100.0)

Table 4: Distribution of histologic variants of adenoid cystic carcinoma in major and minor salivary glands

Histology variants	Frequency (%)
Major glands	
PS	9 (32.1)
PC30%S	1 (3.6)
PCNS	11 (39.3
PTNS	5 (17.9)
Predominantly tubular plus 30% solid	2 (7.1)
Total	28 (100.0)
Minor glands	
PS	9 (29.0)
PC30%S	4 (12.9)
PCNS	9 (29.0)
PTNS	8 (25.8)
Predominantly tubular plus 30% solid	1 (3.2)
Total	31 (100.0)

PS: Predominantly solid, PC30%S: Predominantly cribriform and 30% solid, PCNS: Predominantly cribriform no solid, PTNS: Predominantly tubular no solid

Table 5: Distribution of estimated mean tumor growth rate by anatomic site of adenoid cystic carcinoma in major glands

Anatomic site	EMTGR				
	Mean±SD	Median	Range	Mann-Whitney U	*P*
Parotid	0.691±0.783	0.330	2.99	573.500	0.035**
Submandibular	0.577±0.891	0.130	2.41		

***P* value is statistically significant at $P \leq 0.05$. EMTGR: Estimated mean tumor growth rate, SD: Standard deviation

Table 6: Distribution of estimated mean tumor growth rate by histologic variants of adenoid cystic carcinoma in major and minor glands

Histologic variants	EMTGR					
	Mean±SD	Median	Range	Mean rank	Kruskal-Wallis value	*P*
Major glands						
PC30%S	-	-	-	-	19.500	0.025**
PCNS	0.840±1.009	0.440	2.96	25.36		
PS	0.744±0.769	0.330	1.91	16.44		
PTNS	0.442±0.409	0.280	0.860	19.30		
Predominantly tubular plus 30% solid	0.115±0.148	0.115	0.21	6.75		
Minor glands						
PC30%S	0.275±0.361	0.275	0.51	26.00	22.000	0.017**
PCNS	0.428±0.658	0.140	1.99	6.25		
PS	0.259±0.179	0.210	0.570	12.00		
PTNS	0.509±0.669	0.190	1.92	6.72		

***P* value is statistically significant at $P \leq 0.05$. PS: Predominantly solid, PC30%S: Predominantly cribriform and 30% solid, PCNS: Predominantly cribriform no solid, PTNS: Predominantly tubular no solid, EMTGR: Estimated mean tumor growth rate, SD: Standard deviation

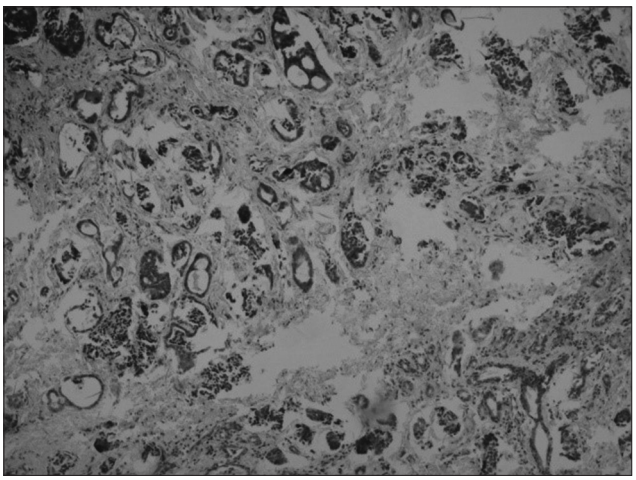

Figure 4: Photomicrograph of predominantly tubular no solid histologic variant (H and E; ×100)

glands ($P = 0.026$); the nature of the association is that males (EMTGR = 0.550 ± 0.622 cm/month) tended to have a higher EMTGR than females (0.350 ± 0.514 cm/month). There was also an association between site of occurrence of ADCC in the minor glands and EMTGR ($P = 0.042$); the nature of this association was such that the palate with an EMTGR of 0.470 ± 0.580 cm/month was significantly higher than EMTGR in any other minor salivary gland sites [Table 7]. In addition, there was also an association between the various histologic variants of ADCC and EMTGR of the lesion ($P = 0.017$); the PTNS (EMTGR = 0.509 ± 0.669 cm/month) had a higher EMTGR than each of PS, PCNS, and PC with 30% solid type [Table 6].

Discussion

Salivary glands neoplasms, although uncommon, represent one of the most complex neoplasia in humans, owing to their wide histological spectrum. These tumors create significant diagnostic and management difficulties to pathologists and surgeons.[1]

ADCC constituted 16.3% of a total of 363 salivary gland tumors in our study; this is slightly higher than previous studies which reported ADCC to account for about 10% of all epithelial salivary gland tumors.[2,8]

ADCC in this series, which displayed a wider age range of 7–83 years, with a mean age of 49.2 years, is similar to that reported in some previous studies[9,10] but almost a decade earlier when compared with mean age from some other studies.[5,11,12]

Furthermore, the mean age in males (54.3 ± 20.5 years) was almost a decade higher than that for females (45.4 ± 12.5 years). The modal age of 31–60 years observed in this study is in agreement with other studies that reported ADCC to be most common in the 4th–6th decades of life.[2,8] In our series, the mean age of ADCC in the major salivary glands was slightly higher than those in the minor glands.

Our study, which showed ADCC to be more common in females than males, is in agreement with report by a number

Table 7: Age, gender, and anatomic site distribution of estimated mean tumor growth rate of adenoid cystic carcinoma in minor salivary glands

Age group of patients (years)	EMTGR					
	Mean±SD	Median	Range	Mean rank	Kruskal-Wallis value	*P*
1-30	1.118±0.895	1.23	1.98	26.50	8.67	0.030**
31-60	0.321±0.426	0.170	1.99	15.83		
61-90	0.257±0.378	0.115	0.99	9.25		
Gender	**Mean±SD**	**Median**	**Range**	**Mann-Whitney U**	***P***	
Male	0.550±0.622	0.400	1.99	325.000	0.026**	
Female	±0.345±±0.514	0.170	1.99			
Anatomic site	**Mean±SD**	**Median**	**Range**	**Mean rank**	**Kruskal-Wallis value**	***P***
Labial mucosa	0.085±0.035	0.085	0.05	4.50	7.45	0.042**
Palate	0.474±0.580	0.210	1.99	19.62		
Tongue	0.125±0.064	0.125	0.09	10.00		

***P* value is statistically significant at $P \leq 0.05$. EMTGR: Estimated mean tumor growth rate, SD: Standard deviation

of other authors[3,5,9-11] although the general consensus is that ADCC has no significant gender preference.[2,4,12] Lesions in the major glands were however slightly more common in males (1.15:1) while those in the minor glands are more common in females (2.1:1) in our series.

In this study, observation that ADCC is more common in the minor salivary glands (52.5%) than the major glands (47.5%) is consistent with findings in the scientific literature.[9,10,12,13]

However, Khafif *et al*.[12] and Ko *et al*.[13] reported ADCC to be more common in major glands.

In our hospital, surgical specimens of a number of major gland tumors operated by general, plastic, and ENT surgeons are sent for histologic diagnosis to the biopsy services of the department of anatomical and molecular pathology. In our series, observation that the palate was the most affected minor gland site and the parotid was the most affected major gland site is similar to observation in other studies which reported parotid and submandibular as the most affected major salivary gland site and the palate and tongue as the most affected minor salivary gland site.[2,8]

We observed that females reported a lower EMTGR than males in minor glands. EMTGR has been used to predict the biological behavior of ameloblastoma[6,7] and is believed to be useful in the present study to estimate clinical behavior of ADCC. It is possible that ADCC appears to grow slower in females than males because of the fact that females tend to seek medical attention earlier than men, at which time tumor size is relatively small and tumors are thus diagnosed earlier, whereas males tend to present much later at which time tumor must have attained an enormous size over a short period.[14]

Observation that in minor salivary glands, patients in younger age group (1–30 years) had a higher EMTGR than patients in the older age groups is not unexpected because tissue turnover is higher in the younger age group than in older age group. This is attributed to the process of aging.[15]

The palate being overwhelmingly the most common site of occurrence of ADCC may explain why this site had a significantly higher EMTGR than any other site of the minor salivary glands.

In the major salivary glands, observation that the parotid gland had a significantly higher EMTGR than submandibular gland may be explained by the fact that, given the same duration, the available unlimited space for growth of the parotid gland tumor relative to the submandibular gland gives adequate opportunity for an expansile growth of a parotid tumor over a short period.

Observation from our study that PCNS and PS histologic variants were the two most common variants of ADCC is consistent with findings by Szanto *et al*.,[11] who reported predominantly cribriform (similar to our PCNS) as the most common, and van Weert *et al*.,[5] who reported ADCC with varying amount of solid component (comparable to our PS) as the most common histologic variant.

Further observation in the major salivary glands that PCNS (EMTGR = 0.840 cm/months) was the fastest growing variant is in contrast to findings in the minor glands where the PTNS (EMTGR = 0.509 cm/month) was noted to be the fastest growing histologic variant. It should however be noted that PS variant occurred as the second fastest histologic variant in the major glands and the slowest growing in the minor glands. The histologic classification scheme for ADCC has been shown to be important for clinical and prognostic correlation. This is further supported by the fact that the clinical behavior and eventual prediction of ADCC differ depending on the dominant histologic pattern within a particular neoplasm.[1] For example, the solid pattern, which has been reported to be a high-grade tumor, has a higher risk of nodal metastasis and invariably a poorer prognosis[3,11,16] while tubular variants have been reported to confer a better prognosis on the tumor.[11,17] Molecular studies have also shown a high percentage of loss of heterozygosity and higher expression of p53 in the solid variant when compared with other histologic variants.[18,19] Therefore, the histopathologic grading of ADCC is important

in determining its prognosis and subsequently the treatment plan and follow-up measures for this neoplasm.

It is not clear at this stage the reason for the peculiar observation from our study that PCNS and PS were the two fastest growing tumor and PTNS was the slowest growing tumor in the major salivary gland, while in the minor salivary glands, PTNS was the fastest growing and PS was the slowest growing. It is possible that factors local to this environment may be responsible and future research should investigate this. Accurately relating a tumor's histology with its projected clinical course would certainly offer the clinician a valuable tool to determine prognosis and thus effectively manage patients.

Conclusion

In conclusion, it appears that the trend of clinical aggression of histological variants based on EMTGR of ADCC varies depending on the type of salivary gland (major vs. minor). In the major salivary glands, PCNS and the PS tend to have the highest EMTGR while the PT had the lowest value of EMTGR. However in the minor salivary glands, the PTNS variant had the highest EMTGR while the PS had the lowest.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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