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## Predictors Of Distant Metastasis In Acinic Cell Carcinoma Of Salivary Gland: Experience Of A Tertiary Cancer Center.

Aishwarya K Verneker<sup>1</sup>, Arava Anu<sup>2\*</sup>, Ashwini Nargund<sup>3</sup>, and Usha Amritham<sup>4</sup>.

<sup>1</sup>Senior Resident, S. Nijalingappa Medical College And Hospital, Bagalkote, Karnataka, India.

<sup>2</sup>Assistant Professor, Annapoorana Medical College And Hospitals, Salem, Tamil Nadu, India.

<sup>3</sup>Associate Professor, Kidwai Memorial Institute Of Oncology, Bangalore, Karnataka, India.

<sup>4</sup>HOD and Professor, Kidwai Memorial Institute Of Oncology, Bangalore, Karnataka, India.

### ABSTRACT

Acinic cell carcinoma is a rare, low to intermediate grade malignant epithelial neoplasm. Distant metastasis is a common treatment failure pattern in acinic cell carcinoma (AciCC) of the major salivary glands; therefore, the main goal of this study is the identification of primary tumor characteristics in acinic cell carcinoma that predisposes patients to develop distant metastasis. This is a retrospective single institutional study conducted at KMIO. The list of the patients with acinic cell carcinoma between the years 2014 to 2020 were obtained. Clinical details of these patients were collected. The histopathological slides of these patients were reviewed and synoptic reporting was done. A total of 15 patients were included in the study. The tumor is evenly distributed between second to sixth decades of life. Most common site of involvement is parotid gland followed by minor salivary glands. 12 patient's undergone definitive surgery with negative margins and lymph node dissection. 4 patients showed high grade transformation with lymph node metastasis. 2 patients with high grade transformation showed recurrence of the tumour at the same site. 4 patients with high grade transformation and lymph node metastasis succumbed to disease due to distant metastasis. Lymph node metastasis and high-grade transformation are independent predictors of distant metastasis. Extensive sampling of the tumor is required to look for high grade transformation.

**Keywords:** Acinic cell carcinoma, predictors of distant metastasis, salivary gland.

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*\*Corresponding author*

## INTRODUCTION

Salivary gland tumors comprise a rare disease process in which malignant cells form in the tissues of the minor and major salivary glands. These can be subdivided into epithelial and non-epithelial neoplasms, approximately 95% of which are epithelial. Approximately 90% of primary epithelial salivary gland tumors occur in the parotid gland; the remainder occur in submandibular, sublingual and other minor salivary glands. The rate of malignancy in each salivary gland is inversely correlated with the size of the salivary gland; approximately 20%-25% parotid gland tumors are malignant in comparison to 60%-80% of minor salivary gland tumors [1]. Amongst primary parotid gland malignancies, acinic cell carcinoma (AiCC) accounts for 1% to 6% of all epithelial salivary gland tumors and 10%-15% of all primary parotid malignant tumors [2]. It is typically diagnosed by pathology, as it can easily be mistaken clinically or radiologically for a different disease process [3].

Acinic cell carcinoma the major salivary gland is relatively uncommon, usually exhibits a relatively non aggressive course [4]. Surgery is the most effective treatment, and adjuvant radiotherapy is the most effective treatment and adjuvant radiotherapy is suggested when there are adverse pathologic characteristics including high grade transformation, neck node metastasis, high tumor stage, perineural invasion and lympho vascular invasion [4-7].

High-grade transformation, formerly known as de-differentiation, is a rarely recognized event in AiCC that has been increasingly reported in the past 10-15 years [8]. A large National Cancer Database (NCDB) study performed by Xiao et al [9] found that amongst eight identified histopathology, AiCC demonstrated positive clinical nodal disease in 10% of cases and occult positive nodal disease in 4.4% of cases. Further, high-grade differentiation was significantly predictive for nodal metastasis and worse overall survival in AiCC. Cases of AiCC with distant metastases are largely reported in case reports and smaller case series in the literature, with such studies identifying higher stage, presence of lymph node involvement, lymphovascular invasion and perineural invasion (PNI) as possible predictive characteristics.

A study from the MD Anderson cancer center [6] reported that almost 20% of the 155 patients with head and neck developed distant metastasis, and both Gomez et al [7] and Zeng et al [10] reported that the most common treatment failure pattern was distance metastasis. Although a number of clinical variables have been associated with distant metastasis in salivary gland adenoid cystic carcinoma. Thus, identification of primary tumour characteristics that predispose patients to developing distant metastases is crucial for appropriate surveillance and adjuvant considerations for this unique patient population. Therefore, we aimed to evaluate the predictors of distant metastasis in acinic cell carcinoma of salivary gland.

## METHODS

The present retrospective cohort study was conducted at KMIO, Bangalore from 2014-2020. Study included 15 biopsy/excision cases of Acinic cell carcinoma of parotid. Since the study is retrospective in design and did not involve any intervention, an exemption from Ethical Committee was taken. A broad consent was taken for patient's clinical details and Procedures. The cases were studied for various parameters including age, male female ratio and site, histomorphology were tabulated. Archived histopathology and immunohistochemistry slides along with data from medical records department were reviewed and synaptic reporting was done by using CAP protocol. The study results were analysed using IBM SPSS version 24.

## RESULTS

A total number of 15 patients (8 females, 7 males) were included in the study and the mean age at diagnosis was 52 years (range: 11-80) years. In 10 patients, the tumour is located in the parotid, 5 patients the tumour was located in the minor salivary glands. Total parotidectomy performed in 9 patients (66%), 1 superficial parotidectomy (6%), 1 mandibulectomy (6%), 1 laryngectomy, 1 wide local excision (6%) and 2 biopsies were (10%) performed.

The pathological tumour stages were distributed as follows: T1 in 5 patients (33.4%), T2 in 6 patients (40%), T3 in 1 patient (6.6%), T4 in 3 cases (20%). 12 patient's undergone definitive surgery

with negative margins and lymph node dissection. The pathological N stage as follows: N0 in 11 patients (91.4%), N1 in 3 patients (20%), and N2 in 1 patient (8.3%). None of the cases showed N3 nodal stage.

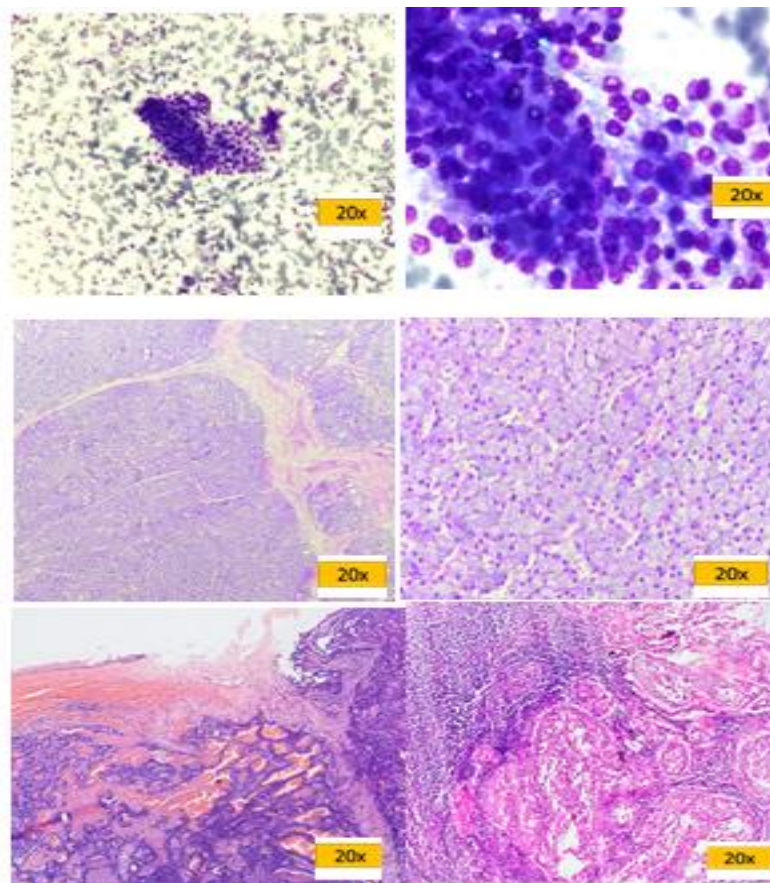
**Table 1: Tumour Staging**

Tumour stage	Number of cases
T1	5
T2	6
T3	1
T4	3

4 patients out of 15 showed high grade transformation (26.6%). 2 patients with high grade transformation showed recurrence at the same site (13.3%). 4 patients with high grade transformation and lymph node metastasis succumbed to disease due to distant metastasis.

**Table 2: Nodal metastasis staging**

Tumour staging	Number of cases
N0	11
N1	3
N2	1
N3	0



**Figure 1 & 2: FNAC of liver lesion showing loosely cohesive groups of acinar like cells (MCG stain) [20x], [40x]. Figure 3&4: Histomorphological section showing tumour composed of large and polyhedral acinar cells with basophilic granular cytoplasm and eccentric nuclei (H&E stain) [20x], [40x]. Figure 5&6: Histomorphological showing acinic cell carcinoma with high grade transformation (H&E stain) [20x], [40x].**

## DISCUSSION

Acinic cell carcinoma is a rare neoplasm that is generally classified as a low-grade salivary gland malignant neoplasm, with an estimated 5-year, disease-specific survival of more than 90%. Although most patients have a favourable prognosis, there is a small population who will ultimately succumb to their disease. Given the rarity of the disease, it remains difficult to identify which patients are at highest risk of death from their disease.

Distant metastasis (DM) is relatively uncommon in most head and neck malignancies; the reported incidence of DM in salivary gland cancers ranges from 20 to 50%, with different tumour sites and histological types [11]. Acinic cell carcinoma is a low-grade disease and usually has good prognosis; therefore, Acinic cell carcinoma might have some unique predictors. This study helps to analyse the predictors of DM in acinic cell carcinomas.

The mean age at diagnosis was 52 years (range: 11-80) years. This is consistent with previous finding by Neskey et al [12] that earlier age of presentation, specifically age < 45, is significantly associated with improved survival. It has been reported that both increasing age and distant metastases are associated with increased risk of death from disease, but there has not been a previous link between age and the development of distant metastases.

One of the main findings in the current study was high grade transformation predicted poor DMC survival. High grade transformation of conventional AcicCC is uncommon and includes a variable proportion of a poorly differentiated high-grade component [13, 14]. Transformed AcicCC is related to poor clinical outcomes because of the tendency for recurrence and the common occurrence of angiolymphatic and perineural invasion [13, 14].

In our study total 15 patients were included and 12 patients had undergone a definitive surgery with lymph node dissection. Positive lymph nodes identified in 5 patients (33.3%); high grade transformation was seen in 7 patients (46%). Similarly in the current study, high grade transformation appeared to have significance in predicting a poorer prognosis. In a study published by Klussmann et al [15], univariate analysis revealed IPN (Intra parotid lymph node) involvement as an additional significant risk factor of tumour recurrence in 55 patients with pN+ tumours. Nisa et al [16] reported that decreased disease-free survival could be expected in patients with IPN involvement.

In our study 4 patients with high grade transformation and lymph node metastasis, in which 2 patients showed IPN metastasis. 4 patients with high grade transformation and lymph node metastasis scummed of the disease. Although a several clinicopathological characteristics, including cellular differentiation, inflammatory response, tumour invasion pattern, lymphatic and/ or vascular invasion, positive margins, lymph node metastasis, in predicting DM in salivary gland carcinomas. High grade transformation and lymph node metastasis, IPN are particularly important in predicting DM and poor survival.

## CONCLUSION

AiCC of the parotid gland is widely viewed as a low-grade neoplasm with good curative outcomes and low likelihood of metastasis. Lymph node metastasis and high-grade transformation are independent predictors of distant metastasis. Extensive sampling of tumour is required to look for high grade transformation. These patients thereby comprise a unique and understudied patient population.

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