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Adenoid Cystic Carcinoma of Head and Neck Region: A Variety in Rarity

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Background: *Adenoid cystic carcinoma affects both major and minor salivary glands of the head and neck region and comprises 30% of salivary gland malignancies. Its occurrence is 4.5 cases in one lakh. It is known for the indolent nature of spread by the perineural route and delayed metastasis. Our study was intended to retrospectively analyze the role of immune histo chemistry in differentiating the tumors of minor and major salivary glands,intrinsic relation of factors such as anatomical and histological subtypes, period of indolence and their impact on survival and treatment in adenoid cystic carcinoma.*

Materials and Methods: *Retrospective analysis was conducted on 81 patients who underwent treatment for adenoid cystic carcinoma with the following objectives. 1) The impact of sub-site, metastasis on disease-free interval and overall survival. 2) The correlation of histological subtypes on the primary tumor subsites of head and neck region.3) To check the period of indolence (remission) as per TNM staging.4) importance of immune histochemistry in appropriately diagnosing mimicking tumors of minor and major salivary glands like pleomorphic adenoma adenoid cystic carcinoma*

Results: *The overall survival rates for 5 –years, 10-years, 15-years, 20 –years, 25 years were 79.8%,67.6%,48,8%, 29.3%, 19.6% respectively (p=0.0001s). Disease-specific survival for 5-years, 10-years, 15 -years, 20- years was 81.2%, 61.1%, 53,7%,21.6% respectively. The period of indolence or remission was observed t be 15 to 20 years, 9.5 to14.7 years, 3.8 t 4.5 years, 18-24 months, 10-15 months and 6-8 months for stages of I, II, III, IVa, IV b, IV c respectively.*

Conclusion: *Immunohistochemistry is the game-changer in tumors involving both minor and major salivary glands, particularly when they mimic in appearance both clinically and histopathologically. In such instances, immunohistochemistry is a very useful tool in establishing the confirmatory diagnosis, particularly for adenoid cystic carcinoma to rule it out from other malignant and benign tumors occurring in the minor and major salivary glands.*

The rate of metastasis was faster in T4 followed by T3, slower in T1 and T2 tumors, by the period of indolence. The period of indolence was slower in T1 and T2 types as compared to T3 and T4 tumors. Histo-pathological and anatomical subtypes were independent of tumor staging and primary sub-site of occurrence in the head and neck region.

Keywords: *adenoid cystic carcinoma (ACC), perineural spread, major and minor salivary glands, immunohistochemistry (IHC).*

Introduction

Adenoid cystic carcinoma comprises 30% of salivary gland malignancies. Up to 60% arise in minor salivary glands throughout the upper aerodigestive tract where it most frequently involves palate, tongue, lower lip retromolar-tonsillar pillar region and sublingual gland. Between 25-33% arise in the parotid gland and submandibular salivary gland. It has a marked propensity for neural invasion and perineural spread which occurs in up to 50% of cases **(**1**)**. The presence of nerve palsy or perineural invasion of large nerves is a well-established adverse prognostic factor (cranial nerves in case of head and neck). It has a greater propensity for spread along Haversian canals of bone with little bony erosion. Lymph node metastasis is rare. ACC may also occur in the ceruminal glands of the external auditory canal as well as lacrimal gland. However, their occurrence in the Thyroid and larynx is very rare.

For head and neck adenoid cystic carcinoma, the age-adjusted incidence rate is 4.5cases per one lakh individuals with a slight female predominance (60% vs40% in males). Cancer can also arise in other locations such as the breast, skin, respiratory system and reproductive organs. 5, 10 and 15-year survival rates after surgical resection have been reported as 77.3%, 59.6% and 44.9% respectively with almost half of patients dying from ACC as opposed to other causes, at long-term follow-up.

Although adenoid cystic carcinoma is slow-growing, its infiltration and invasion and has unique tendency to spread along perineural spaces make it a high-grade malignancy with a poor prognosis. Adenoid cystic carcinoma can embolize along perineural routes often. The tumor commonly spreads hematogenously to the lung, breast, brain, bone and liver some decades even after removal of a tumor. These metastases are slow-growing with a certain time period of indolence and remission, compatible with many years of survival. The period of indolence or remission is the time taken from the presentation of the primary tumor to the time of development of metastasis, whereas remission is considered as the time period between the treatment and the occurrence of metastasis. Local recurrence is seen in 30-50% of cases even after clear surgical margins and many years of disease-free status. Distant metastasis occurs in 24-39% of cases within 10 years.

Adenoid cystic carcinoma may present clinically as circumscribed, unencapsulated or partly encapsulated solid, rubbery to firm tan white or grey pink mass. Histologically it appears as an encapsulated infiltrating neoplasm with varied growth patterns such as cribriform, tubular/ ductular and solid. Most common is the cribriform type with cells arranged in swiss cheese pattern with many oval or circular spaces. These spaces contain a basophilic mucinous substance or hyalinized eosinophilic material. Cribriform and tubular patterns often occur together. The solid variant occurs in 21% of cases and has the worst prognosis. Treatment is generally combined surgery and radiotherapy though there is no evidence that radiotherapy adds any additional chance of cure, rather it delays recurrence.

There are many studies in the literature about adenoid cystic carcinoma of the head and neck region with a follow-up range of 15-25years, describing the tumorbehavior, metastasis, survival rates, histological types, perineural invasion and spread. Our study was planned to retrospectively analyze

1) the importance and role of Immuno histo chemistry in differentiating the mimicking tumors in the minor and major salivary glands of head and neck, particularly pleomorphic adenoma and adenoid cystic carcinoma

2) The correlation of histological subtypes on the primary tumor subsites of head and neck region.

3) The Impact of sub-site on the rate of metastasis on disease-free interval and overall survival.

4) To check the period of indolence (remission) as per p TNM staging.

Materials and methods:

A total of 81 patients who were diagnosed with adenoid cystic carcinoma at various subsites of the head and neck, and underwent treatment (1998-2018) at a Tertiary cancer center, India were retrospectively analyzed and included in the study. Patients were treated either by surgery alone,

surgery and post-operative radiotherapy, chemo-radiotherapy or chemotherapy alone. The age of the patients ranged from 26-78 years. Patients were randomly selected for the study.

Variables such as age, gender, primary site, loco-regional recurrence, cervical nodal metastasis on presentation and after primary treatment, distant metastasis, perineural spread, survival (disease-specific survival and overall survival) were assessed in the study. Non-invasive investigations included contrast-enhanced MRI scan for the regions of the head, neck and thorax. Contrast-enhanced CT scan was advised in selective cases. Pan endoscopy comprising of nasopharyngoscopy, upper gastrointestinal endoscopy/Fiber optic laryngoscopy, bronchoscopy was done depending on the primary site and disease extension loco-regionally or distantly. Incisional biopsy was performed for confirmation of final diagnosis for primary, recurrent and metastatic lesions. Immunohistochemistry was done for cases where there was a diagnostic dilemma (for the skeptical lesions at anatomical sites such as an oral cavity, oropharynx) and for the T4tumors that extended into more than one anatomical site and in metastasis.

The surgical treatment plan was decided and executed based upon the primary site of the tumor, assessment of the extent of the tumor, loco-regional occurrence/ recurrence and metastasis by imaging (MRI contrast, CT contrast in bone involvement) and histopathological diagnosis. Wide local excision (buccal mucosa, tongue, hard palate), infrastructure maxillectomy, medial maxillectomy/ total maxillectomy, segmental mandibulectomy, orbital exenteration, etc were done, in cases of minor salivary glands affecting the oral cavity subsites. For the sinonasal and tumors involving the nasopharynx and paranasal sinuses, methods like, surgical resection, debulking were employed. Revised margins were obtained in resectabletumors, wherever possible. Submandibular gland excision and parotidectomy were done for lesions affecting both the major salivary glands. Patients with cervical lymph node metastasis underwent neck dissection (SOHND, MRND) according to the primary site involvement of the tumor. Postoperative radiotherapy with curative intent was summoned to those patients with positive margins, close margins, perineural spread and aggressive high-grade histological subtypes like solid variants. For unresectable cases, concurrent chemo-radiotherapy was given. Patients with locoregional recurrence were treated with salvage surgery/palliative radiotherapy, while of metastasis, were treated by palliative intent radiotherapy/chemotherapy.

Results:

The primary site-wise distribution of cases in the subsites of head and neck is illustrated in **table 1**, which depicts more number of cases occurring in the decreasing order of parotid gland, maxilla, submandibular gland and sino-nasal regions occupying significant numbers as compared to other sub-sites. Among the histopathological types, cribriform variants were more in number followed by tubular and solid types **(fig 1).**

The patient characteristics and variables are demonstrated **(table 2)**, which typically display the following features. Upon clinical presentation, T3 and T4 size tumors were more in number as compared to T1 and T2 tumors. Among the cervical lymph node status, N0 cases were 59(72.84%), followed by N1 (n=12, 14.81%), N2 (n=9, 11.11%) and N3(n=1, 1.23%). Among N2 cases 6 were N2b and 3 were N2a. The metastasis was typically seen in 8 cases (9.88%) out of 81 cases. Positive surgical margins (<5mm) were obtained in 30 cases (37.04%) and negative margins were obtained in 51 cases(62.96%). Loco-regional recurrences were seen in 46 cases (56.79%). Out of which salvage surgery was performed in 33 cases and for 13 cases palliative radiotherapy was given.

The multivariate analysis suggests that the chances of survival for males are more as compared to females. There is no significant association between gender and outcome (in terms of survivability and survival rate). It means that the odds of survivability in males is 1.25 as compared to females, which is not found to be significant in the study. The overall survival rate was more in stage I and stage II patients as compared to stage III and IV. The overall survival rates for 5 –years, 10-years, 15-years, 20 –years, 25 years were 79.8%,67.6%,48,8%, 29.3%, 19.6% respectively **(p=0.0001s, fig2).**

The combined effect of survivability of patients with positive surgical margins has a higher significant association with survivability, as compared to the negative surgical margins. But no significant association was found between the status of survivability with perineural invasion (independent and relatively slow prognostic factor). However, in histopathology, those with solid and tubular types, have negative value and significant association with survivability (Cox regression analysis, **table 3**).

Disease-specific survival for 5-years, 10-years, 15 -years, 20- years was 81, 2%, 61.1%, 53,7%,21.6% respectively. The period of indolence or remission was observed to be 15 to 20 years, 9.5 to14.7 years, 3.8 t 4.5 years, 18-24 months, 10-15 months and 6-8 months for stages of I, II, III, IV a, IV b, IV c respectively.The total disease survival rate in the whole study, i.e. mean+_ standard deviation 57.9+_57.4 months in which, those who survived, the disease-specific survival is 82.6+_ 61.0. This is significantly higher as compared to those who are dead (24.3+_30.2). The mean survival rates are also presented in **table 4, fig3.**

The survival function of mean of the mentioned covariates are presented **(fig 4).** The total disease survival rate in whole study, i.e. mean+_ standard deviation is 57.9+_57.4 months, in which, those who have survived, the disease specific survival is 82.6+_ 61.0. This significantly higher as compared to those who are dead (24.3+_30.2). The mean survival rates are also presented in the following figures.

Table1. Primary site wise distribution of cases with loco-regional extent of spread, cervical lymph node metastasis and distant metastasis.

Primary site	No. of cases N=81	Extent of Locoregional spread to the adjacent anatomical site	Loco regional recurrences (No of cases)	Cervical lymphnode metastasis	Site of Distant metastasis
Buccal mucosa	5	Mandible, skin of cheek, angle of mouth	2		lungs
Hard palate	17	Soft palate, posterior pharyngeal wall, nasal cavity, oropharynx	4	Ib, II	lungs
maxilla	6	Hard palate, soft palate, nasal cacity, nasal septum, pterygomaxillary fissure, skull base ethmoid,sphenoid destruction/erosion	8	Level II	lungs
Lower gingivo buccal sulcus and floor of the mouth	4	Floor of the mouth, retromolar trigone		Ib	lungs
Submandibular gland	5	Floor of the mouth, masticator space, infra temporal fossa	4	Level IB, II	
Parotid gland	7	Parapharyngeal space	7	Level Ia, II, V	Liver
oropharynx	6	Retromolar trigone, floor of the mouth, pharyngoepiglottic fold	3	II, III	C5 vetebra
nasopharynx	5	Sphenoid, ethmoid	4	II.V	sphenoid destruction, brain
Nasal cavity	8	Upper gingivo buccal sulcus, maxillary sinus	2		
sinonasal	12	Nasal cavity,floor of the orbit/orbital cavity, ethmoid, sphenoid,pterygomaxillary fissure, nasopharynx	8		Brain, skull base
Lacrimal gland	2	Orbit, intra cranial extension	2		
tongue	4	Floor of the mouth	2	Ib	

Table 2: Patient characteristics and variables:

T classification	No	%
T1	4	4.94
T2	15	18.52
T3	27	33.33
T4	35	43.21
N classification on clinical presentation		
N0	59	72.84
N1	12	14.81
N2	9	11.11
N3	1	1.23
M classification		
MO	73	67.90
M1	8	9.88
Overall clinical staging		
I	4	4.94
II	15	18.52
III	27	33.33
IV A	23	28.40
IVB	4	4.94
IVC	8	9.88
Treatment		
CTRT(66-78 Gy)	4	4.94
PALL CT	8	9.88
SURG+ADT	50	61.73
SURG+RT	15	18.28
Surgery alone	4	4.94
Surgical margin status		
Positive(<5mm)	30	37.04
Negative(>_5mm)	51	62.96
Perineural invasion		

Positive	69	85.19
Negative	12	14.81
Loco-regional recurrences	46	56.79
Salvage surgery	33	40.74%
Palliative radiotherapy(30 Gy)	13	16.04%

Table 3: Cox regression analysis of survival of patients by other variables

Factors	OR	95% CI for OR		P-value
		Lower	Upper	
Gender				
Male	1.25	0.70	2.26	0.4530
Female	Ref.			
Surgical margin				
Negative	Ref.			
Positive	1.98	1.04	3.77	0.0390*
PNI				
No	Ref.			
Yes	0.31	0.08	1.32	0.1130
Histopathology				
Cribriform	Ref.			
Solid	0.05	0.01	0.23	0.0001*
Tubular	0.01	0.00	0.50	0.0250*

Table 4: Comparison of outcome (Death and alive) with hospital stay and disease specific survival rate (in months) by independent t test

Outcome	Hospital stay (in days)		Disease survival rate (in months)	
	Mean	SD	Mean	SD
Death	56.6	7.6	25.3	30.2
Alive	51.2	17.2	82.6	61.0

Total	53.5	14.1	57.9	57.4
t-value	1.7184		-5.1053	
p-value	0.0896		0.0001*	

FIG.1 Histopathological types at various sub sites of head and neck

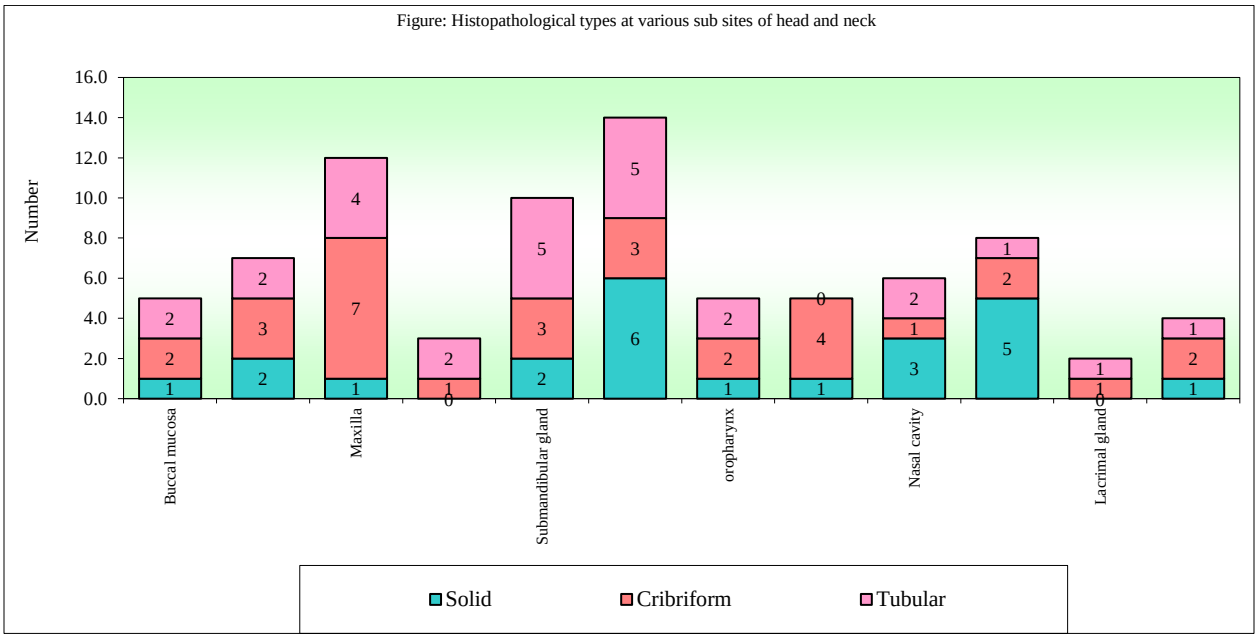


FIG 2: Overall survival rates: P= 0.0001, S

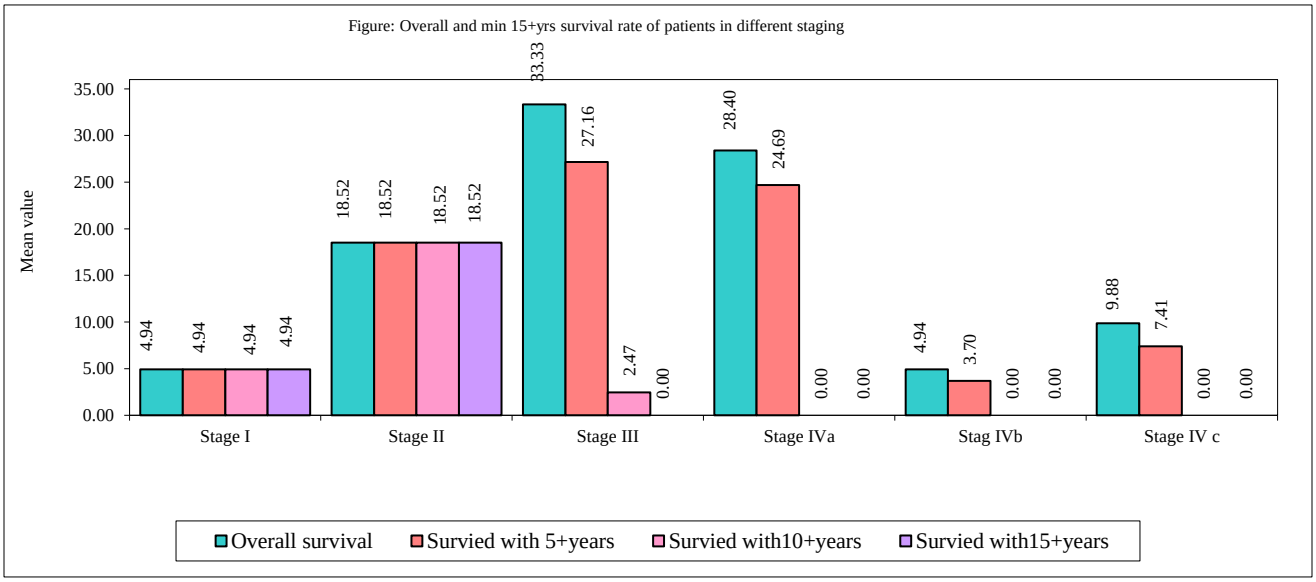


FIG 3: Comparison of outcome (Death and alive) with hospital stay and disease specific survival rate (in months).

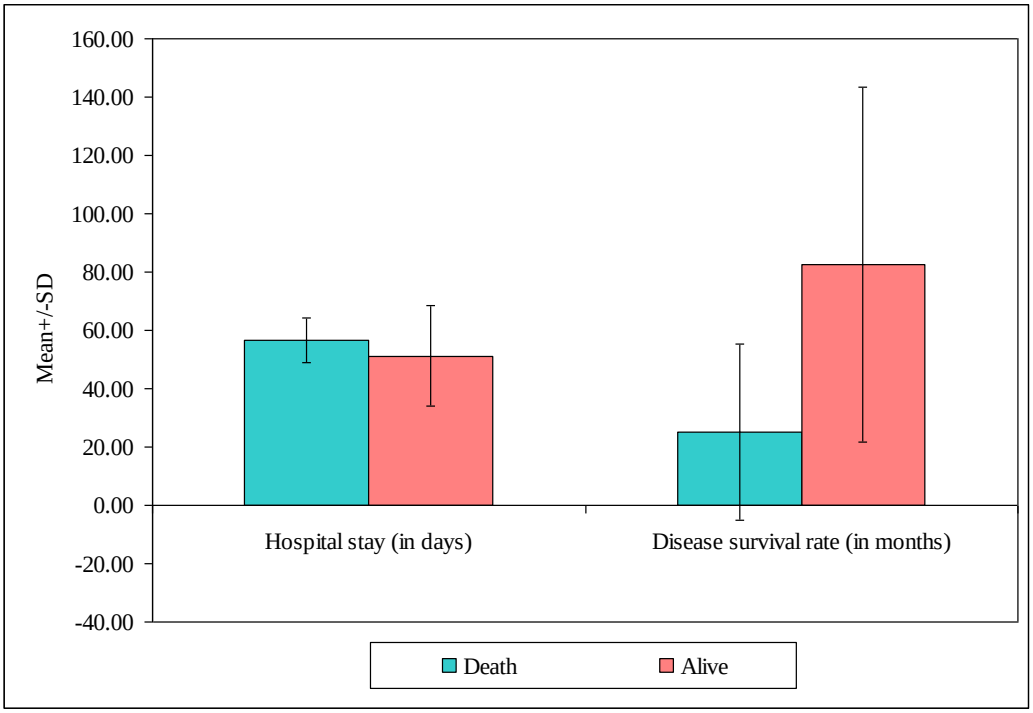


Fig 4: Survival Function at mean of covariates

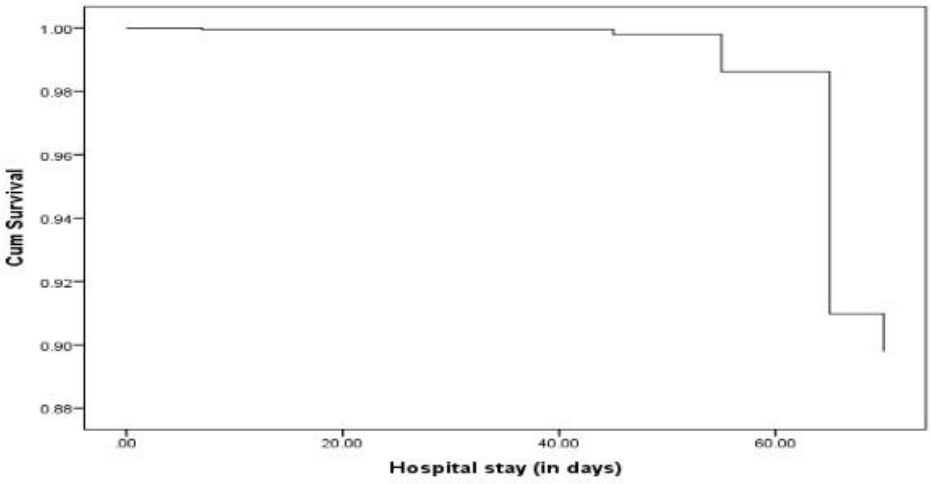


Fig 5 :Adenoid cystic carcinoma of hard palate extending to soft palate and posterior pharyngeal wall

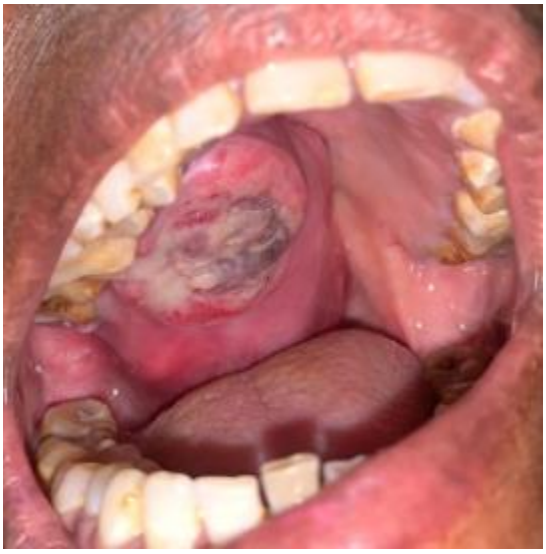
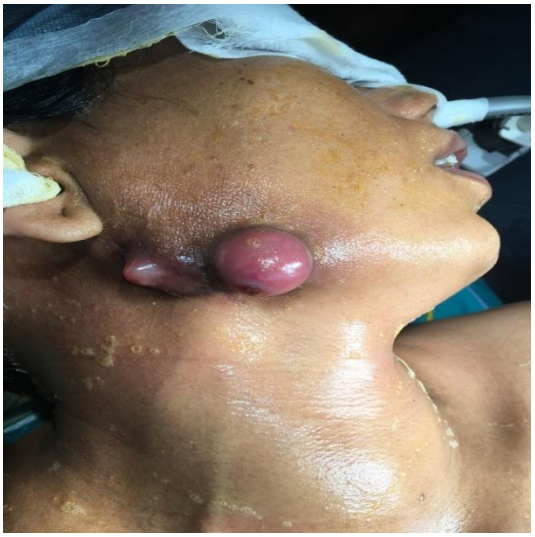


Fig 6: Recurrent adenoid cystic carcinoma of the parotid region after post op, post Radiation therapy.



***Note:** The initial histo pathological reports gave the diagnosis of pleomorphic adenoma in both the above cases. ImmunoHisto chemistry gave the confirmatory diagnosis as adenoid cystic carcinoma**.**

Discussion:

Adenoid cystic carcinoma occurs in major and minor salivary glands of the head and neck with more propensities in the minor salivary glands. Approximately 50% of cases are found in minor salivary glands more especially in the palatine glands. These neoplasms arising in minor salivary glands have a poorer prognosis than those that arise in the major salivary glands **(**1**)**.

Adenoid cystic carcinoma occurs commonly in the 4th to 8th decade of life. It accounts for <1% of all head and neck cancers and <10% of all salivary gland neoplasms. It occurs mainly in the major salivary glands, but more than 1/3rd occur in minor salivary glands in the oral cavity. Metastasis occurs in 40-60% of patients. Patients usually present with swelling or mass with parasthesia, pain, motor nerve involvement with infiltration into bone, which characteristically shows perineural invasion. The underlying cause is not known but it appears to develop from non inherited genetic changes.

Studies on adenoid cystic carcinoma with regards to the significance of p-53, have indicated a higher concentration of p-53 mutations in higher grade adenoid cystic carcinomas with a poor prognosis and found that mutations may be multiple rather than singular. Other evidence indicates mutation of the p-53 tumor suppressor gene in recurrent adenoid cystic carcinoma is that no sign of these mutations is seen in early stages and it becomes significant only later in the course of this tumor's development. There has been evidence that ACC tumor cells develop more protein called "myb" with p53 gene. Immuno-histochemistry shows CK7, myb, myb-NFIB, Cam 5.2, Calponin, SMA, p63, CD17, Ki-67, S100, SOX10 along with tubular, cribriform and solid histo- pathological variants. The genetic profile of adenoid cystic carcinoma is that it is specific to t (6;9) or (8;9) translocation, resulting in fusions involving MYB OR MYBL1 and transcription factor gene NFIB.**(**2,3,4**)**

Our study was designed to check whether the established histopathological types of ACC are specific to any particular primary sub-site of occurrence, to assess the effect of the primary site and histopathological type on the slow or faster rate of metastasis, overall survival and disease-free survival, to check the period of indolence as per TNM staging and the role of immune histo chemistry in diagnosing skeptical tumors like pleomorphic adenoma and ACC occurring denovo or as a sub-type variant.

Keen emphasis on IHC was advocated when there was a diagnostic dilemma in tumors involving the anatomical sub-sites of minor and major salivary glands to establish a concrete final histopathological diagnosis. Apart from the histopathology, advising immune histochemistry to minor and majir salivary gland neoplasms (benign &malignant) fundamentally rules out the main tumor entity from the mimicking tumors, particularly so in cases of pleomorphic adenoma and ACC. Immuno-histochemically specimens were positive for cyclin D1, p53, p63, CD117(C-KIT), E-Cadherin.

Carcinoma ex pleomorphic adenoma shows the malignant transformation up to 9.5% within 15 years of primary occurrence. It is the carcinoma arising from primary (de novo) or recurrent pleomorphic adenoma. The histological subtypes are adenocarcinoma, not otherwise specified, salivary duct carcinoma, mucoepidermoid carcinoma and adenoid cystic carcinoma. The most common histological subtype is adenocarcinoma, not otherwise specified, salivary duct carcinoma, mucoepidermoid carcinoma, and adenoid cystic carcinoma. Few case reports of denovo dedifferentiation in ACC mostly involving the minor salivary glands, parotid and submandibular glands have been reported in the literature. **(**5, 6, 7**)**

In our experience, cases involving the carcinoma ex pleomorphic adenoma of parotid gland changing to dedifferentiated adenoid cystic carcinoma were seen in 3 cases. The carcinoma ex-pleomorphic adenomas, as well as ACC, interpose a diagnostic challenge to clinicians and pathologists which was seen similar with us. In other sub-sites, the direct histopathological diagnosis of ACC was obtained which correlated to postoperative histopathological report. The tumors occurring in the oral cavity and head and neck region pose a great challenge in differentiating and obtaining a proper diagnosis since most lesions mimic others in site and appearance clinically. To obtain a differential diagnosis and further obtain a shrewd final diagnosis is the need. One such was our experience with adenoid cystic carcinoma and pleomorphic adenoma in the head and neck region.

We observed that irrespective of the occurrence of adenoid cystic carcinoma at various sub-sites did not influence the metastasis, overall survival and disease-free survival. Among the histopathological sub-sites, tubular and solid variants had negative value significantly. The overall survival rates for 5 –years, 10-years, 15-years, 20 –years, 25 years were 79.8%,67.6%,48,8%, 29.3%, 19.6% respectively (p=0.0001s). Disease-specific survival for 5-years, 10-years, 15 -years, 20- years was 81.2%, 61.1%, 53.7%, 21.6% respectively. The combined effect of survivability of patients with positive surgical margins has a higher significant association with survivability, as compared to the negative surgical margins. But no significant association was found between the status of survivability with perineural invasion (independent and relatively slow prognostic factor). However, in histopathology, those with solid and tubular types, have negative value and significant association with survivability.

Metastasis in adenoid cystic carcinoma occurs by tissue planes via perineural and hematogenous routes and rarely through lymph nodes. Owing to its infiltrative nature and above two routes of spread, it behaves like a high-grade tumour over a long period. Hematogenously it may spread to the lung, bone, liver and kidneys. In the palate and maxillary sinus, involvement of the greater palatine nerves can lead to early orbital, skull base and brain involvement. Histological typing is important in determining prognosis. Canalicular tumors have the best prognosis in terms of survival, cribriform tumors have an intermediate prognosis and solid tumors with necrosis have a very poor prognosis. The presence of perineural spread and is an indicator of increased local recurrence and distant metastases. **(**8, 9, 10**)**

Perineural invasion was positive in 69(85.1%) cases and negative in 12(14.8%) cases. Contrast-enhanced high-resolution MRI scans were advised to locate perineural invasion. The criteria for perineural spread on MRI included either, or all of these such as, replacement of the normal perineural fat with tumor, perineural enhancement of the Gadilonium, widening of the neural foramen. Distant metastasis was seen in 8(9.88%) cases. Retrospectively we observed the average time period of indolence (remisson) from stage 1-IV tumors till the findings of metastasis were seen which were 15-20+years(stage I), 9.5-14.7years(stage II), 3.8-4.5 years(stage III), 18-24 months(stage IV a),10-15 months(stage IV b), 6-7 months(stage IV c) respectively. This parameter has suggested the necessity of frequency of close follow-up of patients with relevant investigations.

The surgical margins were positive in 30 cases and negative in 51 cases. Owing to the tumor behaviour and perineural spread, specimens for revised surgical margins were taken wherever possible. Radical resection with wide margins, identifying major nerves and following them with frozen section and resection of the nerve along the path, as much as possible surgically was done, followed by postoperative radiotherapy/adjuvant therapy (chemo-radiotherapy). Loco-regional recurrences were noted in 46 cases, out of which for 33 cases salvage surgery was done and 13 cases were managed with palliative radiotherapy. We observed that salvage surgery improved the survivability and period of indolence towards metastasis as compared to patients who received palliative radiotherapy, in cases of recurrence. The possible reasons attributed for this could be, slow rate of metastasis, the feasibility of obtaining revised margins, better patient compliance.

The combined effect of survivability of patients with positive surgical margins, has a higher significant association with survivability, as compared to the negative surgical margins. But no significant association was found between statuses of survivability with perineural invasion. However, in histopathology, those with solid and tubular types, have negative value and significant association with survivability.

The ACC of minor salivary glands often indicates poor prognosis due to difficulty in delineating the extent of disease and clear margins. High grade or low-grade variety, as well as recurrence, can be well appreciated in contrast to enhanced MRI scans. Adenoid cystic carcinoma metastasizes either locally at the primary site or has distant metastasis but rarely has regional metastasis to neck lymph nodes. Selective neck dissection was done in node-positive neck followed by postoperative radiotherapy/adjuvant therapy. Modified radical neck dissection was done where more than two lymph nodes were positive with metastasis. When either of the level Ia, Ib or II level lymph nodes were negative in the frozen section, the neck was not addressed for dissection. T4b disease patients with skull base extension were deemed inoperable and were chosen for radiotherapy/adjuvant therapy alone.

We also observed that unresectability, positive margins, perineural invasion are the possible reasons for recurrence in adenoid cystic carcinoma. Gardens et al, in their 30-year retrospective study, stated that good local control rates were obtained with the combined approach of surgery and post-operative radiotherapy.

We observed that, apart from and perineural invasion of peripheral nerves, involvement of major nerves was a more adverse prognostic factor. They obtained a local control in over 80% of patients with positive margins. They suggested that if a high risk of neck metastasis is suspected elective or selective neck dissection, followed by PORT or super-selective neck dissection is done. They recommended a dose of 60 Gy to the tumor bed, supplemented to 66 Gy for patients with positive margins. They also observed that despite effective local therapy one-third of patients fail systemically. **(**11, 12**)**

It is also to be noted here that there is seldom any role of Neoadjuvant chemotherapy in adenocarcinoma or adenoid cystic carcinoma irrespective of resectable or unresectable tumors. Tumors extending to the skull base with distant metastasis can be palliatively treated by surgery followed by palliative radiotherapy/ chemotherapy. Bradley et al, have stated that surgery and radiotherapy at the skull base region though have been accepted as the standard of care in ACC, appear to be palliative in most of the patients with consideration given to the preservation of the functioning major neurovascular structures involved with the tumor.**(**13**)**

Yoon Ho Ko et al, in their study, stated that high tumor grade and lymph node involvement were predictive of recurrence and overall survival. Despite aggressive treatment, distant metastasis seems to be inevitable. Focus on molecular biomarkers is suggested to predict the clinical outcome and to develop effective treatment.14Quyang et al in their retrospective study of 228 patients in South China, observed that presence of lymphovascular invasion and high T classification were very strong adverse factors and independent predictors for salivary gland ACC prognosis which influenced locoregional control, distant metastasis and survival.**(**15,16**)**

Gandhi et al, found that MRI correctly identifies the extent of disease spread in 25 of 30 nerves (83.3%). This factor is pivotal in achieving complete tumor resection and allowing as much preservation of nerve and tissue as possible.MRI scan with neurography, William's zonal system classification and combined teamwork approach with neurosurgeon and radiotherapist would endeavor better prognostic results. Perineurium of the nerve thickens as it approaches the skull base. This necessitates an aggressive surgical approach as the tumor can spread at nerve branching points. Consideration needs to be given to enbloc resection in regions such as pterygopalatine fossa, superior orbital fissure and infratemporal fossa. Enbloc resection with respective nerves such as V1, V2, V3was advised.**(**17**)**.

Eiichi Ishida et al, in their retrospective study, was done during 25 years follow-up on 58 cases, concluded that in adenoid cystic carcinoma cases both initial surgical treatment and repetitive surgical resection of resectable recurrent lesions, including both locoregional and lung metastasis resulted in longer survival. The major goal of treatment for adenoid cystic carcinoma may be long-term survival including cancer-bearing survival, resulting in either a natural death or undercurrent-disease death, since judging cure of adenoid cystic carcinoma is almost difficult. They found that 10 years, 20 year and 25-year survival rates were 63.7%, 27.3%, and 20% respectively.**(**18**)**

Our multivariate analysis suggests that the chances of survival for males are more as compared to females. There is no significant association between gender and outcome (in terms of survivability and survival rate). The overall survival rate was more in stage I and stage II patients as compared to stage III and IV. The overall survival rates for 5 –years, 10-years, 15-years, 20 –years, 25 years were 79.8%,67.6%,48,8%, 29.3%, 19.6% respectively **(p=0.0001s).** No significant association was found between the status of survivability with perineural invasion (independent and relatively slow prognostic factor). However, in histopathology, those with solid and tubular types, have negative value and significant association with survivability.

Patrick M Dhillon, stated that adenoid cystic carcinomas have a characteristic chromosomal translocation and they pick up additional mutations. Several ongoing trials are testing, agents that inhibit fibroblast growth factor receptor signaling or other signaling pathways. Treatments based on the sequenced tumor genome are under development. **(**19**)**

Many studies have been conducted to discover genetic mutations and biomarkers specific for ACC. Among them, a balanced translocation of v-myb avian myeloblastosis viral oncogene homolog nuclear factor I/B (MYB-NFIB) is considered to be a signature molecular event of ACC oncogenesis. Overexpression of key proteins has also been demonstrated in ACC including c-kit, EGFR, SOX, VEGF and AQP1. ACC tumors carry relatively few mutations (13 and 22) compared to other solid tumors. Therefore, aiming at these molecular changes which have therapeutic implications, targeted genetic and immunotherapy may play a key role in evolving the better outcome for adenoid cystic carcinoma. Results of the better treatment options for improvement of prognosis are awaited in future.**(**20**)**

Conclusion:

Immuno histochemistry occupies a key role in identifying indolent tumors like adenoid cystic carcinoma apart from histopathological diagnosis, particularly in the head and neck region. As this tumor is partially encapsulated or not encapsulated, mainly invading the minor and major salivary glands, it mimics the other tumors which may be malignant or benign that leave the surgeon to be skeptical in the decision making of the treatment plan. By our experience, therefore we suggest establishing a differential diagnosis primarily, for tumors occupying the anatomical sub-sites of minor

and major salivary glands by correlating the clinical features, radiological investigations (CT, MRI, PET scans etc,) and biopsy report of histopathology and secondly to perform immune histochemistry for tumors especially involving the areas minor salivary gland as well as for major salivary glands depending upon the preliminary histopathological report, by intervention with the pathologist.

Perineural invasion is an independent prognostic factor irrespective of tumor site and anatomical sub-site with regards to adenoid cystic carcinoma. The rate of metastasis was faster in T4 followed by T3, slower in T1 and T2 tumors, in accordance with the period of indolence. Histo-pathological subtypes were independent of tumor staging and primary sub-site of occurrence in the head and neck region. There was no significant difference in the rate of metastases in relation to major and minor salivary glands.

Conflicts:

There are no conflicts of interest to authors

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