Review Article

Prognostic Biomarkers for Salivary Adenoid Cystic Carcinoma: A Systematic Review

Abstract

Background: Salivary Adenoid Cystic Carcinoma (ADCC), also known as "Wolf in Sheep's clothing," is associated with poor prognosis. Regardless of the vigorous treatment, ADCC has been known to recur and metastasize. Hence, identifying informative prognostic biomarkers for Salivary ADCC is of great importance to better predict tumor behavior and to guide treatment planning. Various immunohistochemical biomarkers along with other factors like the histologic grade of the tumor, site of tumor, and age have been studied to establish their correlation with the prognosis of ADCC. **Aim:** The aim of the systematic review was to identify various markers that have the potential to predict the prognosis in salivary ADCC. **Materials and Methods:** A literature search was conducted using PubMed and Scopus as database and Google Scholar as an additional source. Studies that performed immunohistochemical analysis predicting the overall survival of patients with salivary ADCC were included in this review. Studies published from 1977 to August 2018 were included. Case reports, review, letter to editors, and articles in languages other than English were excluded from the review. The following outcomes were examined: overall/disease-free survival, metastasis, and recurrence using immunohistochemistry as a prognostic marker. **Results:** A number of biomarkers were identified by the evaluation of 68 studies, which predicted overall survival and prognosis in terms of recurrence and metastasis. Out of these biomarkers, four markers most frequently assessed markers were Ki-67, p53, vascular endothelial growth factor (VEGF), and cyclin D1, which showed reproducible results. Many other markers showed significant results, but since only a single study was carried out with these markers, it was difficult to assess their predictability. **Conclusion:** The review thus identified that Ki-67, p53, VEGF could effectively predict metastasis and recurrence in salivary ADCC. More research work is, however, required to validate the accuracy of these markers for their prognostic significance. Many other markers also showed a significant correlation to prognosis; however, multiple studies are required to establish their prognostic value.

Keywords: *Prognosis, salivary adenoid cystic carcinoma, tumor markers*

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Introduction

Adenoid cystic carcinoma (ADCC) is a relatively uncommon salivary gland neoplasm and accounts for 10% of all salivary gland tumors having a predisposition for minor salivary glands.[1] Among the major salivary glands, parotid gland ADCC accounts for 2%–3% of all tumors.[2] Although ADCC appears innocuous due to its slow growth and size, it has an invasive potential.[3] The clinical course of ADCC is aggressive and has a predisposition to distant metastasis and recurrence after the removal of the primary tumor. The most common site of distant metastasis of ADCC is the lungs.[2] This tumor also has a tendency for perineural invasion.[3]

Histologically, ADCC shows ductal and myoepithelial cell differentiation and is also known as "cylindroma" due to its histologic appearance. Three patterns of ADCC have been recognized: solid, tubular, and cribriform. The cribriform type shows a typical Swiss cheese pattern due to the cyst-like spaces within the tumor. The solid pattern is found to be associated with poor outcome.[3]

Complete surgical resection followed by radiotherapy remains the treatment of choice for ADCC. However, recurrence and distant metastasis still prevail. The median survival duration following disease metastasis is about 3 years.[4] Hence, it becomes necessary to identify the various factors that predict the prognosis of the tumor and improve the survival outcome. Although factors such as histologic grade,

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age, site and size of the primary tumor and positive resection margins have been suggested to have an impact on the survival and prognosis of the tumor, their role has not been clearly established.[3] Hence, it becomes essential to recognize biomarkers that could predict the prognosis in terms of metastasis and recurrence.

Various immunohistochemical markers have also been studied that speculate the progressive nature of ADCC. Immunohistochemistry is often used to establish the diagnosis of ADCC. Expression of biomarkers like p53 and Ki-67 have been associated with poor prognosis of the disease. Few markers like bcl-2 have also been predicted to have a role in the pathogenesis of ADCC. However, the prognostic specificity of such markers remains unexplored.[3]

The aim of this systematic review was to compile the data that shows the expression of various immunohistochemical markers and its correlation with recurrence/metastasis along with the overall survival of the patients, thereby aiding the surgeon to render effective treatment.

Materials and Methods

Location

A comprehensive search of PubMed and Scopus databases, along with additional searches in search engines such as Google Scholar, was done.

Data selection

The following keywords were used for the selection of studies - tumor markers AND prognosis AND salivary ADCC. Synonyms of the keywords were also used for the search. Studies published from 1977 to August 2018 were included. Only studies that were published in English were selected. Additional citations identified through the reference lists of the selected studies and bibliographic linkages were included in the review. Editorials, review, case reports, study on cell lines, articles in languages other than English were excluded from the study.

Data extraction and synthesis

A standard pilot form in excel sheet was initially used. Data extraction was done for one article and this form was reviewed by an expert and finalized. This was followed by data extraction for all the articles.

Results

The objective of the study was to evaluate the efficiency of various biomarkers in predicting the prognosis of salivary ADCC. Through the initial literature search, 326 articles were retrieved, of which 59 articles were excluded due to overlapping of data. By screening of titles, 158 articles were selected. The abstracts and full texts of these 158 articles were further screened for relevance and 58 articles were excluded. Twenty-seven case reports and reviews were ruled out. Of the remaining 73 articles, 5 articles were excluded due to data in other languages. Hence, a total of 68 articles were selected for data extraction [Figure 1]. A number of immunohistochemical markers showed prognostic significance in salivary gland ADCC. Ki-67, p53, vascular endothelial growth factor (VEGF), and cyclin D1 are the makers that were most frequently assessed, which also showed reproducible results.

Study characteristics are provided in Table 1.

Discussion

The combination of keywords tumor markers, prognosis, metastasis, patient survival, and salivary ADCC used for literature search in the databases showed 326 articles in the initial search, of which 68 articles fitted our criteria of immunohistochemical markers showing prognostic significance in salivary ADCC.

The primary objective of this systematic review was to identify the IHC markers, which could predict the prognosis of salivary ADCC in terms of recurrence, metastasis, and overall survival.

Many studies evaluated IHC markers such as Myb,[5] SMR3A,[6] c-MET,[7] LC3,[8] ALDH1,[9] CEACAM1,[10] PIN1,[11,12] bcl-2,[13,14] and HIF-1a[15] for their prognostic significance but no substantial correlation was found between the expression of these markers and prognosis. A study by Shintani *et al*.[16] showed that tenascin, an extracellular matrix protein, plays a role in the invasion of ADCC, but its relation with distant metastasis and recurrence was not demonstrated.

Few studies demonstrated the role of markers such as VEGF,[17] MCM3,[18] CD166,[19] LC3, and LAMP[20] as diagnostic markers for malignant tumors, thereby differentiating them from benign tumors. This highlighted their role in the progression of the tumor. However, their role as prognostic indicators was not established in these studies.

Other markers like MACC1,[21] EphA2/ephrinA1,[22] and NCAM[23] did not show any correlation with prognosis of tumor but were closely related to other clinicopathologic characteristics like perineural invasion. Similarly, Xia *et al*.,[24] showed decreased immunohistochemical expression of EDNRB to have a significant correlation with the growth of tumor, but no correlation was found between its expression and other characteristics like metastasis.

Dos Santos *et al*.[25] in a study showed that the transformed areas, in high-grade transformation of ADCC, had an increased expression of adipophilin as compared to the conventional areas, thereby suggesting the role of lipid droplets in proliferation and progression of ADCC. However, no data was available for its role in other factors of prognosis.

Table 1: Study characteristics

Author	Year	Site	Numberof cases	Males	Females	Age	Perineural invasion, nodal involvement	Local recurrence, distant metastasis	Followup	Median survival duration	Median DFS duration	Antibody
Bazarsad S *et al.*	2018	Parotid: 3, submandibular: 8, sublingual: 1, minor: 36	48	25	23	55	Perineural invasion: 29	Local recurrence: 2, distant metastasis: 18, death: 10.4%	60 months	Nil	Nil	Myb, ATM, p53
Li S *et al.*	2017	Nil	74	38	36	51	Perineural invasion: 28, lymph node: 14	Recurrence: 12	Nil	Nil	Nil	NPM1
Salzman R *et al.*	2016	Parotid: 6, submandibular: 6, sublingual: 2, minor salivary glands: 6	20	8	12	56.4	Nodal involvement: 6	Distant metastasis: 1	5-286.1 months	46.7 months	Nil	podoplanin
Yi C *et al.*	2016	Nil	102	48	54	Nil	Perineural invasion: 69, lymph node involvement: 18	Locoregional recurrence: 62, distant metastasis: 55	5 years, 10 years	Nil	Nil	Bmi-1, Snail, Slug, E-cadherin
Thierauf J *et al.*	2016	Parotid: 32.6%, 10.5%: submandibular, 3.5%: sublingual, 9.5: palate, 4.8: base of tongue	40	Nil	Nil	54.3	Nil	Nil	Nil	75 months	Nil	SMR3A
Dos Santos HT *et al.*	2016	Submandibular: 2, palate: 1, lip: 1, parotid: 1	5	Nil	Nil	55.8	Nil	Distant metastasis: 2	37.3 months	Nil	Nil	Adipophilin
Kaira K *et al.*	2015	Parotid: 7, submandibular: 1, sublingual: 2, minor salivary gland: 14, others: 2	26	18	8	55	Nil	Nil	63 months	Nil	Nil	GRP78/BiP, PERK, Ki-67, CD34
Huang CF *et al.*	2015	Nil	74	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	LC3, LAMP2, NRF2, KEAP1
Schneider T *et al.*	2015	Parotid: 9, submandibular: 4, minor: 10	23	11	12	Nil	Lymph node involvement: 6	Nil	Nil	Nil	Nil	EGFR antibody
Li H *et al.*	2015	Nil	65	34	31	50	Perineural invasion: 37, lymph node metastasis: 10	Recurrence: 8	Nil	Nil	Nil	MACC1
Xia RH *et al.*	2015	Major gland: 17, minor glands: 16	33	15	18	49	Perineural invasion: 22	Nil	Nil	Nil	Nil	EDNRB
Bell D *et al.*	2015	Parotid: 29, hard palate: 28, maxillary sinus: 26, submandibular and sublingual: 20	200	102	98	52	Nil	Distant metastasis: 67	36 months	Nil	Nil	c-MET

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Author	Year	Site	Numberof cases	Males	Females	Age	Perineural invasion, nodal involvement	Local recurrence, distant metastasis	Followup	Median survival duration	Median DFS duration	Antibody
Schneider S *et al.*	2015	Minor salivary glands: 23	23	Nil	Nil	Nil	Nil	Nil	101 months	47 months	Nil	β-catenin, cyclin D1, PIN1
Chen Z *et al.*	2015	Nil	65	39	26	48.2	Nil	Distant metastasis: 11	61.8 months	Nil	Nil	LC3A/B, BNIP3, HIF-1a
Tadbir AA *et al.*	2014	Nil	14	Nil	Nil	58.2	Nil	Nil	Nil	Nil	Nil	CD166
Dai W *et al.*	2014	Nil	135	85	50	Nil	Perineural invasion: 75, lymph node metastasis: 61	Nil	Nil	Nil	Nil	USP22, Ki-67
Zhao D *et al.*	2013	Major: 49, minor: 45	94	Nil	Nil	Nil	Perineural invasion: 46	Recurrence: 47, distant metastasis: 31	42 months	Nil	Nil	ILK, snail, E-cadherin, N-cadherin
Chen D *et al.*	2013	Parotid: 7, submandibular: 13, sublingual: 11, minor: 19	50	28	22	49.5	Perineural invasion: 17	Distant metastasis: 16	Nil	Nil	Nil	FAK, ILK, PTEN
Xia R *et al.*	2013	Major salivary gland: 27, major salivary gland: 39	66	36	30	53.02	Perineural invasion: 50	Recurrence: 21, distant metastasis: 34	77.24 months	Nil	Nil	H3K9me3, H3K9Ac
Brazao-Silva MT *et al.*	2013	Palate: 11, base of the tongue: 7, buccal mucosa: 3, maxillary sinuses: 2, upper lip: 2, retromolar trigone: 1, floor of the mouth: 1, and submandibular: 10, parotid: 8 and sublingual glands: 4	49	32	17	56.7	Perineural invasion: 13	Metastasis: 14, recurrence: 8	84.7 months	Nil	25 months	Metallothionein
Faur A *et al.*	2013	Parotid: 2, submandibular: 2	4	2	2	Nil	Neural invasion: 3, vascular invasion: 2	Nil	Nil	Nil	Nil	VEGF
Ashkavandi ZJ *et al.*	2013	Parotid: 3, submandibular: 4, minor: 11	18	6	12	54.5	Nil	Nil	Nil	Nil	Nil	MCM3, Ki-67
Qi C *et al.*	2013	Major: 37, minor: 59	96	42	54	46	Perineural invasion: 44	Recurrence: 17, distant metastasis: 19	42 months	Nil	Median recurrence time: 28.5 months, median metastasis time: 42.5 months	PDCD4

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Author	Year	Site	Numberof cases	Males	Females	Age	Perineural invasion, nodal involvement	Local recurrence, distant metastasis	Followup	Median survival duration	Median DFS duration	Antibody
Shao Z *et al.*	2013	Nil	49	24	25		Perineural invasion: 33	Nil	Nil	Nil	Nil	EphA2, ephrinA1 and S-100, P-Tyr, CD-34
Tadbir AA *et al.*	2012	Nil	19	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	CD105, Ki-67
Lee SK *et al.*	2012	Parotid: 18; submandibular: 12, minor: 18	48	19	29	49.7	Perineural invasion: 22, lymph node metastasis: 6	recurrence: 19	70.9 months	38 months	24.9 months	c-kit, EGFR, VEGF
Jiang L *et al.*	2012	Parotid: 15, submandibular: 26, sublingual: 12, minor: 26	79	47	32	47.9	Lymph node involvement: 10, perineural invasion: 39	Nil	50 months	Nil	Nil	LC3A/B, beclin-1, GRP78,
Zhou JH *et al.*	2013	Nil	216	103	113	52	Perineural invasion: 131	Nil	Nil	Nil	Nil	ALDH1
Wu HM *et al.*	2012	Major: 20, minor: 20	40	18	22	51.9	Nil	Recurrence: 11, 16 distant metastasis: 16	64.95 months	Nil	Nil	podoplanin
Lin YC *et al.*	2012	Nil	101	44	57	49	Perineural invasion: 71	Recurrence: 56, distant metastasis: 22	100 months	163.9 months	Nil	Ki-67, E-cadherin, p16, cyclinD1
Dahl A *et al.*	2011	Major: 12, minor: 22	34	24	10	59.9	Perineural invasion: 10	Distant metastasis: 13, recurrence: 17	98 months			L1, CEACAM1
Bell D *et al.*	2011	Parotid: 29, submandibular and sublingual: 20, minor: 151	200	99	101	52	Nil	Distant metastasis: 67	Nil	Nil	Nil	EN1
Wang Y *et al.*	2011	Major: 36, Minor: 39	75	36	39		Perineural invasion: 20	Recurrence: 22, Metastasis: 28	99.37 months	Nil	Nil	Ezrin, CD44v6, Ki-67, iNOS
Tang Q *et al.*	2011	Parotid: 7, submandibular: 9, sublingual: 10, minor: 34	60	29	31	53	Perineural invasion: 28, lymph node involved: 6	Recurrence: 15, distant metastasis: 20	8-120 months	98 months	Nil	Cyr61, Ki-67
Yang X *et al.*	2010	Parotid: 17, submandibular: 11, sublingual: 3, minor: 41	72	32	40	Nil	Perineural invasion: 35	30: Recurrence, 27: Distant metastasis	76.76 months	Nil	Nil	EMMPRIN, MMP: 2, MMP: 9, VEGF, ki-67, CD31

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Table 1: Contd...

Author	Year	Site	Numberof cases	Males	Females	Age	Perineural invasion, nodal involvement	Local recurrence, distant metastasis	Followup	Median survival duration	Median DFS duration	Antibody
Tang Y *et al.*	2010	Major: 58, minor: 63	121	54	67	Nil	Perineural invasion: 47	Recurrence: 30, distant metastasis: 39	Nil	Nil	Nil	Anti-slug
Ramer N *et al.*	2009	Major: 13, minor: 22	35	11	24	51.5	Nil	Recurrence: 18, distant metastasis: 14	111 months	Nil	Nil	p63
Vekony H *et al.*	2008	Major: 19, Minor: 2	21	Nil	Nil	54.9	Nil	Recurrence: 5, metastasis: 11	73.6 months	Nil	27 months	p53, p16, E2F1, Ki-67, cyclin D1, BMI1, EZH2
Maiorano E *et al.*	2007	Nil	28	11	17	55	Nil	Nil	Nil	Nil	Nil	Numb, Ki-67
Zhang J *et al.*	2005	Nil	80	34	46		Perineural invasion: 31, vascular invasion: 26	Recurrence: 40, distant metastasis: 29	72 months	Nil	Nil	NF-κB p65, iNOS, VEGF, CD34
Teymoortash A *et al.*	2006	Parotid: 5, submandibular: 5, sublingual: 1, minor: 24	35	14	21	59.9	Perineural invasion: 11	Distant metastasis: 9	90.1 months	90 months	61.2 months	Galactin-3
Jia L *et al.*	2004	Parotid: 2, submandibular: 4, minor: 33	39	10	29	58.7	Nil	Nil	Nil	Nil	Nil	p53, mdm2, bcl-2
Preissegger KH *et al.*	2001	Nil	26	Nil	Nil	Nil	Nil	Recurrence: 4	Nil	Nil	Nil	p53, P-gp, GST-pi, Topo, bcl-2
Kiyoshima T *et al.*	2000	Submandibular: 3, sublingual: 1, minor: 13	17	8	9	54.8	Lymph node metastasis: 3	Recurrence: 1	Nil	Nil	Nil	p53, Ki-67
Takata T *et al*	1999	Nil	29	13	16	60.9	Nil	Metastasis: 15	107.5 months	Nil	Nil	p27
Cho KJ *et al.*	1999	Parotid: 5, submandibular: 8, minor: 17	30	10	20	51.5	Nil	Recurrence: 12, metastasis: 16	Nil	Nil	47 months	PCNA, c-erbB-2
Hirabayashi S	1999	Nil	24	11	13	56	Nil	Recurrence: 9, metastasis: 10	Nil	Nil	Nil	Ki-67, topo-II,
Shintani S *et al.*	1996	Nil	15	4	11	Nil	Nil	Nil	Nil	Nil	Nil	Type IV collagen, laminin, fibronectin, tenascin
Nordgard S *et al.*	1997	Nil	44	21	23	58	Nil	Nil	6.2 years	Nil	Nil	Ki-67
Karja V *et al.*	1994	Nil	26	10	16	62	Nil	Nil	Nil	Nil	Nil	cerB-2

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Author	Year	Site	Numberof cases	Males	Females	Age	Perineural invasion, nodal involvement	Local recurrence, distant metastasis	Followup	Median survival duration	Median DFS duration	Antibody
Zhou CX *et al.*	2006	Parotid: 19, submandibular: 11, sublingual: 18, palatine: 17	65	24	41	41.3	Perinueral invasion: 49	Recurrence: 24, metastasis: 6	Nil	Nil	Nil	β-catenin, cyclin D1, PIN1
Spaak LN *et al.*	1999	Major: 14, minor: 17	31	15	16	60	Nil	Nil	5 years	Nil	Nil	bcl-2, Ki-67
Chang B *et al.*	2014	Nil	50	Nil	Nil	Nil	Nil	Distant metastasis: 8, recurrence: 11	64 months	98.7 months for high expression and 135.2 months for low expression	Nil	bmi-1
Vered M *et al.*	2002	Minor: 18, major: 16	34	14	20	Nil	Nil	Nil	Nil	Nil	Nil	EGFR
Taghavi N *et al.*	2018	Major: 6, minor: 26	32	12	20	49.96	Perineural invasion: 18, lymph node metastasis: 4	Nil	Nil	Nil	Nil	p63, maspin, MMP-2
Beppu S *et al.*	2017	Nil	46	22	23	62	Lymph node metastasis: 6, perineural invasion: 30	Recurrence: 10, metastasis: 15	Nil	Nil	Nil	MAGE-A, NY-ESO-1
Ouyang Dq *et al.*	2016	Nil	120	Nil	Nil	Nil	Nil	Nil	60.5 months	114 months	95 months	p-Akt, p-mTOR, PI3K, IGF-1Rβ
Yue H *et al.*	2016	Major: 16, minor: 34	50	18	32	Nil	Perineural invasion: 26	Metastasis: 14	Nil	Nil	Nil	TARP
Gao X *et al.*	2017	Major: 58, minor: 63	121	54	67	Nil	Perineural invasion: 47	Recurrence: 30, metastasis: 39	Nil	Nil	Nil	CK-14
Wang S *et al.*	2016	Major: 29, minor: 16	45	20	25	Nil	Nil	Recurrence and metastasis: 10	Nil	Nil	Nil	CD133
Xia Y *et al.*	2014	Nil	81	37	44	47	Perineural invasion: 40	Recurrence: 46, metastasis: 29	Nil	Nil	Nil	TACSTD2
Costa AF *et al.*	2012	Nil	26	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	HIF-1a
Schwarz S *et al.*	2008	Nil	25	8	17	57.3	Nil	Nil	Nil	Nil	Nil	Maspin

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Table 1: Contd...

Author	Year	Site	Numberof cases	Males	Females	Age	Perineural invasion, nodal involvement	Local recurrence, distant metastasis	Followup	Median survival duration	Median DFS duration	Antibody
Shang J *et al*.	2007	Parotid: 11, submandibular: 6, sublingual: 3, minor: 29	49	22	27	Nil	Perineural invasion: 33, lymph node involvement: 6	Nil	Nil	Nil	Nil	NCAM
Do Nascimento KC *et al*.	2006	Nil	21	Nil	Nil	Nil	Nil	Metastasis: 10	6.9 years	Nil	Nil	NM23
Kaira K *et al*.	Nil	Parotid: 8, submandibular: 1, sublingual- 2, minor-19	30	21	9	56	Nil	Nil	69 months	Nil	Nil	LAT1, CD98, CD34, Ki-67, p53
Bell D *et al*.	2010	Nil	199	93	106	51.4	Nil	Metastasis: 74	62.1 months	Nil	Nil	c-kit, EGFR
Nagler RM *et al*.	2003	Nil	4	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Bcl-2, p53

Author	Positive cases	Positive cases with metastasis	Positive cases with perineural invasion	Positive cases with lymph node involvment	Positive cases with recurrence	OS	DFS (metastasis free and recurrence free)	Summary	Remarks
Bazarsad S *et al*.	Myb: 85.4%, ATM in cancer cells: 41.7%, ATM in cancer stroma: 39.6%, p53: 79.2%	ATM in cancer cells: 27.8%, ATM in stroma: 22.2%, p53: 72.2%	Myb: 72.4%, ATM in cancer cells: 41.4%, ATM in stroma: 24.1%, p53: 79.3%	Nil	Nil	Nil	Nil	Low ATM expression in cancer cells was correlated with poor survival along with positive p53 expression. Myb did not show any correlation with patient survival	Nil
Li S *et al*.	High expression: 50%	Nil	67.85%	78.57%	Nil	Nil	Nil	The nuclear and cytoplasmic expression of NPM1 in ADCC tissue was overexpressed and was tightly linked to perineural invasion and lymph node metastasis	Nil

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Table 1: Contd...

Author	Positive cases	Positive cases with metastasis	Positive cases with perineural invasion	Positive cases with lymph node involvment	Positive cases with recurrence	OS	DFS (metastasis free and recurrence free)	Summary	Remarks
Salzman R *et al.*	Intratumoral lymphatics: 100%, peritumoral lymphatics: 93.8%	Nil	Nil	Nil	Nil	Nil	Nil	The comparative study shows the density of peri and intra-tumoral lymphatics to be higher in ADCC than in PA and normal salivary gland tissue	ADCC has the ability to stimulate the formation of new lymphatics, which corresponds to its biologic aggressiveness
Yi C *et al.*	Bmi-1: 61.8% (high expression); E-cadherin: 68.6% (High expression); Snail: 49% (high expression); Slug: 25.4% (high expression)	Bmi-1: 81.8% (high expression), E- cadherin: downregulated, Snail: 61.8%, Slug: 34.5%	Bmi-1: 65.2%(high), 34.8%(low)	Nil	Nil	5 years survival Bmi-1: 80.5 (for high expression cases), 91.9% (for low expression cases) E-cadherin: 89.3% (high), 74.2% (low) Snail: 83.9% (high), 85.8% (low) Slug: 81.3 (low) 10 years survival Bmi-1: 73.4 (high), 68.9% (low) E-cadherin: 84% (high), 52.2% (low) Snail: 73.8 (high), 77.2% (low) Slug: 67.9% (low)	5 years survival Bmi-1:52%(high), 86.6%(low) E-cadherin: 76.3%(high), 40.6%(low) Snail: 55.3%(high), 74.1% (low) Slug: 70.4%(low) 10 years survival Bmi-1: 25.4%(high), 39.5%(low) E-cadherin: 39.8% (high), 16.9% (low) Snail: 18.6%(high), 56%(low) Slug: 34.3% (low)	High levels of Bmi-1, Snail and Slug expression as well as reduced E-cadherin expression and their interaction were significantly linked to distant metastasis in ADCC	High levels of Bmi-1 expression displayed corellation with high expression of Snail and Slug. RT-PCR showed higher Bmi-1 mRNA level in tumor tissue than in normal tissue
Thierauf J *et al.*	27.50%	Nil	Nil	Nil	Nil	1 year: 92% 5 years: 53.7%	Nil	No significant correlation was found between expression of SMR3A and OS	Nil

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Table 1: Contd...

Author	Positive cases	Positive cases with metastasis	Positive cases with perineural invasion	Positive cases with lymph node involvment	Positive cases with recurrence	OS	DFS (metastasis free and recurrence free)	Summary	Remarks
Dos Santos HT *et al*.	Conventional ACC: 50%, Transformed ACC: 83.3%	Nil	Nil	Nil	Nil	Nil	Nil	A significant difference was seen between conventional and transformed areas of HGT-ADCC regarding the quantity of adipophilin+LD	The study showed that cellular proliferation has a direct relationship with the up-regulated lipogenesis of HGT-ADCC as LDs would play a role in supplying cell division
Kaira K *et al*.	GRP78/BiP: 58%, PERK: 35%, CD34: 42%, Ki-67: 35%	Nil	Nil	Nil	Nil	5 years BIP: 36% (high expression), 90.9%(low expression) PERK: 33.3 (high), 71.5%(low) Ki-67: 38.9%(high), 81.6% (low) CD34: 54.5%(high), 77.8% (low)	Nil	GRP78/BiP was found to be an unfavorable prognostic marker for patients with ADCC, having a significant correlation with proliferation and angiogenesis. High expression of Ki-67 showed lower OS	Nil
Huang CF *et al.*	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Positive expression of LC3 and LAMP2 in ADCC was significantly higher when compared with normal salivary gland and PA	LC3, LAMP2 and KEAP1-NRF2 pathway are over-expressed in human adenoid cystic carcinoma tissues, indicating increased level of autophagy activity and oxidative stress thereby helping in cancer progression

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Table 1: Contd...

Author	Positive cases	Positive cases with metastasis	Positive cases with perineural invasion	Positive cases with lymph node involvment	Positive cases with recurrence	OS	DFS (metastasis free and recurrence free)	Summary	Remarks
Schneider T *et al.*	78%	Nil	Nil	Nil	Nil	Nil	Nil	No correlation was found between EGFR and prognosis	Nil
Li H *et al.*	Nucleus: 73.84%(high), cytoplasm: 44.61% (high)	Nil	Nucleus: 78.3% (high), cytoplasm: 37.83% (high)	Nucleus: 70% (high), cytoplasm: 50% (high)	Nucleus: 75%(high), cytoplasm: 50%(high)	Nil	Nil	Metastasis-associated in colon cancer-1 is overexpressed in ADCC tissues compared to normal salivary tissue. MACC1 nuclear overexpression was closely related to the histological grading of tumours, perineural invasion and surrounding tumour invasion	Nil
Xia RH *et al.*	36.4% (high), 63.6% (low)	Nil	77.27% (low), 22.72% (high)	Nil	Nil	Nil	Nil	EDNRB protein expression in ADCC tumor tissues was significantly lower than that in adjacent normal glands. EDNRB expression in patients at the advanced T stage was significantly lower than that in patients at the early T stage. Low EDNRB expression played a role in the development and progression of ADCC	Nil
Bell D *et al.*	53.2% (high)	Nil	Nil	Nil	Nil	58.50%	Nil	There was no correlation between c-MET overexpression and clinicopathologic parameters or patient's OS	Absence of correlation with survival implies that c-MET expression can't be used as a prognostic marker in salivary gland ADCC

Contd...

Table 1: Contd...

Author	Positive cases	Positive cases with metastasis	Positive cases with perineural invasion	Positive cases with lymph node involvment	Positive cases with recurrence	OS	DFS (metastasis free and recurrence free)	Summary	Remarks
Schneider S *et al.*	β-catenin: 89%, Cyclin D1: 95%, PIN1: 88%	Nil	Nil	Nil	Nil	5 years: 62%	Nil	High expression of membranous β-catenin was linked to significantly better OS in patients with adenoid cystic carcinoma	Nil
Chen Z *et al.*	BNIP3: 63.1%, HIF-1a: 80%, LC3: 56.9%	BNIP3: 63.63%, HIF-1a: 63.63%, LC3: 54.54%	Nil	Nil	Nil	Nil	Nil	OS in the negative BNIP3 expression group was better than in the positive BNIP3 expression	BNIP3 expression was positively correlated with HIF-1a expression, while was not correlated with LC3 expression in head and neck adenoid cystic carcinoma. This suggested that BNIP3-induced autophagy may not play a dominant role in hypoxia-induced autophagy in ADCC tissues
Tadbir AA *et al.*	92.80%	Nil	Nil	Nil	Nil	Nil	Nil	CD166 expression in ADCC and MEC was significantly higher than in the PA	CD166 has a signaling role in proteolysis and CD166 overexpression can enhance MMP-2 activity and the breakdown of the extracellular matrix, hence, resulting in increased tumor invasiveness and progression

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Table 1: Contd...

Author	Positive cases	Positive cases with metastasis	Positive cases with perineural invasion	Positive cases with lymph node involvment	Positive cases with recurrence	OS	DFS (metastasis free and recurrence free)	Summary	Remarks
Dai W *et al.*	USP22: 76.3% (high), Ki-67: 71.1% (high)	Nil	USP22: 74.66%(high)	USP22: 90.16% (high)	Nil	Nil	Nil	Patients with high expression of USP22 had shorter OS and DFS than those with low USP22 expression	High USP22 expression group showed higher Ki-67 expression (78.6%) and higher lymph node metastasis than the low USP22 expression group 46.9%
Zhao D *et al.*	ILK: 76.59%, snail: 80.85%, E-cadherin: 73.40, N-cadherin: 68%	ILK: 90.32%, snail: 90.32%, E-cadherin: 48.38%, N-cadherin: 70.96%	ILK: 78.26%, Snail: 82.6%, E-cadherin: 65.21%, N-cadherin: 82.6%	Nil	ILK: 70.21%, snail: 82.97%, E-cadherin: 63.82%, N-cadherin: 61.70%	Nil	Nil	The present results strongly suggest that ILK participates not only in the progression but also in metastasis of ADCC, possibly through EMT involving upregulation of Snail and consequent aberrant expression of E-cadherin and N-cadherin. ILK should be considered as a potential therapeutic molecular target	Nil
Chen D *et al.*	FAK: 94%, ILK: 48%, PTEN: 30%	FAK: 93.75%, ILK: 62.5%	FAK: 88.23%, ILK: 64.70%	Nil	Nil	Nil	Nil	High expression of FAK and ILK is implicated in the invasion and metastasis of ADCC along with down regulation of PTEN as compared to normal salivary gland tissue	Nil

Contd...

Table 1: Contd...

Author	Positive cases	Positive cases with metastasis	Positive cases with perineural invasion	Positive cases with lymph node involvment	Positive cases with recurrence	OS	DFS (metastasis free and recurrence free)	Summary	Remarks
Xia R *et al.*	H3K9me3: 56%, H3K9Ac: 27.27%	H3K9me3: 76.47% (high), 23.52% (low) H3K9Ac: 23.52% (high), 76.47% (low)	H3K9me3: 44%(low), 56% (high) H3K9Ac: 72%(low), 28%(high)	Nil	H3K9me3: 28.57% (low), 71.42% (high) H3K9Ac: 71.42% (low), 28.57% (high)	Nil	Nil	Patients whose tumors had high levels of H3K9me3 showed significantly poorer OS outcomes than those with low levels of H3K9me3, while patients with high H3K9Ac expression had a significantly better OS than those with low expression levels	Nil
Brazao-Silva MT *et al.*	79.59%	85%	Nil	Nil	Nil	Nil	Nil	Consistent patterns of MT expression were observed to correlate with metastatic behaviour, indicating that MT may potentially serve as a prognostic marker for ADCC	Nil
Faur A *et al.*	75%	Nil	Nil	Nil	Nil	Nil	Nil	Higher VEGF expression in malignant salivary tumours versus benign tumours	Nil
Ashkavandi ZJ *et al.*	MCM3:100%, Ki-67: 100%	Nil	Nil	Nil	Nil	Nil	Nil	MEC and ADCC had a higher proliferation activity as compared to PA	MCM3 can be used for differential diagnosis between malignant and benign salivary gland tumors
Qi C *et al.*	35.41% (high), 64.58% (low)	Nil	65.90% (low), 34% (high)	Nil	Nil	5 year: 70.8%, 80.3% (high) 65.9% (low)	Nil	OS in the group of decreased PDCD4 expression was significantly lower than that of high PDCD4 expression	PDCD4 expression was decreased in 64.6% (62/96) of ADCC samples at the protein level

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Table 1: Contd...

Author	Positive cases	Positive cases with metastasis	Positive cases with perineural invasion	Positive cases with lymph node involvment	Positive cases with recurrence	OS	DFS (metastasis free and recurrence free)	Summary	Remarks
Shao Z *et al.*	EphA2: 69.4% (high); ephrinA1: 79.6% (moderate to high)	Nil	EphA2: 84.84%(high); ephrinA1: 93.93% (high)	Nil	Nil	Nil	Nil	The results of the present study showed high expression of EphA2 and ephrinA1 in ADCC specimens	EphA2/ephrinA1 overexpression could contribute to promoting ADCC angiogenesis
Tadbir AA *et al.*	CD105: 65%; Ki-67: 84%	Nil	Nil	Nil	Nil	Nil	Nil	It was observed a higher rate of angiogenesis and cellular proliferation was noted in malignant tumors compared to benign tumors, but no correlation was observed between these two markers	Unavailability of information associated with prognosis, survival and follow up of the patients, it was impossible to assess the relationship between Ki-67 marker and factors associated with prognosis
Lee SK *et al.*	c-kit: 94%; EGFR: 56%; VEGF: 88%	Nil	c-kit: 50% (high) EGFR: 59%, VEGF: 54.54%	c-kit: 66.66%, VEGF: 66.66%	Nil	5 years survival: 88.2%	72.90%	No marker was significantly correlated with recurrence or the survival rate	Only lymph node metastasis showed a close relationship to the survival rate
Jiang L *et al.*	LC3A/B: 57%, beclin 1: 44.3%, GRP78: 51.9%	Nil	LC3:53.84%, beclin-1: 38.46%, GRP78: 51.28	LC3: 20%, beclin-1: 20%, GRP78: 40%	Nil	Nil	Nil	LC3 expression showed no significant difference for the OS rate in patients with ADCC; the OS in the positive beclin 1 expression group tended to be better than in the negative beclin 1 expression group; the OS in the positive GRP78 expression group tended to be better than in the negative GRP78 expression group	Nil

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Table 1: Contd...

Author	Positive cases	Positive cases with metastasis	Positive cases with perineural invasion	Positive cases with lymph node involvment	Positive cases with recurrence	OS	DFS (metastasis free and recurrence free)	Summary	Remarks
Zhou JH *et al*.	78.24%	Nil	Nil	Nil	Nil	Nil	Nil	No correlation was found between ALDH1 expression and overall survuval	Nil
Wu HM *et al*.	77.5%, high expression (32.5%), low expression (45%)	56.25% (high)	Nil	Nil	36.36% (high)	Nil	Nil	Positive staining is correlated with distant metastasis; high expression showed shorter OS compared to lower	Nil
Lin YC *et al*.	Ki-67: 53.5%(high); E-cadherin: 90.1%, p16: 36.6%, cyclinD1: 18.3%	Nil	Nil	Nil	Nil	5 years survival: 68.3%, 10 years survival: 56%	5 years: 54.9%, 10 years: 22.2%	High Ki-67 expression was correlated with poor prognosis	Nil
Dahl A *et al*.	L1: 91.17%, CEACAM1: 70.58%	Nil	Nil	Nil	Nil	38%	Nil	A significant positive association between intense L1 expression and death from ADCC, as well as between intense L1 expression and metastasis was seen. CEACAM1 had no corelation with OS	Nil
Bell D *et al*.	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Increased EN1 protein expression in solid type ADCC, which correlated with a significantly lower survival rate	Nil
Wang Y *et al*.	Ezrin: 92%; CD44: 80%, I NOS: 85.33%	Nil	Nil	Nil	Nil	66.66%	Nil	Study demonstrated that Ezrin expression is significantly associated with histologic pattern, tumor diameter, distant metastasis, clinical stage, and poor survival time	Nil

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Table 1: Contd...

Author	Positive cases	Positive cases with metastasis	Positive cases with perineural invasion	Positive cases with lymph node involvment	Positive cases with recurrence	OS	DFS (metastasis free and recurrence free)	Summary	Remarks
Tang Q *et al.*	Cyr61: 65%; Ki-67: 58% (low), 42% (high)	Cyr61: 70%	Cyr61: 79%	Cyr61: 83%	Cyr61: 67%	Cyr61: 3 year: 74%, 5 year: 67%; Ki-67: 5 years: 92% (low), 22% (high)	Nil	Cyr61 expression is significantly correlated with Ki-67 expression and has potential in screening high-risk ADCC cases for recurrence and metastasis, as well as indicating a poor prognosis for patients	High Cyr61 expression had a poorer survival rate
Yang X *et al.*	EMMPRIN: 62.5%, MMP-2: 65.27%, MMP-9: 76.38%, VEGF: 73.61%, Ki-67: 48.61 (high)	EMMPRIN: 81.48%	EMMPRIN: 71.42%	Nil	EMMPRIN: 76.66%	44.40%	Nil	EMMPRIN expression was positively associated with perineuralinvasion, vascular invasionand distant metastasisof ADCCs. Patients with positive EMMPRIN expression had a significantly poor survival than those with negative EMMPRIN expression	EMMPRIN expression was positively correlated with the expression of VEGF, MMP-2 and MMP-9 in ADCCs
Tang Y *et al.*	71.90%	87.17%	82.97%	Nil	90%	5 years survival: 12.8% for distant metastasis, 32.7% for recurrence 10 years survival: 0 for distant metastasis, 21.6% for recurrence	Nil	Elevated levels of slug expression were significantly associated with perineural invasion, local regional recurrence, and distant metastasis of ADCC, and that the patients with positive slug had a poorer prognosis than those with negative slug, which suggests that this marker may be an indicator of poor prognosis in ADCC	Nil

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Table 1: Contd...

Author	Positive cases	Positive cases with metastasis	Positive cases with perineural invasion	Positive cases with lymph node involvment	Positive cases with recurrence	OS	DFS (metastasis free and recurrence free)	Summary	Remarks
Ramer N *et al.*	100%	Nil	Nil	Nil	Nil	31.40%	Nil	Increased p63 expression in tumor cells correlated with poorer survival, compared with tumors with relatively reduced p63 expression	Nil
Vekony H *et al.*	EZH2: 28.57%(high)	Nil	Nil	Nil	Nil	71.42%	Nil	EZH2 was associated with aggressive behaviour of the tumor	Nil
Maiorano E *et al.*	Numb: 67.85%(high), Ki-67: 85.71%	Nil	Nil	Nil	Nil	Nil	Nil	Reduced numb expression was found to be associated with metastasis and recurrence	Nil
Zhang J *et al.*	iNOS: 90%(high), VEGF: 76.25%, NF-kB: 35% (high)	iNOS: 89.65%(high), VEGF; 79.31% (high), NF-kB: 62.06%(high)	iNOS: 87.9%(high), VEGF: 83.87% (high), NF-Kb: 54.83%	Nil	iNOS: 90%(high), VEGF: 85% (high), NF-kB: 57.5%	63.70%	Nil	Survival rates of patients with high NF-κB, iNOS, VEGF, and MVD expression were significantly worse than that of patients with low or moderate NF-κB, iNOS, VEGF, and MVD expression	Nil
Teymoortash A *et al.*	48.60%	100%	54.50%	Nil	Nil	5 years: 54.5%, 10 years: 43.7%	5 years: 49% 10 years: 44.1%	Galectin-3 expression was associated with the increased incidence of regional and distant metastasis in ADCC of the head and neck. The immunohistochemical evaluation of galectin-3 might be valuable to identify ADCC patients at high risk for the development of metastasis.	Nil

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Table 1: Contd...

Author	Positive cases	Positive cases with metastasis	Positive cases with perineural invasion	Positive cases with lymph node involvment	Positive cases with recurrence	OS	DFS (metastasis free and recurrence free)	Summary	Remarks
Jia L *et al*.	p53: 64.1%, mdm2: 76.9%, bcl-2: 51.3%	Nil	Nil	Nil	Nil	64.10%	Nil	The present study suggests that p53 expression and the level of apoptosis could be useful as prognostic values in salivary gland ADCC, and that bcl-2 protein plays a role in the down-regulation of apoptosis and is also potentially useful as a prognostic parameter in salivary gland ADCC.	14 patients died of recurrence and metastasis. Patients with p53-positive expression had a worse cumulative survival than those with p53-negative
Preissegger KH *et al*.	p53: 30.76%, P-gp: 30.76%, GST-pi: 15.38%, Topo: 19.23%, bcl-2: 19.23%	Nil	Nil	Nil	Nil	Nil	Nil	The prognostic value of a p53 alteration serves as an independent prognostic marker	Nil
Kiyoshima T *et al.*	Nil	Nil	Nil	Nil	Nil	Nil	Nil	No correlation was found between IHC staining of p53 and factors of ADCC	Nil

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Table 1: Contd...

Author	Positive cases	Positive cases with metastasis	Positive cases with perineural invasion	Positive cases with lymph node involvment	Positive cases with recurrence	OS	DFS (metastasis free and recurrence free)	Summary	Remarks
Takata T *et al*	44.82%	20%	Nil	Nil	Nil	Nil	Nil	The number of p27Kip1 positive cells was significantly smaller in ACCs with metastasis than in those without metastasis	Nil
Cho KJ *et al*.	PCNA: 58.62 (low), 44.82% (high); c-erbB-2: 17.24%	PCNA: 62.5%(high), c-erbB-2: 18.75%	Nil	Nil	PCNA: 58.3%, c-erbB-2: 25%	Nil	Nil	The high PCNA group showed higher incidence of local recurrence, metastasis, and death. Disease-free interval and OS periods were also shorter in the high PCNA group than in the low PCNA group, with statistical significance with OS rate. Tumors with c-erbB-2 overexpression showed a significantly shorter disease-free interval than did c-erbB-2-negative cases	Nil
Hirabayashi S	Ki-67: 41.66%(high), topo-II: 45.83%	Nil	Nil	Nil	Nil	Ki-67: <10%: 92 months, >10%: 30 months; topo-II: <10%: 95 months, >10%: 35 months	Nil	Topo-II values of more than 10% are the most significant indicator of the shortterm clinical course of the disease	Nil

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Table 1: Contd...

Author	Positive cases	Positive cases with metastasis	Positive cases with perineural invasion	Positive cases with lymph node involvment	Positive cases with recurrence	OS	DFS (metastasis free and recurrence free)	Summary	Remarks
Shintani S *et al.*	Laminin: 86.66%, collagen type IV: 86.66%, fibronectin: 60%, tenascin: 66.66%	Nil	Nil	Nil	Nil	Nil	Nil	Laminin and type IV collagen were totally or partially absent in the ADCC invasive areas. Tenascin was expressed in the stroma and cytoplasm and was associated with tumor cell proliferation. It can be concluded that basement membrane represents a barrier that is lost during cell invasion and tenascin may be involved in the detachment of cancer cells, increasing the invasive potential of ADCC	No correlation was found between extracellular matrix proteins and recurrence and metastasis
Nordgard S *et al.*	Nil	Nil	Nil	Nil	Nil	Nil	Nil	High Ki-67 expression was found to be associated with short-term clinical course	Nil
Karja V *et al.*	57.70%	Nil	Nil	Nil	Nil	Nil	Nil	c-erbB-2 expression did not bear any effect on patient survival	Nil
Zhou CX *et al.*	beta catenin: 22%(C/N) 78%(membranous), cyclin D1: 63%, PIN1: 78%(high)	Beta catenin: 100%, cyclin D1: 83%, PIN1: 83%	Cyclin D1: 82%, PIN1: 79%(high), B-catenin	Nil	Cyclin D1: 71%, PIN1: 79%(high)	Nil	Nil	Pin1 was overexpressed in 51 cases of ADCC (78%), and high levels of Pin1 expression correlated with cyclin D1 positive expression	Reduced membranous expression of ß-catenin was detected in the cases with metastasis (11/14)
Spaak LN *et al.*	Bcl-2: 77.41%	Nil	Nil	Nil	Nil	Nil	67.74%	No significant correlation was found between bcl-2 and Ki-67 with prognosis	Nil

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Table 1: Contd...

Author	Positive cases	Positive cases with metastasis	Positive cases with perineural invasion	Positive cases with lymph node involvment	Positive cases with recurrence	OS	DFS (metastasis free and recurrence free)	Summary	Remarks
Chang B *et al.*	100%	75% (high)	Nil	Nil	45.45%	Nil	Nil	Upregulation of Bmi-1 was associated with 5 years OS and DFS of the ADCC patients	Nil
Vered M *et al.*	85%	Nil	Nil	Nil	Nil	Nil	Nil	Most salivary gland ADCC stained positively for EGFR and in some the staining was intense	Nil
Taghavi N *et al.*	p63: 96.8%, maspin: 90.6%, MMP-2: 93.75%	Nil	Nil	P63: 100%, maspin: 75% (high), MMP: 2:50%	Nil	Nil	Nil	Higher frequency of P63 and maspin expression in better differentiated tumors, which suggests p63 and maspin as useful markers for pre-dicting biologic behavior of ADCC	Nil
Beppu S *et al.*	MAGE-A: 65%, NY-ESO-1: 35%	Nil	Nil	Nil	Nil	5 years: 94%, 10 years: 88%	5 years: 54%, 10 years: 37%	These findings suggest that cancer testis antigens may be expressed in a variety of salivary gland carcinomas, especially in those with higher histological grades. In addition, MAGE-A, which is frequently expressed in ADCC cases, may be a useful prognostic factor for poorer loco-regional recurrence-free survival	Nil

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Table 1: Contd...

Author	Positive cases	Positive cases with metastasis	Positive cases with perineural invasion	Positive cases with lymph node involvment	Positive cases with recurrence	OS	DFS (metastasis free and recurrence free)	Summary	Remarks
Ouyang Dq *et al.*	p-Akt-100%, p-mTOR- 87.5%, IGF-1Rβ-84.7%	Nil	Nil	Nil	Nil	Nil	Nil	Low nuclear p-Akt (Ser473), low nuclear p-Akt (Thr308), and low cytoplasmic and nuclear p-mTOR expression were associated with poor OS	Nil
Yue H *et al.*	88%	92.85%	Nil	Nil	Nil	Nil	Nil	TARP expression was enhanced in metastasis	Nil
Gao X *et al.*	28.92%	Nil	38.29%	Nil	50%	5 years: 22.6%, 10 years: 8.9%	Nil	CK14 expression in the invasive front, local regional recurrence and distant metastasis were independent and significant prognostic factors in ADCC patients	Nil
Wang S *et al.*	46.67%	90%	Nil	Nil	Nil	Nil	Nil	The rate of CD133 positive expression in patients with local regional recurrence and distant metastasis was higher than without	Nil
Xia Y *et al.*	77.77%	89.65%	Nil	Nil	86.95%	Nil	Nil	The expression of TACSTD2 was significantly associated with local recurrence and distant metastasis	Nil
Costa AF *et al.*	HIF-1a-100%,	Nil	Nil	Nil	Nil	Nil	Nil	No significant correlation was seen between HIF-1a and tumor agressiveness	Nil
Schwarz S *et al.*	76%	Nil	Nil	Nil	Nil	5 years: 31.3%	Nil	Low maspin expression is related to poor prognosis	Nil

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Table 1: Contd...

Author	Positive cases	Positive cases with metastasis	Positive cases with perineural invasion	Positive cases with lymph node involvment	Positive cases with recurrence	OS	DFS (metastasis free and recurrence free)	Summary	Remarks
Shang J *et al*.	57%	Nil	72.72%	100%	Nil	Nil	Nil	Positive NCAM staining was detected in all primary lesions and perineural invasion identified in most cases, highlighting the relationship between lymph node metastases and NCAM expression/perineural invasion	Nil
Do Nascimento KC *et al*.	68.70%	60%	Nil	Nil	Nil	Nil	Nil	Nuclear NM23 protein could be a biomarker for salivary gland neoplasms capable of metastasis	Nil
Kaira K *et al*.	CD98: 23%, LAT1: 27%, Ki-67: 46.66%, CD34: 33.33%, p53: 50%	Nil	Nil	Nil	Nil	5 years: 65%, LAT1: 15.6%, CD98: 17.8%, Ki-67: 44.6%, CD34: 45.7%, p53: 38.1%	Nil	High LAT1 expression can serve as an independent prognostic factor to predict poor outcomes after surgical resection and may be an important indicator of therapy for patients with ACC	We observed a significant association between LAT1 and CD98 expression

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Table 1: Contd...

Author	Positive cases	Positive cases with metastasis	Positive cases with perineural invasion	Positive cases with lymph node involvment	Positive cases with recurrence	OS	DFS (metastasis free and recurrence free)	Summary	Remarks
Bell D *et al*.	EGFR: 7.6%, c-kit: 29.9%; c-kit: 24.18% (22 of 91) cribriform pattern, 22.22% (10 of 45) tubular pattern, and in 71.43% (15 of 21) of the solid tumors. EGFR: 4.44% (2 of 45) of and in 10.99% (10 of 91) of the cribriform. EGFR staining was negative in the solid type	Nil	Nil	Nil	Nil	3 years: 82.8%, 5 years: 71.7%, 10 years: 50.9%	Nil	A significant statistical correlation was observed between c-Kit expression and a poor 3 years outcome, and EGFR expression was correlated with a better 3 years outcome	Nil
Nagler RM *et al.*	Nil	Nil	Nil	Nil	Nil	5 years: 75%	Nil	No significant correlation was found between expression of both markers and prognosis	Nil

ADCC: Adenoid cystic carcinoma, PA: Pleomorphic adenoma, RT PCR: Real-time polymerase chain reaction, ACC: Adenoid cystic carcinomas, LDs: Lipid droplets, OS: Overall survival, EGFR: Epidermal growth factor receptor, ENDRB: Endothelial receptor B, DFS: Disease free survival, ILK: Integrin-linked kinase, EMT: Epithelial-mesenchymal transition, FAK: Focal adhesion kinase, VEGF: Vascular endothelial growth factor, MEC: Mucoepidermoid carcinoma, MVD: Microvascular density, IHC: Immunohistochemistry, PCNA: Proliferating cell nuclear antigen, HGT: High grade transformation, PTEN: Phosphatase and tensin homolog, MT: Metallothionein

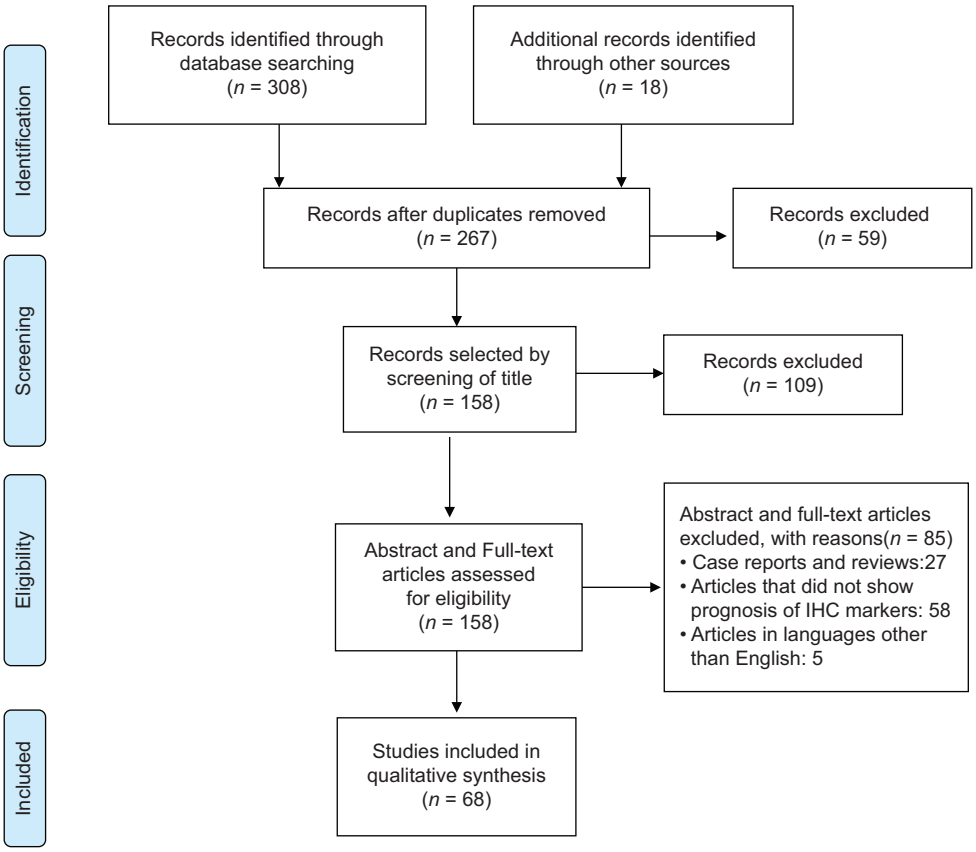

Figure 1: PRISMA 2009 Flow Diagram showing the identification and selection of article

Further, many markers like NPM1,[26] BNIP3,[27] HIF-1a,[27] USP22,[28] FAK,[29] H3K9me3,[30] podoplanin,[31,32] L1,[10] EN1,[33] Ezrin,[34] Cyr61,[35] EMMPRIN,[36] EZH2,[37] NF-KB,[38] iNOS,[38] galactin-3,[39] PCNA,[40] topo II,[41] MAGE-A,[42] TARP,[43] CK14,[44] CD133,[45] TACSTD2,[46] NM23[47] and LAT1[48] were shown to have a correlation with prognosis in terms of metastasis and patient survival. Since only a single study was done, it is difficult to evaluate the relevance of these markers as prognostic indicators.

Bazarsa *et al*.[5] showed that the low expression of Ataxia- Telangiectasia-Mutated protein, a cell cycle regulator, is related to a poor survival rate. Similar results were shown by Yi *et al*.[49] and Zhao *et al*.[50] in their studies, where reduced expression of E-cadherin and N-cadherin correlated with the metastatic progression of SACC. Decreased expression of PTEN,[29] H3K9Ac,[30] MT,[51] PDCD4,[52] beclin 1,[8] GRP78,[8,53] Numb,[54] p27,[55] and B-catenin,[11,12] p-Akt,[56] p-mTOR[56] and maspin[57,58] was also related to shorter overall survival; nevertheless, not many studies were conducted for the same to predict their prognostic significance.

Few studies showed that high expression of markers like c-kit,[59,60] EGFR,[59-62] and c-erbB[40,63] was related to unfavorable prognosis. However, other studies that evaluated the same markers did not demonstrate any correlation of these markers to prognosis. Bmi-1,[49,64] snail,[49,50] slug,[49,65] ILK,[29,50] and p63[57,66] markers were evaluated in two studies, each of which demonstrated their significant correlation with poor prognostic factors.

Other markers such as Ki-67, p53, VEGF, and cyclin D1, were repeatedly evaluated and showed reproducible results.

Analysis of Ki-67 as a prognostic marker

The expression of cell proliferation marker, Ki-67, was evaluated in 14 studies, of which 6 studies did not show any direct correlation with the prognosis of the tumor.[18,28,37,67-69] Wang *et al*.,[34] in 2011, showed that high expression of Ki-67 was significantly related to poor prognosis of ADCC ($P < 0.037$). Similar results were seen in studies conducted by Hirabayashi.[41] and Nordgård *et al*.[70] where statistically significant association was present between the expression of Ki-67 and short-term prognosis for patients with ACC. Kaira *et al*.[53] and Tang *et al*.[35] showed that high expression of Ki-67 was related to low 5-year overall survival rate (38.9% and 22%, respectively). Lin *et al*.[71] demonstrated that along with high expression of Ki-67, other factors like old age (>60), advanced tumor stage, and higher histologic grading of the tumor also contribute as predictors of poor prognosis of ADCC. Studies by Yang *et al*.[36] and Kaira *et al*.[48] demonstrated Ki-67 nuclear immunopositivity in ADCC and its higher expression in the solid histotype, and both factors were shown to have a poor prognostic effect on the overall survival.

Analysis of p53 as a prognostic marker

The role of cell cycle regulatory protein, p53, in predicting the prognosis of ADCC was evaluated in 6 studies. Out of these six studies, two studies by Kiyoshima *et al*.[68] and Nagler *et al*.[14] did not show any correlation between the expression of p53 and prognosis. A study by Bazarsad *et al*.[5] showed that, though a positive expression of p53 was correlated with poor survival rate, it was not statistically significant. Jia *et al*.,[13] in a study on prognosis of apoptosis-associated markers in ADCC, showed that the positive expression of p53 and short-term survival of patients in ADCC had a statistically significant correlation along with a solid histologic pattern. Preisegger *et al*.[72] studied the immunohistochemical analysis along with mutation analysis of p53 and showed that p53 could be an independent marker for poor prognosis. Similar results were shown by Kaira *et al*.[48] in a study, where p53 expression was significantly associated with poor prognosis.

Analysis of vascular endothelial growth factor as a prognostic marker

VEGF promotes angiogenesis, hence plays a role in tumor growth and metastasis. Three studies evaluated the prognostic significance of VEGF in ADCC Lee *et al*.[59] found that there was no relationship between VEGF expression and survival rate, metastasis, or recurrence in ADCC. Inconsistent with the above-mentioned study, Yang *et al*.[36] and Zhang *et al*.[38] attributed VEGF expression to be one of the factors responsible for poor prognosis along with other factors like the clinical stage, histotype, vascular invasion, perineural invasion, metastasis, and recurrence.

Cyclin D1 as a prognostic marker

Cyclin D1, a cell cycle regulator protein, was evaluated in 3 studies for its prognostic significance. All these studies produced consistent results. Schneider *et al*.[11] and Zhou *et al*.[12] in their studies investigated the prognostic significance of cyclin D1, PIN1, and β-catenin in ADCC, and no significant association was seen between the expression of cyclin D1 and patient outcome. A study by Lin *et al*.[71] showed similar results where the expression of cyclin D1 was not correlated with prognosis.

Conclusion

Evaluation of prognostic factors for ADCC is important as recurrence, metastasis and a short disease-free duration is a common finding after resection. The prognostic factors evaluated in our study were recurrence, metastasis, and overall survival. The study showed that many researches correlated prognosis with the overall survival and not the disease-free survival; as a result, recurrence and presence of any residual tumor could have been missed. Amongst the various prognostic markers, the histologic tissue section represents the grade of the tumor more accurately, and immunohistochemistry is the best means known to assess the tissue and its contents. Although various IHC markers have been studied to predict the prognosis of ADCC, a few markers were used repeatedly for validation of their prognostic predictability. These markers were p53, Ki-67, VEGF, and cyclin D1. However, the results obtained were not homogenous and no conclusive data could be arrived upon. Other markers that displayed an impact on outcome need additional assessment since only a single study was done. Further, comprehensive researches are therefore required in this direction to enhance the prognostic assessment.

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Conflicts of interest

There are no conflicts of interest.

References

1. Bradley PJ. Adenoid cystic carcinoma of the head and neck: A review. Curr Opin Otolaryngol Head Neck Surg 2004;12:127-32.
2. Godge P, Sharma S, Yadav M. Adenoid cystic carcinoma of the parotid gland. Contemp Clin Dent 2012;3:223-6.
3. Dillon PM, Chakraborty S, Moskaluk CA, Joshi PJ, Thomas CY. Adenoid cystic carcinoma: A review of recent advances, molecular targets, and clinical trials. Head Neck 2016;38:620-7.
4. Li Q, Huang P, Zheng C, Wang J, Ge M. Prognostic significance of p53 immunohistochemical expression in adenoid cystic carcinoma of the salivary glands: A meta-analysis. Oncotarget 2017;8:29458-73.
5. Bazarsad S, Kim JY, Zhang X, Kim KY, Lee DY, Ryu MH, *et al*. Ataxia-telangiectasia-mutated protein expression as a prognostic marker in adenoid cystic carcinoma of the salivary glands. Yonsei Med J 2018;59:717-26.
6. Thierauf J, Veit JA, Grünow J, Döscher J, Weißinger S, Whiteside T, *et al*. Expression of submaxillary gland androgen-regulated protein 3A (SMR3A) in adenoid cystic carcinoma of the head and neck. Anticancer Res 2016;36:611-5.
7. Bell D, Ferrarotto R, Fox MD, Roberts D, Hanna EY, Weber RS, *et al*. Analysis and significance of c-MET expression in adenoid cystic carcinoma of the salivary gland. Cancer Biol Ther 2015;16 Suppl 6:834-8.
8. Jiang L, Huang S, Li W, Zhang D, Zhang S, Zhang W, *et al*. Expression of autophagy and ER stress-related proteins in primary salivary adenoid cystic carcinoma. Pathol Res Pract 2012;208:635-41.
9. Zhou JH, Hanna EY, Roberts D, Weber RS, Bell D. ALDH1 immunohistochemical expression and its significance in salivary adenoid cystic carcinoma. Head Neck 2013;35:575-8.
10. Dahl A, Teegen J, Altevogt P, Löning T, Schumacher U. Glycoconjugate expression in adenoid cystic carcinoma of the salivary glands: Up-regulation of L1 predicts fatal prognosis. Histopathology 2011;59:299-307.
11. Schneider S, Thurnher D, Seemann R, Brunner M, Kadletz L, Ghanim B. The prognostic significance of b-catenin, cyclin D1 and PIN1 in minor salivary gland carcinoma: B-catenin predicts overall survival. Eur Arch Otorhinolaryngol 2015;273 Suppl 5:1283-92.

12. Zhou CX, Gao Y. Aberrant expression of ß-catenin, Pin1 and cylin D1 in salivary adenoid cystic carcinoma: Relation to tumor proliferation and metastasis. Oncol Rep 2006;16:505-11.
13. Jia L, Esguerra RL, Tang X, Yin H, Sakamoto K, Okada N, *et al*. Prognostic value of apoptosis and apoptosis-associated proteins in salivary gland adenoid cystic carcinoma. Pathol Int 2004;54:217-23.
14. Nagler RM, Kerner H, Ben-Eliezer S, Minkov I, Ben-Itzhak O. Prognostic role of apoptotic, Bcl-2, c-erbB-2 and p53 tumor markers in salivary gland malignancies. Oncology 2003;64:389-98.
15. Costa AF, Tasso MG, Mariano FV, Soares AB, Chone CT, Crespo AN, *et al*. Levels and patterns of expression of hypoxia-inducible factor-1a, vascular endothelial growth factor, glucose transporter-1 and CD105 in adenoid cystic carcinomas with high-grade transformation. Histopathology 2012;60 Suppl 5:816-25.
16. Shintani S, Alcalde RE, Matsumura T, Terakado N. Extracellular matrices expression in invasion area of adenoid cystic carcinoma of salivary glands. Cancer Lett 1997;116:9-14.
17. Faur AC, Lazar E, Cornianu M. Vascular endothelial growth factor (VEGF) expression and microvascular density in salivary gland tumours. APMIS 2014;122:418-26.
18. Ashkavandi ZJ, Najvani AD, Tadbir AA, Pardis S, Ranjbar MA, Ashraf MJ. MCM3 as a novel diagnostic marker in benign and malignant salivary gland tumors. Asian Pacific J Cancer Prev 2013;14 Suppl 6:3479-82.
19. Andisheh-Tadbir A, Ashraf MJ, Khademi B, Ahmadi S. Clinical implication of CD166 expression in salivary gland tumor. Tumour Biol 2015;36:2793-9.
20. Huang CF, Deng WW, Zhang L, Zhang WF, Sun ZJ. Expression of LC3, LAMP2, KEAP1 and NRF2 in salivary adenoid cystic carcinoma. Pathol Oncol Res 2015;22 Suppl 1:109-14.
21. Li H, Liao X, Liu Y, Shen Z, Gan X, Li H, *et al*. The expression of MACC1 and its role in the proliferation and apoptosis of salivary adenoid cystic carcinoma. J Oral Pathol Med 2015;44:810-7.
22. Shao Z, Zhu F, Song K, Zhang HZ, Liu K, Shang Z. EphA2/EphrinA1 mRNA expression and protein production in adenoid cystic carcinoma of salivary gland. J Oral Maxillofac Surg 2013;71:869-78.
23. Shang J, Sheng L, Wang K, Shui Y, Wei Q. Expression of neural cell adhesion molecule in salivary adenoid cystic carcinoma and its correlation with perineural invasion. Oncol Rep 2007;18:1413-6.
24. Xia RH, Wang Z, Zhang CY, Hu YH, Zhou RR, Wang LZ, *et al*. Low expression of endothelial receptor B (EDNRB) is related to H3K9me3 binding with the EDNRB promoter region and is associated with the clinical T tumor stage in salivary adenoid cystic carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol 2015;120 Suppl 2:258-68.
25. Dos Santos HT, Silva RN, Piña AR, de Souza do Nascimento J, de Almeida OP, Egal ES, *et al*. Lipid droplets are involved in the process of high-grade transformation of adenoid cystic carcinoma. Histopathology 2016;69:160-2.
26. Li S, Zhang X, Zhou Z, Huang Z, Liu L, Huang Z. Downregulation of nucleophosmin expression inhibited proliferation and induced apoptosis in salivary gland adenoid cystic carcinoma. J Oral Pathol Med 2017;46:175-81.
27. Chen Z, Wu H, Huang S, Li W, Zhang S, Zheng P, *et al*. Expression of BNIP3 and its correlations to hypoxia-induced autophagy and clinicopathological features in salivary adenoid cystic carcinoma. Cancer Biomark 2015;15:467-75.
28. Dai W, Yao Y, Zhou Q, Sun CF. Ubiquitin-specific peptidase 22, a histone deubiquitinating enzyme, is a novel poor prognostic factor for salivary adenoid cystic carcinoma. PLoS One 2014;9:e87148.
29. Chen D, Zhang B, Kang J, Ma X, Lu Y, Gong L. Expression and clinical significance of FAK, ILK, and PTEN in salivary adenoid cystic carcinoma. Acta Otolaryngol 2013;133:203-8.
30. Xia R, Zhou R, Tian Z, Zhang C, Wang L, Hu Y, *et al*. High expression of H3K9me3 is a strong predictor of poor survival in patients with salivary adenoid cystic carcinoma. Arch Pathol Lab Med 2013;137:1761-9.
31. Salzman R, Stárek I, Kučerová L, Skálová A. Differing Lymphatic Vessels Density in Salivary Adenoid Cystic Carcinoma and Pleomorphic Adenoma. Pathol Oncol Res 2017;23:545-50.
32. Wu HM, Ren GX, Wang LZ, Zhang CY, Chen WT, Guo W. Expression of podoplanin in salivary gland adenoid cystic carcinoma and its association with distant metastasis and clinical outcomes. Mol Med Rep 2012;6:271-4.
33. Bell D, Bell A, Roberts D, Weber RS, El-Naggar AK. Developmental transcription factor EN1--a novel biomarker in human salivary gland adenoid cystic carcinoma. Cancer 2012;118:1288-92.
34. Wang YY, Chen WL, Huang ZQ, Yang ZH, Zhang B, Wang JG, *et al*. Expression of the membrane-cytoskeletal linker Ezrin in salivary gland adenoid cystic carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:96-104.
35. Tang QL, Fan S, Li HG, Chen WL, Shen XM, Yuan XP, *et al*. Expression of Cyr61 in primary salivary adenoid cystic carcinoma and its relation to Ki-67 and prognosis. Oral Oncol 2011;47:365-70.
36. Yang X, Dai J, Li T, Zhang P, Ma Q, Li Y, *et al*. Expression of EMMPRIN in adenoid cystic carcinoma of salivary glands: Correlation with tumor progression and patients' prognosis. Oral Oncol 2010;46:755-60.
37. Vékony H, Raaphorst FM, Otte AP, van Lohuizen M, Leemans CR, van der Waal I, *et al*. High expression of Polycomb group protein EZH2 predicts poor survival in salivary gland adenoid cystic carcinoma. J Clin Pathol 2008;61:744-9.
38. Zhang J, Peng B, Chen X. Expressions of nuclear Factor KB, inducible nitric oxide synthase, and vascular endothelial growth factor in adenoid cystic carcinoma of salivary glands: Correlations with the angiogenesis and clinical outcome. Clin Cancer Res 2005;11 Suppl 20:7334-43.
39. Teymoortash A, Pientka A, Schrader C, Tiemann M, Werner JA. Expression of galectin-3 in adenoid cystic carcinoma of the head and neck and its relationship with distant metastasis. J Cancer Res Clin Oncol 2006;132:51-6.
40. Cho KJ, Lee SS, Lee YS. Proliferating cell nuclear antigen and c-erbB-2 oncoprotein expression in adenoid cystic carcinomas of the salivary glands. Head Neck 1999;21:414-9.
41. Hirabayashi S. Immunohistochemical detection of DNA topoisomerase type II alpha and Ki-67 in adenoid cystic carcinoma and pleomorphic adenoma of the salivary gland. J Oral Pathol Med 1999;28:131-6.
42. Beppu S, Ito Y, Fujji K, Saida K, Takino H, Masaki A, *et al*. Cancer-testis antigens in salivary gland cancers. Histopathology 2017;71 Suppl 2:305-15.
43. Yue H, Cai Y, Song Y, Meng L, Chen X, Wang M, *et al*. Elevated TARP promotes proliferation and metastasis of salivary adenoid cystic carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol 2017;123:468-76.
44. Gao XL, Wu JS, Cao MX, Gao SY, Cen X, Jiang YP, *et al*.

Cytokeratin-14 contributes to collective invasion of salivary adenoid cystic carcinoma. PLoS One 2017;12:e0171341.
45. Wang SS, Gao XL, Liu X, Gao SY, Fan YL, Jiang YP, *et al*. CD133+ cancer stem-like cells promote migration and invasion of salivary adenoid cystic carcinoma by inducing vasculogenic mimicry formation. Oncotarget 2016;7:29051-62.
46. Xia Y, Li B, Gao N, Xia H, Men Y, Liu Y, *et al*. Expression of tumor-associated calcium signal transducer 2 in patients with salivary adenoid cystic carcinoma: Correlation with clinicopathological features and prognosis. Oncol Lett 2014;8:1670-4.
47. do Nascimento KC, de Faria PR, Dib LL, Ferreira de Aguiar MC, Cardoso SV, Chen J, *et al*. Immunohistochemical localization of the NM23 protein in salivary gland neoplasms with distinct biological behavior. Virchows Arch 2006;449:660-6.
48. Kaira K, Toyoda M, Shino M, Sakakura K, Takahashi K, Tominaga H, *et al*. Clinicopathological significance of L-type amino acid transporter 1 (LAT1) expression in patients with adenoid cystic carcinoma. Pathol Oncol Res 2013;19:649-56.
49. Yi C, Li BB, Zhou CX. Bmi-1 expression predicts prognosis in salivary adenoid cystic carcinoma and correlates with epithelial-mesenchymal transition-related factors. Ann Diagn Pathol 2016;22:38-44.
50. Zhao D, Yang K, Tang XF, Lin NN, Liu JY. Expression of integrin-linked kinase in adenoid cystic carcinoma of salivary glands correlates with epithelial-mesenchymal transition markers and tumor progression. Med Oncol 2013;30:619.
51. Brazão-Silva MT, Cardoso SV, de Faria PR, Dias FL, Lima RA, Eisenberg AL, *et al*. Adenoid cystic carcinoma of the salivary gland: A clinicopathological study of 49 cases and of metallothionein expression with regard to tumour behaviour. Histopathology 2013;63:802-9.
52. Qi C, Shao Y, Li N, Zhang C, Zhao M, Gao F. Prognostic significance of PDCD4 expression in human salivary adenoid cystic carcinoma. Med Oncol 2013;30:491.
53. Kaira K, Toyoda M, Shimizu A, Shino M, Sakakura K, Takayasu Y, *et al*. Expression of ER stress markers (GRP78/BiP and PERK) in adenoid cystic carcinoma. Acta Otolaryngol 2016;136:1-7.
54. Maiorano E, Favia G, Pece S, Resta L, Maisonneuve P, Di Fiore PP, *et al*. Prognostic implications of NUMB immunoreactivity in salivary gland carcinomas. Int J Immunopathol Pharmacol 2007;20:779-89.
55. Takata T, Kudo Y, Zhao M, Ogawa I, Miyauchi M, Sato S, *et al*. Reduced expression of p27(Kip1) protein in relation to salivary adenoid cystic carcinoma metastasis. Cancer 1999;86:928-35.
56. Ouyang DQ, Liang LZ, Ke ZF, Zheng GS, Weng DS, Yang WF, *et al*. Association between high expression of phosphorylated Akt and mammalian target of rapamycin and improved survival in salivary gland adenoid cystic carcinoma. Head Neck 2017;39:1145-54.
57. Taghavi N, Khozestani PK, Yazdani F, Baghban AA. Prognostic value of P63, Maspin, and MMP-2 expressionin salivary gland adenoid cystic carcinoma. Int J Cancer Manag 2018;11 Suppl 2:E7564.
58. Schwarz S, Ettl T, Kleinsasser N, Hartmann A, Reichert TE, Driemel O. Loss of Maspin expression is a negative prognostic factor in common salivary gland tumors. Oral Oncol 2008;44:563-70.
59. Lee SK, Kwon MS, Lee YS, Choi SH, Kim SY, Cho KJ, *et al*. Prognostic value of expression of molecular markers in adenoid cystic cancer of the salivary glands compared with lymph node metastasis: A retrospective study. World J Surg Oncol 2012;10:266.
60. Bell D, Roberts D, Kies M, Rao P, Weber RS, El-Naggar AK. Cell type-dependent biomarker expression in adenoid cystic carcinoma: Biologic and therapeutic implications. Cancer 2010;116:5749-56.
61. Schneider T, Strehl A, Linz C, Brands R, Hartmann S, Beckford F, *et al*. Phosphorylated epidermal growth factor receptor expression and KRAS mutation status in salivary gland carcinomas. Clin Oral Investig 2016;20:541-51.
62. Vered M, Braunstein E, Buchner A. Immunohistochemical study of epidermal growth factor receptor in adenoid cystic carcinoma of salivary gland origin. Head Neck 2002;24:632-6.
63. Kärjä V, Syrjänen S, Kataja V, Syrjänen K. c-erbB-2 oncogene expression in salivary gland tumours. ORL J Otorhinolaryngol Relat Spec 1994;56:206-12.
64. Chang B, Li S, He Q, Liu Z, Zhao L, Zhao T, *et al*. Deregulation of Bmi-1 is associated with enhanced migration, invasion and poor prognosis in salivary adenoid cystic carcinoma. Biochim Biophys Acta 2014;1840:3285-91.
65. Tang Y, Liang X, Zhu G, Zheng M, Yang J, Chen Y. Expression and importance of zinc-finger transcription factor Slug in adenoid cystic carcinoma of salivary gland. J Oral Pathol Med 2010;39:775-80.
66. Ramer N, Wu H, Sabo E, Ramer Y, Emanuel P, Orta L, *et al*. Prognostic value of quantitative p63 immunostaining in adenoid cystic carcinoma of salivary gland assessed by computerized image analysis. Cancer 2010;116:77-83.
67. Tadbir AA, Pardis S, Ashkavandi ZJ, Najvani AD, Ashraf MJ, Taheri A, *et al*. Expression of Ki67 and CD105 as proliferation and angiogenesis markers in salivary gland tumors. Asian Pac J Cancer Prev 2012;13:5155-9.
68. Kiyoshima T, Shima K, Kobayashi I, Matsuo K, Okamura K, Komatsu S, *et al*. Expression of p53 tumor suppressor gene in adenoid cystic and mucoepidermoid carcinomas of the salivary glands. Oral Oncol 2001;37:315-22.
69. Norberg-Spaak L, Dardick I, Ledin T. Adenoid cystic carcinoma: Use of cell proliferation, BCL-2 expression, histologic grade, and clinical stage as predictors of clinical outcome. Head Neck 2000;22:489-97.
70. Nordgård S, Franzén G, Boysen M, Halvorsen TB. Ki-67 as a prognostic marker in adenoid cystic carcinoma assessed with the monoclonal antibody MIB1 in paraffin sections. Laryngoscope 1997;107:531-6.
71. Lin YC, Chen KC, Lin CH, Kuo KT, Ko JY, Hong RL. Clinicopathologic features of salivary and non-salivary adenoid cystic carcinomas. Int J Oral Maxillofac Surg 2012;41:354-60.
72. Preisegger KH, Beham A, Kopp S, Jessernigg G, Gugl A, Stammberger H. Prognostic impact of molecular analyses in adenoid cystic carcinomas of the salivary gland. Onkologie 2001;24:273-7.