Invited Review

Diagnostic reliability of c-KIT (CD117) in salivary gland tumours – A systematic review and meta-analysis

Gopikrishnan Vijayakumar, Mala Kamboj, Anjali Narwal, Gitika Sharma

Department of Oral Maxillofacial Pathology and Microbiology, Post Graduate Institute of Dental Sciences, Pandit Bhagwat Dayal Sharma University of Health Sciences, Rohtak, Haryana, India

Abstract

c-KIT is an important diagnostic marker in salivary gland tumours and is expressed in most adenoid cystic carcinomas. Histologically similar salivary gland tumours with variable immunohistochemical expression for c-KIT pose a challenge and make diagnostic reliability ambivalent. An electronic search was performed in MEDLINE by PubMed, Google Scholar, Scopus, Trip, Cochrane Library, and EMBASE up to 31 December 2023, without period restriction. The articles that investigated CD117 or c-KIT in salivary gland tumours were included for review. Sensitivity, specificity, and positive and negative predictive values of c-KIT immunohistochemical expressions were derived and subjected to meta-analysis using Open Meta analyst for Sierra software. The risk of bias in selected studies was analysed using the QUADAS-2 tool, and RevMan 5.4 was used to output the result. Forty-three articles were reviewed, and 2285 salivary gland cases were analysed. Adenoid cystic carcinoma had an overall expression of 84.9%. A similar expression was found in epimyoepithelial carcinoma (79.1%), lymphoepithelial carcinoma (75%), myoepithelial carcinoma (60.8%), monomorphic adenoma (94.1%), and pleomorphic adenoma (74.7%). The sensitivity, specificity, and positive and negative predictive values of c-KIT/CD117 for adenoid cystic carcinoma with other salivary gland tumours were 84.99%, 69.09%, 84.79%, and 69.41%, respectively. Current evidence shows that c-KIT, despite its sensitivity, is not specific and therefore cannot be a useful diagnostic marker for distinguishing adenoid cystic carcinoma from other salivary gland tumours. Further research on other salivary gland tumours that exhibit comparable expression is necessary to validate the diagnostic accuracy of c-KIT.

Keywords: Adenoid cystic carcinoma, CD117, c-KIT, immunohistochemistry, polymorphous adenocarcinoma, salivary gland tumours

Address for correspondence: Dr. Mala Kamboj, Department of Oral Maxillofacial Pathology and Microbiology, Post Graduate Institute of Dental Sciences, Pandit Bhagwat Dayal Sharma University of Health Sciences, Rohtak - 124 001, Haryana, India.
E-mail: malskam@gmail.com

Submitted: 13-Mar-2024, **Accepted:** 18-Mar-2024, **Published:** 15-Apr-2024

INTRODUCTION

c-KIT, also known as CD117, is a tyrosine kinase receptor located on the long arm of chromosome 4. It plays a crucial role in various developmental processes including hematopoiesis, spermatogenesis, migration, and the development of germ cells and melanocytes.[1] This 145 to 165 kD proto-oncogene is structurally similar to the receptor for platelet-derived growth factor and

Access this article online

Quick Response Code:

Website: https://journals.lww.com/JPAT/

DOI: 10.4103/jomfp.jomfp_70_24

How to cite this article: Vijayakumar G, Kamboj M, Narwal A, Sharma G. Diagnostic reliability of c-KIT (CD117) in salivary gland tumours – A systematic review and meta-analysis. J Oral Maxillofac Pathol 2024;28:11-20.

colony-stimulating factor.[1-3] The receptor–ligand interaction, also known as steel, stem cell, or mast cell growth factor, promotes phosphorylation and activates signaling pathways such as phosphoinositide 3-kinase and mitogen-activated protein kinase. In normal human tissue, c-KIT is found in mammary epithelial cells, melanocytes, mast cells, and the interstitial Cajal cells. Overexpression of c-Kit has been observed in various tumours such as gastrointestinal stromal tumour (GIST), myeloid leukaemia, testicular germ cell tumour, endometrial carcinoma, papillary and follicular thyroid carcinoma, renal and hepatic angiomyolipoma, synovial sarcoma, osteosarcoma, and Ewing's sarcoma.[1-3]

The immunohistochemical expression of c-KIT in human salivary gland neoplasms is variable. Although characteristic histopathologic features remain the gold standard for diagnosis, histologically similar lesions and small biopsies with fewer tumour foci require the assistance of immunohistochemistry. Studies suggest that most adenoid cystic carcinomas (ACCs) show overexpression of c-KIT, making it a crucial marker for distinguishing it from other salivary gland tumours. Polymorphous adenocarcinoma (PAC) resembles ACC with similar infiltrating solid and cribriform patterns, the presence of cystic spaces, and neurotropism, increasing the diagnostic challenge.[1,4-9]

The sensitivity and specificity of c-KIT for the differentiation of salivary gland tumours are controversial as molecular studies have also reported different results. Therefore, there is doubt as to whether c-KIT plays a role in ACC oncogenesis and/or tumour maintenance.[3,10-18] KIT mutations, currently effective in targeted therapy of tumours such as GIST, have failed to reciprocate similar results in ACC. Reports of questionable therapeutic benefits and poor prognosis in ACC raise concerns about the role of c-KIT in salivary gland tumours.[19-24]

Therefore, this systematic review was designed to evaluate the immunohistochemical and molecular expression of c-KIT and its diagnostic reliability in salivary gland tumours.

MATERIAL AND METHODS

This study followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and was registered at the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42022339930).

Review question

Based on 'PICOS' (Population, Intervention, Comparison, Outcome, type of Studies), the review question was formulated as follows: "Does c-KIT/CD117 have significant diagnostic utility in the diagnosis of different salivary gland tumours?"

Strategy for identification of studies

An extensive literature search was performed in various databases like MEDLINE by PubMed, Google Scholar, Scopus, Trip, Cochrane Library, and EMBASE until 31 December 2023, without period restriction. The search strategy keywords were ALL ('Salivary gland tumour' OR 'Salivary gland lesion') AND ALL (CD117 OR c-KIT). The cross-references of the published articles were also searched for any article which fulfilled the inclusion criteria.

Eligibility criteria

Articles were included if they met at least one of the following criteria: (1) Complete original studies of salivary gland tumours and c-KIT/CD117 in English; (2) All studies of salivary gland tumours with any diagnostic method using c-KIT/CD117.

Article screening and eligibility evaluation

Two independent authors (GK and GS) screened the article titles and abstracts in the initial data pool for inclusion and exclusion in the study. The same authors did the eligibility evaluation by reading the full text and justifying the reasons for inclusion and exclusion. In case of any disagreements, the full text of the article was discussed and consulted with a third author in a consensus meeting (MK).

Study selection and data extraction

Data were extracted by one author (GK) and revised by the second (GS) to ensure content integrity. The data parameters were author(s), year of publication, type of salivary gland tumour, number of cases, demographic data, affected gland, diagnostic modality used, expression intensity and percentage of c-KIT/CD117, diagnostic results, sensitivity, specificity, and positive predictive and negative predictive values in case-control studies.

Summary measures, data synthesis, and analysis

The primary outcome of the review was the analysis of c-KIT/CD117 expression in salivary gland tumours. All extracted data parameters were tabulated and processed in Microsoft Excel (Microsoft Corporation. 2019). An Open Meta analyst for Sierra (10.12) software was used to conduct the meta-analysis. Pooled sensitivity, specificity, and diagnostic odds ratio (DOR) were calculated using a bivariate random-effects regression model. Forest plots

of each study and pooled estimates for sensitivity and specificity with 95% confidence intervals (95% CI) were presented. Heterogeneity between eligible studies was calculated by using inconsistency indices (IÇ); $I^2 > 50\%$ was considered an indicator of substantial heterogeneity.

Quality assessment

The Quality Assessment in Diagnostic Accuracy (QUADAS 2) tool was used to assess the risk of bias of the included original and/or diagnostic accuracy studies. The checklist items to assess risk bias and applicability concerns were patient selection, index test, reference standard, and flow and timing. Two reviewers (GK and AN) independently assessed the methodological quality of the included articles, and then a third author was consulted for arbitration (MK). The dedicated software Review Manager (RevMan v5.4, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to output the result of QUADAS 2.

RESULTS

Studies selection

The keyword search strategy in various scientific databases identified 471 articles published up to 31 December 2023. After removing duplicates, the data pool comprised 135 articles, which were further screened to 43 after examining the title and abstract and selected for suitability assessment, which was further assessed through full-text reading and risk assessment. The final selection included 43 articles for qualitative synthesis and 17 articles for meta-analysis [Figure 1].

Study characteristics

A total of 43 articles with 26 observational cross-sectional studies and 17 case-control studies were included in this review, reporting 2285 salivary gland cases distributed among 23 malignant and seven benign tumours and normal salivary gland tissue. Immunohistochemical data on c-KIT/CD117 were available for a total of 2133 cases, of which 1425 were positive and 708 were negative cases. ACC comprised the maximum (n = 1397), followed by mucoepidermoid carcinoma (MEC, n = 130) and PAC (n = 103) among the malignancies, while pleomorphic adenoma (PA, n = 94) followed by basal cell adenoma (BCA, n = 42) in the benign category [Table 1].

Demographic distribution of salivary gland lesions

Of the articles reviewed, only 30 provided details of tumour location and case demographics, while the remainder presented combined data as major or minor salivary glands. The parotid gland was found to be the most commonly studied major salivary gland (n = 280), followed by the submandibular (n = 113) and the sublingual (n = 9). Among the minor salivary glands, the glands on the palate (n = 133) were frequently studied, followed by paranasal sinuses (n = 91), lips (n = 24), buccal mucosa (n = 20), and others in the retromolar region, tongue, and cheek (n = 524). The study population had a mean age of 54.3 years (age range, 6 to 92 years) with a male-to-female ratio of 1:1.5.[1,3-8,13-17,25-44]

Expression of c-KIT/CD117 in malignant salivary gland tumours

The expression of c-KIT/CD117 revealed a similar expression in carcinoma ex pleomorphic adenoma,[11,33,37,44] epi-myoepithelial carcinoma,[2,13,26,37,44] basal cell adenocarcinoma,[2,13,25,27,36,44,45] and lymphoepithelial carcinoma in comparison to ACC.[2,11,27] While MEC,[2,6,11,13,25,27,37,40,43-46] acinic cell carcinoma,[2,11,13,25,27,28,40,45] salivary duct carcinoma,[2,11,13,25,27,37,44,45] adenocarcinoma NOS,[2,11,13,27,37,44,45] mammary analogue secretory carcinoma/secretory carcinoma,[40,41] sebaceous carcinoma,[25] and oncocytic carcinomas[2] had comparatively lower expression percentages. A single case of cystadenocarcinoma[27] and carcinosarcoma[2] were positive for c-KIT, yielding 100% positivity; this could be due to the small sample examined.

PAC, the histologic mimic of ACC, showed a percent positivity of only 48.5% (50 positive out of 103) when comparing c-KIT/CD117 expression, while in ACC cases, it was 84.9% (1093 positive out of 1286).[1,2,4-9,11,25,27,43] The percentage expression in each malignant salivary gland tumour is listed in Table 1.

Expression of c-KIT/CD117 in benign salivary gland tumours

The percentage expression of c-KIT/CD117 in benign salivary gland tumours is shown in Table 1. In the reviewed articles, 68 of 91 cases of PA were positive (positivity 74.7%)[2,8,25,43,44,46,47] and 27 of 36 Warthin's tumour (positivity 76%)[25,33,44,46] were positive for c-KIT/CD117. However, two articles reported 100% positivity in PA cases.[2,47] c-KIT expression in monomorphic adenomas, canalicular adenoma (7 CA), and basal cell adenomas (10 BCA) was 94.1%, whereas it was 45% positive for BCA alone.[1,2,25,36,39,40,44] Interestingly, an article on sialadenitis also found 100% positivity.[2]

c-KIT/CD117 expression in malignant versus benign salivary gland tumours

The sensitivity, specificity, and positive predictive and negative predictive values of c-KIT/CD117 for distinguishing between a benign and a malignant salivary gland tumour were 67.14%, 32.32%, 90.58%, and 9.21%, respectively. The positive expression in the malignant and benign groups was 67.1% and 67.6%, respectively.

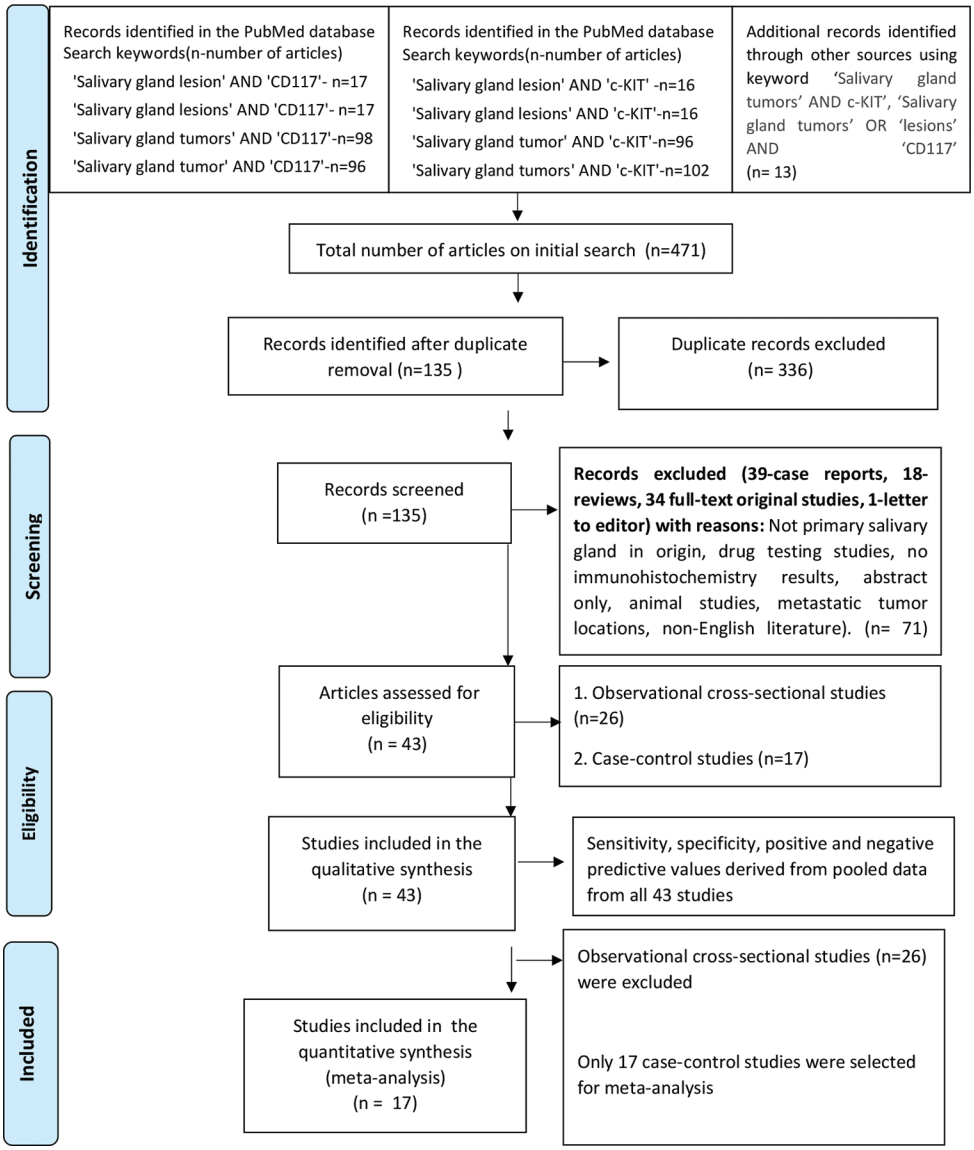

Figure 1: Flowchart of study selection adapted from PRISMA

Expression of c-KIT/CD117 in normal salivary gland tissue

The normal internal control salivary gland tissues were negative overall, while two of the 15 normal salivary gland control tissues were positive for c-KIT/CD117 (positivity 13.3%).[29,43]

Expression of c-KIT/CD117 in histological variants of adenoid cystic carcinoma

When sub-categorizing the expression of c-KIT into different histological variants of ACC, namely, solid, cribriform, and tubular, 13 articles were found. The solid form showed maximum positivity (90.4%), followed by tubular (88.3%) and cribriform (85.9%), while the combined tubular and cribriform histological patterns showed 87.1% positivity.[4,7,11,12,14-17,29,30,31,48,49] Two articles on ACC with high-grade transformation showed (8/8) 100% positivity with strong immunohistochemical expression of c-KIT [Table 2].

Molecular analysis of c-KIT/CD 117 positive adenoid cystic carcinoma cases

From the reviewed literature, 11 articles on ACC[3,10-18] and a single article each on SDC and acinic cell carcinoma[28] contained data on molecular analysis of c-KIT mutations. The most common c-KIT mutations in ACC were missense point and silent point mutations. They were mainly examined on exons 9, 11, 13, and 17, which were considered similar to other tumours with proven KIT oncogene mutations. Twenty-two ACC cases had missense (7 in exon 9, 8 in exon 11, 4 in exon 13 and 3 in exon 17) and 11 cases had silent point mutations (2 in exon 9, one in exon 11, three in exon 13, missing in exon 17 and 5 unclassified cases) [Table 3]. The c-KIT mutations were negative for SDC, while no data on Kit mutations in acinic cell carcinoma were presented.[28]

Table 1: Distribution of salivary gland lesions with immunohistochemical analysis on c-KIT/CD117

Salivary gland neoplasms/lesions	Total cases	Cases with IHC results	Positive cKIT/CD117	Negative cKIT/CD117	Percentage positivity
Adenoid cystic carcinoma	1397	1286	1093	193	84.9
Mucoepidermoid carcinoma	130	113	18	95	15.9
Polymorphous adenocarcinoma	103	103	50	53	48.5
Acinic cell carcinoma	99	87	20	67	22.9
Adenocarcinoma NOS	52	51	9	42	17.6
Salivary duct carcinoma	48	48	3	45	6.25
Carcinoma ex pleomorphic adenoma	49	49	29	20	59.1
Mammary analogue secretory carcinoma	34	34	8	26	23.5
Epi-myoepithelial carcinoma	24	24	19	5	79.1
Myoepithelial carcinoma	23	23	14	9	60.8
Basal cell adenocarcinoma	27	24	6	18	25
Squamous cell carcinoma	13	13	2	11	15.3
Basal cell carcinoma	11	11	0	11	0
Lymphoepithelial carcinoma	12	12	9	3	75
Adenosquamous carcinoma	5	5	1	4	20
Basaloid squamous cell carcinoma	6	6	3	3	50
Sebaceous carcinoma	6	6	1	5	16.6
Poorly differentiated carcinoma	5	5	0	5	0
Oncocytic carcinoma	4	4	1	3	25
Cystadenocarcinoma	1	1	1	0	100
Undifferentiated carcinoma	3	3	1	2	33.3
Carcinosarcoma	1	1	1	0	100
Malignant mixed tumour	11	11	0	11	0
Pleomorphic adenoma	94	91	68	23	74.7
Basal cell adenoma	42	40	18	22	45
Warthin tumour	39	36	27	9	75
Monomorphic (CA, BCA) adenoma	17	17	16	1	94.11
Oncocytoma	7	7	0	7	0
Sialadenitis	5	5	5	0	100
Myoepithelioma	2	2	0	2	0
Normal Salivary gland	15	15	2	13	13.3
43 articles, 30 salivary gland lesions	2285	2133	1425	708	

IHC: immunohistochemistry; CA: canalicular adenoma; BCA: basal cell adenoma

Sensitivity, specificity, and positive predictive value and negative predictive value of c-KIT/CD117 from case-control studies

When evaluating the case-control studies, the sensitivity percentage for distinguishing ACC from other malignant salivary gland tumours was in the range of 82.92–86.90%, the specificity was 65.33–72.67%, the positive predictive value was 83.20–86.26%, and the negative predictive value was 66.36–72.30%, while the combined average values were 84.99%, 69.09%, 84.79%, and 69.41%, respectively. The average sensitivity, specificity, and positive and negative predictive values of c-KIT/CD117 for distinguishing PAC from other malignant salivary gland tumours were 48.54%, 31.81%, 3.88%, and 91.60%, while between ACC and PAC, it was 84.99% 51.46%, 95.63%, and 21.54%, respectively [Table 4].

Quality Assessment (risk of bias and applicability concern)

Based on the QUADAS-2 tool, of 43 original studies (17 case-control and 26 cross-sectional), 27 achieved low risk, while 16 had a high risk of bias across all domains [Figure 2]. Seven studies were considered as high risk in patient selection, and all were low risk in the index test domain. One study each had a high and unclear risk in the reference standard, while seven had a high and two an unclear risk in the flow and timing domains. Seven studies were high risk in patient selection, all were low risk in index testing, and one each was high and unclear risk in the reference standard for applicability [Figure 2].

Meta-analysis

Seventeen case-control studies were included for meta-analysis [Table 3], and the pooled sensitivity and specificity of c-KIT/CD117 in predicting adenoid cystic carcinoma were 0.85 (95% CI: 0.78 ± 0.90) and 0.63 (95% CI: 0.48 ± 0.76) [Figure 3]. The positive and negative odds ratios were 2.40 (95% CI, 1.76 ± 3.27) and 0.22 (95% CI, 0.13 ± 0.38), respectively. The summary diagnostic odds ratio (DOR) was 13.17 (95% CI: 5.82 ± 29.81). There was also significant heterogeneity between the studies (I^2 = 70.48%, P = <0.001) [Figure 3].

DISCUSSION

The role of cKIT immunohistochemical expression, mutations, and subsequent targeted therapy in salivary

Table 2: Expression of c-KIT/CD117 in histological grades of adenoid cystic carcinoma

Staining intensity Grading	Histological grades of adenoid cystic carcinoma				
	Tubular	Cribriform	Combined Tubular/cribriform	Solid	Total
Negative	14	38	13	11	76
Weak	6	33	5	8	52
Moderate	16	16	1	8	41
Strong	6	15	10	18	49
Positive cases (without any staining intensity grading)	78	169	72	70	389
Total positive (Positivity percentage)	106 (88.3%)	233 (85.9%)	88 (87.1%)	104 (90.4%)	531
Total cases (*n*)	120	271	101	115	607

Table 3: Studies and inference of molecular analysis in c-KIT/CD117 positive adenoid cystic carcinoma

Author/Year	Molecular Method	IHC inference	Location	Inference
Holst *et al.*/1999[10]	PCR	27/30 of ACC (90% positive)	Exon 11,17	Negative for any gene mutation
Jeng *et al.*/2000[11]	PCR	20/25 of ACC (90% positive)	Exon 11, 17	Negative for any gene mutation
Freier *et al.*/2005[12]	FISH	49/55 of ACC (89% positive)	Bacterial artificial chromosome clone RP11-586A2	copy gain – (3/49 cases) (2-tubular, 1 cribriform)
Sørensen *et al.*/2006[13]	PCR	12/13 of ACC (92%positive)	codon 816	Negative for any gene mutation
Sato *et al.*/2007[30]	PCR	1/1 of SDC (100%positive)	exons 9, 11, 13 and 17	Negative for any gene mutation
Vila *et al.*/2009[14]	PCR, DNA sequencing	14/14 of ACC (100% positive)	exon 9,11,13,17	c-KIT missense point mutations (7 cases)- seven in exon 11, two in exon 9, two in exon 13, and two in exon 17. c-KIT silent point mutations (5 cases)- eight silent point mutations detected Missense mutations in more than one exon (2 cases) Mutations seen similar to GIST- Pro551Leu and Lys558Glu (5' end of exon 11), Leu576Phe (3' end of exon 11), Val643Ala (exon 13) and Asn822Ser (exon 17)
Sequeiros-Santiago *et al.*/2009[15]	PCR	12/21 of ACC (57% positive)	Exon 2	Gene Amplification ERBB1 (67%), CCND1 (46%), PIK3CA (38%), MYC,(9%), KIT (5%), MDM2 (0%)
Bell *et al.*/2010[16]	FISH	132/157 84% cases positive	-	c-KIT gain mutation 13/27 cases (10/16 cribriform, 2/6 tubular, 1/5 solid). c-KIT amplification (1/27 case) (cribriform) Normal signal (13/27) cases (6 cribriform, 4 solid and one tubular).
Tetsu *et al.*/2010[17]	PCR, WB	15/17 of ACC (88% positive)	Exons 9,11,13 and 17.Codon 664/796	2/17 cases-had mutation in nt 1990G→A in exon 13 and nt2386A→G in exon 17 Codon 664/796 mutation seen
Sung *et al.*/2012[3]	FISH	22/33 (66.7%) cases positive	exons 9, 11, 13, and 17	c-KIT missense and silent point mutations (9/33 cases) c-KIT missense point mutations (5/13 cases) five in exon 9, one in exon 11, and one in exon 13 Silent point mutations (4/33 cases) two in exon 9, one in exon 11 and three mutations in exon 13. No mutation was noted in exon 17.
Tang *et al.*/2014[18]	Cell lines, WB, rt-PCR, cell proliferation, wound healing assay, Mammosphere, flow cytometry, Luciferase assay, IHC, Xenograft mouse	108/121 (89.26%) cases positive		Ectopic overexpression of c-kit in ACC cell lines is sufficient for acquisition of mesenchymal traits, enhanced cell invasion. c-kit cooperated with oncogenic Ras to promote tumorigenesis *in vivo*. c-kit was abnormally overexpressed and correlated with the prognosis of ACC.

PCR: Polymerase chain reaction; WB: Western blot; FISH: Fluorescent *in situ* hybridisation; IHC: Immunohistochemistry; ACC: Adenoid cystic carcinoma

gland tumours remains unclear. Although it is considered a diagnostic marker for ACC, benign and malignant histological mimickers like PAC, small biopsies of canalicular adenoma, and even PAs still pose a problem in its diagnosis.[4]

The studies that compared the immunohistochemical expression of c-KIT/CD117 to differentiate benign and malignant salivary gland tumours yielded different results.[1,2,5,26,36,40,43,44,46,47] In the present review, comparable expression of c-KIT/CD117 was observed in various benign and malignant tumours, proving that c-KIT is an unimportant marker for the differentiation of tumours such as PA,[1,2,8,25,43,44,46,47] CA, BCAs,[2,25,36,39,40,44] and other histologically similar monomorphic adenomas,[1] particularly

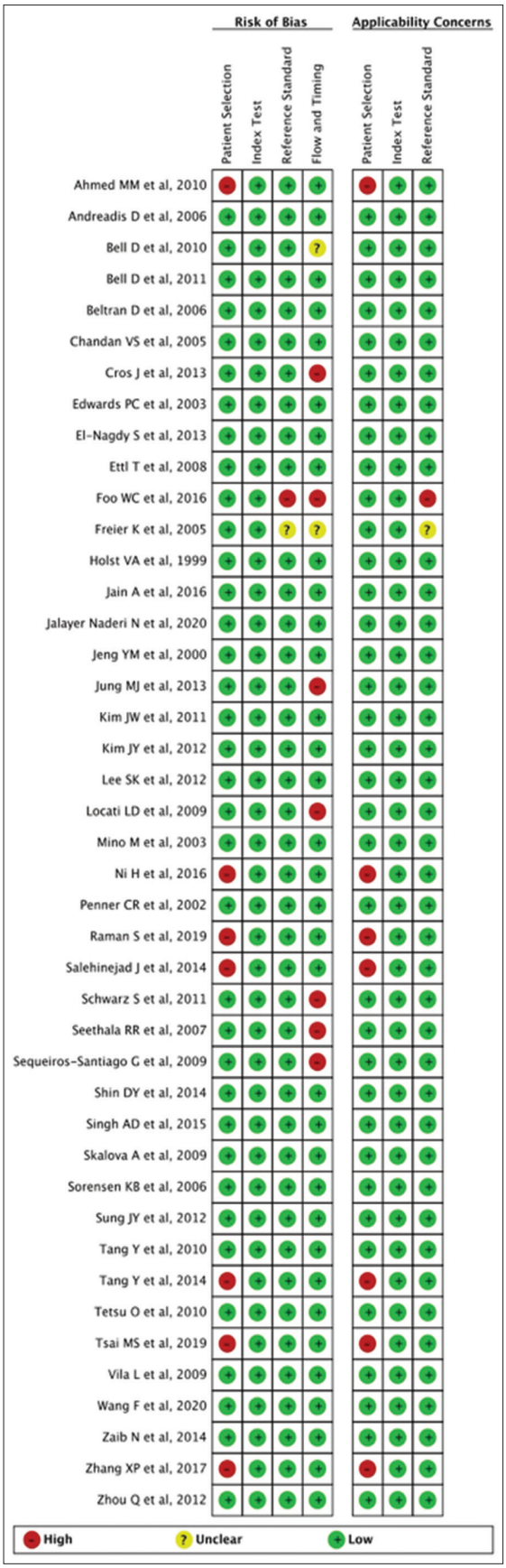

Figure 2: Quality Assessment- Risk of bias and applicability concern of included studies

in small biopsies with less evidence of characteristic histological features.

The diagnostic reliability of c-KIT could be assessed using sensitivity, specificity, and positive and negative predictive values. In individual case-control studies on ACC compared with other salivary gland tumours,[1,2,4-9.11,13,25,27,37,43-45,47] the lowest reported sensitivity was 36.6%, in a study by Foo *et al*.[44] The positive predictive value was the least in a study by Andreadis *et al*.,[2] whereas specificity was nil in a study by Chandan *et al*.[47] and 5.8% in Edwards PC *et al*.'s study.[1] The overall sensitivity, positive predictive value, specificity, and negative predictive values of c-KIT demonstrate that it is an unreliable marker for distinguishing ACC from other malignant salivary gland tumours [Table 3]. The sensitivity of c-KIT was higher in ACC than in PAC but less specific, again highlighting its unreliability. Certain salivary gland tumours such as epimyoepithelial carcinoma, basal cell adenocarcinoma, lymphoepithelial carcinoma, Warthin's tumour, and undifferentiated carcinomas had comparable percentage expression to ACC. However, the smaller number of cases analysed calls into question the meaning of this expression.

Faulty protein expression is the reflection of a genetic mutation. Therefore, the molecular analysis found consistent c-KIT mutations in exons 9, 11, 13, and 17 in GIST, exon 17 (codon 816), and exon 11 in systemic mastocytosis in adults. Furthermore, treatment with c-KIT inhibitors proved successful in GIST but not in systemic mastocytosis in adults. The same exon mutations gave inconsistent results when analysed in ACC, reinforcing the unreliability of the KIT mutations in ACC. Also, c-KIT-positive ACC with these mutations of exons and codons showed a variable therapeutic response.[19-24] One could conclude that such variability is due to either missing exon during molecular detection of c-KIT-positive ACC or the questionable connection of c-KIT with its pathogenesis.

Multilevel disparity of c-KIT/CD117 in salivary gland tumours was observed from functioning as a diagnostic marker of protein expression to uniform molecular expression levels. The meta-analyses conducted summarised 17 case-control studies with 361 ACC and 699 control cases. The pooled sensitivity of c-KIT/CD117 was satisfactory in predicting salivary gland ACC, whereas the pooled specificity was limited [Figure 3]. This suggests that c-KIT/CD 117 cannot be considered a reliable diagnostic marker for distinguishing ACC from other salivary gland tumours.

However, the smaller number of other salivary gland tumours analysed with c-KIT/CD117 reduces the

Table 4: Sensitivity, specificity, positive predictive value and negative predictive value of c-KIT/CD117 to distinguish adenoid cystic carcinoma and polymorphous adenocarcinoma from other salivary gland lesions

	No of Test cases (ACC) (P/T)*	No of Control cases (other tumors) (P/T)*	Sensitivity (%) (95% CI#)	Specificity (%) (95% CI#)	Positive Predictive value (%) (95% CI#)	Negative Predictive value (%) (95% CI#)
ACC v/s other malignant salivary gland tumors Case-control studies						
Jeng YM, 2000[11]	20/25	8/54	80	85	71.4	90.1
Penner CR, 2002[4]	9/9	8/14	100	42.8	52.9	100
Edwards PC, 2003[1]	15/15	32/34	100	5.8	31.9	100
Mino M, 2003[25]	62/66	16/98	93.9	83.6	79.4	95.3
Chandan VS, 2004[47]	10/10	15/15	100	0	60	0
Andreadis D, 2006[2]	11/14	59/84	78.5	29.7	15.7	89.2
Sørensen KB, 2006[13]	12/13	6/60	92.3	90	66.6	98.1
Beltran D, 2006[5]	12/12	2/10	100	80	85.7	100
Ettl T, 2008[27]	23/25	32/76	92	57.8	41.8	95.6
Locati LD, 2009[45]	42/54	5/61	77.7	91.8	89.3	82.3
Schwarz S, 2011[6]	12/14	0/8	85.7	100	100	80
Cros J, 2013[37]	34/37	21/70	91.8	70	61.8	94.2
El-Nagdy S, 2013[7]	12/12	2/8	100	75	85.7	100
Zaib N, 2013[8]	14/20	20/30	70	33.3	41.1	62.5
Salehinejad J, 2014[43]	9/9	23/37	100	37.8	28.1	100
Foo WC, 2016[44]	4/11	5/35	36.3	85.7	44.4	81
Jalayer Naderi N, 2020[9]	11/15	2/5	73.3	60	84.6	42.8
Total cases from 43 articles (case-control + observational) ACC v/s other malignant salivary gland tumors	1093/1286	196/634	84.99% (82.92%-86.90%)	69.09% (65.33%-72.67%)	84.79% (83.20%-86.26%)	69.41% (66.36%-72.30%)
PAC v/s other malignant salivary tumors Case-control studies						
Jeng YM, 2000[11]	0/4	28/75	0	62.6	0	92.15
Penner CR, 2002[4]	8/14	9/9	57.1	0	47	0
Edwards PC, 2003[1]	16/17	31/32	94.1	3.1	34	50
Mino M, 2003[25]	2/8	76/156	25	48.7	2.5	93
Andreadis D, 2006[2]	7/14	63/84	50	25	10	75
Beltran D, 2006[5]	2/10	12/12	20	0	14.2	0
Ettl T, 2008[27]	1/1	54/100	100	46	1.8	100
Schwarz S, 2011[6]	0/8	12/14	0	14.2	0	20
El-Nagdy S, 2013[7]	2/8	12/12	25	0	14.2	0
Zaib N, 2013[8]	6/10	28/40	60	30	17.6	75
Salehinejad J, 2014[43]	4/4	28/42	100	33.3	12.5	100
Jalayer Naderi N, 2020[9]	2/5	11/15	40	26.6	15.3	57.1
Total cases from 43 articles (case-control + observational) PAC v/s other malignant salivary gland tumors	50/103	1239/1817	48.54% (38.58%-58.60%)	31.81% (29.67%-34.01%)	3.88% (3.19%-4.70%)	91.60% (89.93%-93.01%)
ACC v/s PAC Total cases from 43 articles (case-control + observational)	1093/1286	50/103	84.99% (82.92%-86.90%)	51.46% (41.40%-61.42%)	95.63% (94.71%-96.39%)	21.54% (17.94%-25.65%)
Total malignant v/s total benign salivary gland tumors studied in 43 articles (case-control + observational)	1289/1920	134/198	67.14% (64.98%-69.24%)	32.32% (25.87%-39.32%)	90.58% (89.68%-91.41%)	9.21% (7.59%-11.14%)

*P/T-Positive/Total cases; #CI: Cconfidence interval; ACC: Adenoid cystic carcinoma; PAC: Polymorphous adenocarcinoma

significance compared to a much larger sample of adenoid cystic carcinomas. The need to analyse other salivary gland tumours like epimyoepithelial carcinoma, myoepithelial carcinoma, basal cell adenocarcinoma, lymphoepithelial carcinoma, and canalicular adenoma with comparable immunohistochemical expression for KIT mutations is warranted in the future.

CONCLUSION

Current evidence from the systematic review and meta-analysis suggests that c-KIT/CD117 is not a useful diagnostic marker for distinguishing ACC from other salivary gland tumours, including PAC. Although the percentage of immunohistochemical expression of c-KIT is higher in ACC, differentiation from other salivary gland tumours is unreliable. The higher expression percentage in ACC could be due to the higher number of cases examined. This marker, despite the high sensitivity percentage, is less specific for distinguishing between adenoid cystic carcinoma and polymorphic adenocarcinoma. The corresponding molecular analysis showed variable mutations of codons and exons, which increases the ambiguity of this protein expression. Further research is required to determine the

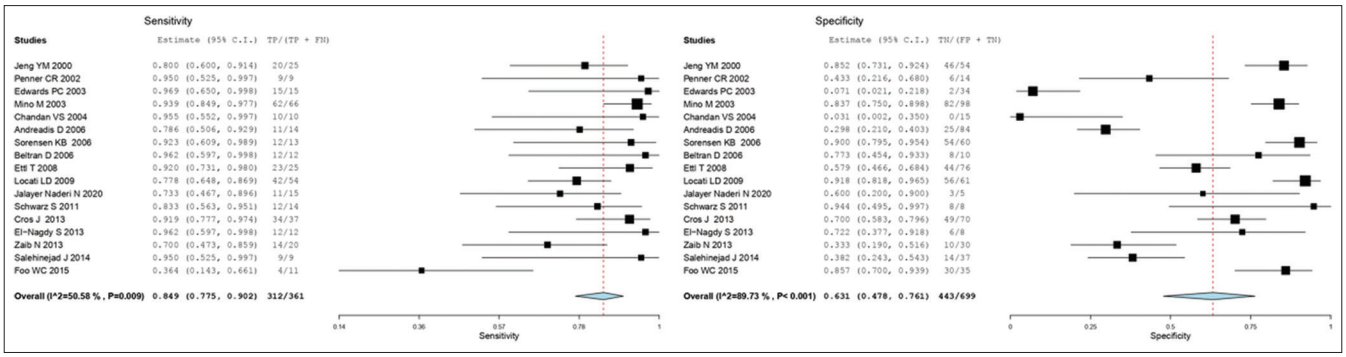

Figure 3: Forest plot pooled sensitivity and specificity estimate of studies included in meta-analysis

diagnostic utility and therapeutic advantages of c-KIT in relation to other salivary gland lesions.

Ethical approval

This article does not contain any studies with human participants performed by the author. The study is registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42022339930).

Informed consent

For this type of study informed consent is not required.

Consent for publication

For this type of study consent for publication is not required.

Data availability statement

Articles including salivary gland tumors with any studies on CD117 OR c-KIT examined in databases of MEDLINE by PubMed, Google Scholar, Scopus, Trip, Cochrane Library and EMBASE until 31st December 2023, without period restriction.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Edwards PC, Bhuiya T, Kelsch RD. C-kit expression in the salivary gland neoplasms adenoid cystic carcinoma, polymorphous low-grade adenocarcinoma, and monomorphic adenoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003;95:586-93.
2. Andreadis D, Epivatianos A, Poulopoulos A, Nomikos A, Papazoglou G, Antoniades D, *et al.* Detection of C-KIT (CD117) molecule in benign and malignant salivary gland tumours. Oral Oncol 2006;42:56-64.
3. Sung JY, Ahn HK, Kwon JE, Jeong H, Baek CH, Son YI, *et al.* Reappraisal of KIT mutation in adenoid cystic carcinomas of the salivary gland. J Oral Pathol Med 2012;41:415-23.
4. Penner CR, Folpe AL, Budnick SD. C-kit expression distinguishes salivary gland adenoid cystic carcinoma from polymorphous low-grade adenocarcinoma. Mod Pathol 2002;15:687-91.
5. Beltran D, Faquin WC, Gallagher G, August M. Selective immunohistochemical comparison of polymorphous low-grade adenocarcinoma and adenoid cystic carcinoma. J Oral Maxillofac Surg 2006;64:415-23.
6. Schwarz S, Müller M, Ettl T, Stockmann P, Zenk J, Agaimy A. Morphological heterogeneity of oral salivary gland carcinomas: A clinicopathologic study of 41 cases with long-term follow-up emphasizing the overlapping spectrum of adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma. Int J Clin Exp Pathol 2011;4:336.
7. El-Nagdy S, Salama N, Mourad M. Immunohistochemical clue for the histological overlap of salivary adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma. Interv Med Appl Sci 2013;5:131-9.
8. Zaib N, Mushtaq S, Mamoon N, Akhter N, Ayaz B. Immunohistochemical pattern of pleomorphic adenoma, polymorphous low-grade adenocarcinoma and adenoid cystic carcinoma in minor salivary glands. J Dent (Tehran) 2014;11:38-46.
9. Jalayer Naderi N, Ashouri M, Tirgari F, Kharazi Fard MJ, Jafari Z. An immunohistochemical study of CD117 C-kit in adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma salivary gland tumours. Daneshvar Medicine 2011;18:1-8.
10. Holst VA, Marshall CE, Moskaluk CA, Frierson HF Jr. KIT protein expression and analysis of c-kit gene mutation in adenoid cystic carcinoma. Mod Pathol 1999;12:956-60.
11. Jeng YM, Lin CY, Hsu HC. Expression of the c-kit protein is associated with certain subtypes of salivary gland carcinoma. Cancer Lett 2000;154:107-11.
12. Freier K, Flechtenmacher C, Walch A, Devens F, Mühling J, Lichter P, *et al.* Differential KIT expression in histological subtypes of adenoid cystic carcinoma (ACC) of the salivary gland. Oral Oncol 2005;41:934-9.
13. Sørensen KB, Godballe C, Stricker KD, Krogdahl A. Parotid carcinoma: Expression of kit protein and epidermal growth factor receptor. J Oral Pathol Med 2006;35:286-91.
14. Vila L, Liu H, Al-Quran SZ, Coco DP, Dong HJ, Liu C. Identification of c-kit gene mutations in primary adenoid cystic carcinoma of the salivary gland. Mod Pathol 2009;22:1296-302.
15. Sequeiros-Santiago G, Garcia-Carracedo D, Fresno MF, Suarez C, Rodrigo JP, Gonzalez M. Oncogene amplification pattern in adenoid cystic carcinoma of the salivary glands. Oncol Rep 2009;21:1215-22.
16. 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.
17. Tetsu O, Phuchareon J, Chou A, Cox DP, Eisele DW, Jordan RC. Mutations in the c-Kit gene disrupt mitogen-activated protein kinase signaling during tumor development in adenoid cystic carcinoma of the salivary glands. Neoplasia 2010;12:708-17.
18. Tang YL, Fan YL, Jiang J, Zheng M, Chen W, Ma XR, *et al.* C-kit induces epithelial-mesenchymal transition and contributes to salivary adenoid cystic cancer progression. Oncotarget 2014;5:1491-501.

19. Hotte SJ, Winquist EW, Lamont E, MacKenzie M, Vokes E, Chen EX, *et al*. Imatinib mesylate in patients with adenoid cystic cancers of the salivary glands expressing c-kit: A Princess Margaret Hospital phase II consortium study. J Clin Oncol 2005;23:585-90.
20. Pfeffer MR, Talmi Y, Catane R, Symon Z, Yosepovitch A, Levitt M. A phase II study of Imatinib for advanced adenoid cystic carcinoma of head and neck salivary glands. Oral Oncol 2007;43:33-6.
21. Ghosal N, Mais K, Shenjere P, Julyan P, Hastings D, Ward T, *et al*. Phase II study of cisplatin and imatinib in advanced salivary adenoid cystic carcinoma. Br J Oral Maxillofac Surg 2011;49:510-5.
22. Wong SJ, Karrison T, Hayes DN, Kies MS, Cullen KJ, Tanvetyanon T, *et al*. Phase II trial of dasatinib for recurrent or metastatic c-KIT expressing adenoid cystic carcinoma and for nonadenoid cystic malignant salivary tumors. Ann Oncol 2016;27:318-23.
23. Demiray M, Sahinbas H, Atahan S, Demiray H, Selcuk D, Yildirim I, *et al*. Successful treatment of c-kit-positive metastatic Adenoid Cystic Carcinoma (ACC) with a combination of curcumin plus imatinib: A case report. Complement Ther Med 2016;27:108-13.
24. Miller LE, Au V, Mokhtari TE, Goss D, Faden DL, Varvares MA. A contemporary review of molecular therapeutic targets for adenoid cystic carcinoma. Cancers (Basel) 2022;14:992.
25. Mino M, Pilch BZ, Faquin WC. Expression of KIT (CD117) in neoplasms of the head and neck: An ancillary marker for adenoid cystic carcinoma. Mod Pathol 2003;16:1224-31.
26. Seethala RR, Barnes EL, Hunt JL. Epithelial-myoepithelial carcinoma: A review of the clinicopathologic spectrum and immunophenotypic characteristics in 61 tumors of the salivary glands and upper aerodigestive tract. Am J Surg Pathol 2007;31:44-57.
27. Ettl T, Schwarz S, Kleinsasser N, Hartmann A, Reichert TE, Driemel O. Overexpression of EGFR and absence of C-KIT expression correlate with poor prognosis in salivary gland carcinomas. Histopathology 2008;53:567-77.
28. Skálová A, Sima R, Vanecek T, Muller S, Korabecna M, Nemcova J, *et al*. Acinic cell carcinoma with high-grade transformation: A report of 9 cases with immunohistochemical study and analysis of TP53 and HER-2/neu genes. Am J Surg Pathol 2009;33:1137-45.
29. Ahmed MM, Abo-Hager EA. Differential expression of c-kit and CD43 in histological subtypes of adenoid cystic carcinoma of salivary gland. Saudi Dent J 2010;22:27-34.
30. Tang Y, Liang X, Zheng M, Zhu Z, Zhu G, Yang J, *et al*. Expression of c-kit and Slug correlates with invasion and metastasis of salivary adenoid cystic carcinoma. Oral Oncol 2010;46:311-6.
31. Bell D, Roberts D, Karpowicz M, Hanna EY, Weber RS, El-Naggar AK. Clinical significance of Myb protein and downstream target genes in salivary adenoid cystic carcinoma. Cancer Biol Ther 2011;12:569-73.
32. Kim JW, Kwon GY, Roh JL, Choi SH, Nam SY, Kim SY, *et al*. Carcinoma ex pleomorphic adenoma of the salivary glands: Distinct clinicopathologic features and immunoprofiles between subgroups according to cellular differentiation. J Korean Med Sci 2011;26:1277-85.
33. Kim JY, Yoo YS, Kwon JE, Kim HJ, Park K. Fine-needle aspiration cytology with c-kit immunocytochemical staining in the diagnosis of Warthin's tumor. Acta Cytol 2012;56:474-80.
34. Zhou Q, Chang H, Zhang H, Han Y, Liu H. Increased numbers of P63-positive/CD117-positive cells in advanced adenoid cystic carcinoma give a poorer prognosis. Diagn Pathol 2012;7:119.
35. 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.
36. Jung MJ, Roh JL, Choi SH, Nam SY, Kim SY, Lee SW, *et al*. Basal cell adenocarcinoma of the salivary gland: A morphological and immunohistochemical comparison with basal cell adenoma with and without capsular invasion. Diagn Pathol 2013;8:171.
37. Cros J, Sbidian E, Hans S, Roussel H, Scotte F, Tartour E, *et al*. Expression and mutational status of treatment-relevant targets and key oncogenes in 123 malignant salivary gland tumours. Ann Oncol 2013;24:2624-9.
38. Shin DY, Jang KS, Kim BY, Choi JE, Yoon H, Ko YH, *et al*. Comparison of adenoid cystic carcinomas arising from the parotid gland vs. the submandibular gland: focus on systemic metastasis and tumor-associated blood vessels. J Oral Pathol Med 2014;43:441-7.
39. Singh AD, Majumdar S, Ghosh AK, Gandi L, Choudaha N, Sharma I, *et al*. Basal cell adenomaclinicopathological, immunohistochemical analysis and surgical considerations of a rare salivary gland tumor with review of literature. Niger J Surg 2015;21:31-4.
40. Ni H, Zhang XP, Wang XT, Xia QY, Lv JH, Wang X, *et al*. Extended immunologic and genetic lineage of mammary analogue secretory carcinoma of salivary glands. Hum Pathol 2016;58:97-104.
41. Zhang XP, Ni H, Wang X, Chen H, Shi SS, Yu B, *et al*. [Clinicopathologic features of mammary analogue secretory carcinoma of salivary glands]. Zhonghua Bing Li Xue Za Zhi 2017;46:34-7.
42. Wang F, Li B, Wang Y, Shen Y, Yang H. Clinical and pathological analysis of 10 cases of salivary gland epithelial-myoepithelial carcinoma. Medicine (Baltimore) 2020;99:e22671.
43. Salehinejad J, Mohtasham N, Bagherpour A, Abbaszadeh-Bidokhty H, Ghazi A. Evaluation of c-kit protein (CD117) expression in common salivary gland neoplasms. J Oral Maxillofac Pathol 2014;18:177-82.
44. Foo WC, Jo VY, Krane JF. Usefulness of translocation-associated immunohistochemical stains in the fine-needle aspiration diagnosis of salivary gland neoplasms. Cancer Cytopathol 2016;124:397-405.
45. Locati LD, Perrone F, Losa M, Mela M, Casieri P, Orsenigo M, *et al*. Treatment relevant target immunophenotyping of 139 salivary gland carcinomas (SGCs). Oral Oncol 2009;45:986-90.
46. Raman S, Sherlin HJ. Utility of smooth muscle actin and CD117 as reliable markers in the diagnosis of salivary gland neoplasms. J Oral Maxillofac Pathol 2019;23:218-23.
47. Chandan VS, Wilbur D, Faquin WC, Khurana KK. Is c-kit (CD117) immunolocalization in cell block preparations useful in the differentiation of adenoid cystic carcinoma from pleomorphic adenoma? Cancer 2004;102:207-9.
48. Jain A, Shetty DC, Rathore AS, Kumar K. Characterization and localization of c-kit and epidermal growth factor receptor in different patterns of adenoid cystic carcinoma. J Cancer Res Ther 2016;12:834-9.
49. Tsai MS, Hsieh MS, Huang HY, Huang PH. Nuclear immunoreactivity of BLM-s, a proapoptotic BCL-2 family member, is specifically detected in salivary adenoid cystic carcinoma. Hum Pathol 2019;84:81-91.