This is an Accepted Manuscript for *The Journal of Laryngology & Otology*
DOI: 10.1017/S0022215124001841

Title

Pre-operative radiological and radiomic features predicting Carcinoma Ex Pleomorphic Adenoma: Systematic Review

Authors:

Dr Seraphina Key MD[1]

Dr Zubair Hasan MBBS FRACS[1,2]

Dr Michael Lee MBBS MPhil[1]

Mr Raghav C Dwivedi MBBS FRCS (ORL-HNS)[2,3,4]

A/Prof Faruque Riffat MBBS (Hons 1) FRACS (ORL)[1,5]

A/Prof Purnima Sundaresan MBBS, FRANZCR[1,6]

Affiliations:

[1]Faculty of Medicine and Health, University of Sydney, NSW 2145, Australia

[2]Department of Otolaryngology - Head and Neck Surgery, John Hunter Hospital, Sydney, New South Wales, Australia.

[3]Department of Otolaryngology - Head and Neck Surgery, University College London Hospitals NHS Foundation Trust, London NW1 2BU, United Kingdom

[4]Division of Surgery and Interventional Science- University College London, Gower Street, London, WC1E 6BT, United Kingdom

[5]Department of Otolaryngology - Head and Neck Surgery, Westmead Hospital, New South Wales, Australia Corner Hawkesbury Road and, Darcy Road, Westmead, New South Wales, 2145

[6]Department of Radiation Oncology, Crown Princess Mary Cancer Centre, Westmead Hospital, Westmead, NSW, 2145, Australia

Corresponding Author:

Dr Seraphina Key MD

Address: Faculty of Medicine and Health, University of Sydney, NSW 2145, Australia

Email: seraphinakey@gmail.com

Phone: +61 4340 95343

ORCID: 0000-0002-1019-5986

Conflicts of Interest

There are no conflicts of interest for this paper.

This manuscript was included as part of a Masters of Philosophy with the University of Sydney.

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

Abstract

Objective: Carcinoma ex pleomorphic adenoma (CXPA) is a rare malignant salivary gland tumour for which distinct radiological features are unclear. We aim to identify radiological features that may pre operatively predict for CXPA and its degree of invasion.

Methods: Systematic review of Medline, Embase, SCOPUS, Web of Science, Cochrane, and OpenGrey from inception to 29th April 2023 Primary outcomes of interest were radiological features in MRI, CT and ultrasound.

Results: Of 1729 studies, 12 studies (n=426) underwent qualitative synthesis. Imaging findings for MRI, CT, and ultrasound were reported in eleven studies (n=337), five (n=253), and one study (n=89) respectively. MRI features of lower mean ADC values, and heterogenous T2 intensity were reported.

Conclusion: MRI has the greatest utility in predicting for CXPA. Within the limits a heterogenous body of evidence, in addition to general radiologic features of malignancy, lower mean ADC values and heterogenous T2 intensity may indicate CXPA.

Word count: 149 words

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

Summary

- Pre-operative imaging, particularly MRI, is a key step in the evaluation of salivary gland tumours such as carcinoma ex pleomorphic adenoma (CXPA) as it can clarify malignant features such as perineural involvement, size, and margins
- MRI with high or heterogenous T2 signal, and lower mean ADC values, are associated with CXPA.
- Future research could consider examining CT, ultrasound, and T1 signal findings.

MESH Keywords

Salivary Gland Neoplasms

Pleomorphic Adenoma

Magnetic Resonance Imaging

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

Introduction

Carcinoma ex pleomorphic adenoma (CXPA) is a rare malignant salivary gland neoplasm arising from malignant transformation of a pre-existing pleomorphic adenoma (PA).[1] As CXPA is typically considered a high grade tumour, counselling patients regarding the decision between surveillance and excision of the benign PA is guided by the risk of malignant transformation across a patient's lifetime. Pre-operative imaging is a key step in the evaluation of salivary gland tumours (SGTs) based upon current guidelines.[2] Imaging modalities used in characterising SGTs include ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI).[3-7]

MRI is particularly useful as it allows identification of perineural involvement and features such as size and margin definition, which is known to portend malignancy in SGTs.[6, 8] There is contemporary interest in MRI features, as it has been suggested that assessment of apparent diffusion coefficient (ADC) on MRI may be useful in predicting mortality for SGTs, including CXPA;[9] and in differentiating benign from malignant tumours.[5, 9, 10] Furthermore, MRI features predicting perineural invasion preoperatively is of clinical interest, as it guides prognosis, preoperative discussion and treatment decision-making. In addition, it assists with planning for adjuvant therapies such as radiotherapy.[11] Ultrasound is another imaging modality with utility in predicting malignancy using features such as irregularity, poorly-defined borders, and poor enhancement of posterior echo.[3] Additionally, contemporary studies have begun utilizing emerging technologies such as radiomic analysis to further predict the risk of malignancy, and by doing so, stratify the need for surgery.[4]

Due to the rarity of CXPA, there is limited high-level evidence to guide its diagnosis and pre-operative decision-making. This systematic review aims to identify the radiological features

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

that may pre operatively predict for CXPA and its degree of invasion in ultrasound, CT, and MRI. The hypothesis under investigation is: in salivary gland tumours, do radiological features on ultrasound, CT, and MRI, predict CXPA?

Materials and Methods

This systematic review was registered prospectively on PROSPERO (CRD42023421449). This protocol was written in accordance with the PRISMA-P protocol for systematic reviews.

A systematic search of MeSH indexed phrases relating to "carcinoma ex pleomorphic adenoma", "radiology", "magnetic resonance imaging", "computed tomography", and "ultrasound" was performed from database inception to 29th April 2023.(Supplement 1: Search Strategy) Peer-reviewed literature was searched for via Ovid Medline, Embase, SCOPUS, Web of Science (BIOSIS), Cochrane CENTRAL, and the Cochrane database of systematic reviews. To include emerging radiological modalities, the grey literature including conference proceedings were searched for via Embase, SCOPUS, Web of Science (BIOSIS), OpenDOAR, and GreyNet International (OpenGrey). Systematic review databases including PROSPERO and Cochrane Library were searched for existing reviews. Reference lists of included articles were checked to identify further articles for screening. Database search was limited to "humans" and "English".

One author (SK) screened all abstracts for full-text review. Papers selected for full-text screening subsequently underwent data extraction on a pre-determined spreadsheet by two independent reviewers (SK, ZH). A third reviewer (PS) was consulted to resolve discrepancies. The systematic review management software, Covidence,[12] was used for review management.

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

Papers that met all of the inclusion criteria and none of the exclusion criteria were included in the data analysis. PICOs for this study were:

- (P) Confirmed histological diagnosis of CXPA in the major or minor salivary glands
- (I) Magnetic resonance imaging, computed tomography, ultrasound
- (O) Radiological features unique to each modality predicting CXPA:
    - Ultrasound: irregular shape, ill-defined borders, and posterior echo enhancement
    - CT: attenuation and enhancement;
    - MRI: signal, enhancement, and ADC.

Study types for inclusion were randomized controlled trials (RCTs), cohort studies, case-control studies, cross-sectional studies from cancer databases, and case reports with ≥3 patients. Exclusion criteria were (1) insufficiently discrete data from other salivary gland cancers (2) no pre-operative radiological data (3) non-humans.

Clinicopathological features such as patient age, sex, invasiveness, and primary salivary gland of interest were collected. Additional pathognomonic radiological features highlighted in the included studies were collected for further discussion. Where available, prognostic information for follow-up duration, mortality, and recurrence rates were collected.

Descriptive statistics was used to synthesize aggregate data for clinical and radiological features, and Shapiro–Wilk test was used to test normal distribution. Subgroup analysis was performed for non-invasive and minimally invasive CXPA against frankly invasive CXPA.

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

Risk of bias assessment was performed by two independent reviewers (SK, ML), and a third reviewer (PS) was available to resolve any discrepancies. For prognostic and prediction studies, the Quality in Prognostic Studies (QUIPS) tool was used.[13] The Center for Evidence Based Medicine (CEBM) Levels of Evidence was collected for each included article.[14]

Results and Analysis

Of 1729 unique studies, 127 studies underwent full-text screening, and 12 studies (n=426 patients) met criteria for independent data extraction. There were seven cohort studies,[3, 5, 9, 15-18] four case-control studies,[6, 7, 19, 20] and one case series.[21] (Fig 1: PRISMA) There was high inter-rater agreement between study authors for studies identified for inclusion into the study.

Demographic data indicated median age was 62 years (n=330 patients), and 54.18% were male (n=227/419). In 419 patients, the most common primary subsite was in the parotid gland (76.85%, n=322/419), followed by submandibular gland (15.75%, n=66/419), and minor salivary glands (7.40%, n=31/419) respectively. In studies reporting invasiveness, most tumours were frankly invasive (76.92%, n=260/338), compared to non- or minimally invasive (23.08%, n=78/338). Clinical evidence of perineural invasion was reported in 14.08% (n=10/71) of patients. TNM staging and previous PA history was not well reported. Limited prognostic data was reported. Recurrent disease was reported in 19.23% of patients (n=5/26). Median follow-up duration for CXPA was poorly reported.(Table 1)

Magnetic Resonance Imaging (MRI)

Eleven studies (n=337 patients) reported on MRI in CXPA.[5-7, 9, 15-21](Table 2) Seven studies reported using 1.5T MRI,[5-7, 9, 15, 16, 21] and one study used both 1.5T and 3T MRI;[17] it was unclear which type of MRI was used for three studies.[18-20] A graphical depiction of major

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

MRI findings is included in Figure 2. Most studies described T2, and ADC characteristics for CXPA, wherein CXPA typically demonstrated T2 heterogenous or high intensity, and lower mean ADC values on DWI compared to benign tumours.

Six studies performed ADC calculations on DWI imaging,[5, 7, 9, 15, 20, 21] in which four quantified ADC values. In two studies which provided pooled ADC values, mean ADC was $0.83\times10^{-3}mm^2/s$ (SD 0.09),[15] and $1.2310^{-3}mm^2/s$ (SD 0.19)[9] respectively. In a study of 6 patients with CXPA, Seok et al. reported four of six patients had low ADC values ($<1.2 \times 10^{-3}mm^2/s$), whilst two had medium ADC values ($1.2\times 10^{-3}mm^2/s$).[20] In Wang et al's study of 212 patients with CXPA, ADC values were available for 22 patients. Mean ADC ($\times 10^{-3}mm^2/s$) for five non- and minimally invasive CXPA was 1.0 (range 0.8 to 1.1), and seventeen frankly invasive CXPA was 0.91 (0.6–1.5). The mean ADC was 0.93 (range 0.6 to 1.5), but this was not statistically significant between levels of invasiveness (p=0.455).[5] Additionally, in a case-control study of 22 CXPA and 115 PA patients, Wada et al. synthesized mean ADC values into a histogram utilizing machine learning techniques. This was used to produce a radiomics-based model and compare it against a one-point ADC measurement, suggesting the former can overcome lower levels of operator experience.[7] Kato et al. related radiology features of CXPA to their histopathological benign and malignant components. In three of the patients, ADC values for the CXPA component was higher than the surrounding benign component, although the exact ADC value was not specified. These CXPA components demonstrated T2 mild to moderate hyperintensity.[21]

Of eleven studies examining MRI, seven studies reported on T2 characteristics.[5, 6, 16, 18-21] In these 272 patients, most (70.22%, n=191/272) reported heterogenous findings. [5, 6, 18-21] In the remaining 29.78% (n=81/272), ten patients reported an association between high T2 intensity

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

and CXPA.[5, 19-21] The T2 signal of the remaining patients were unknown. Other T2 findings of note were a hypointense rim in seven of ten CXPA patients.[18]

In the two studies with eight patients reporting T1, [19, 20] there was no unified consensus. One study with one patient reported moderate T1 intensity,[19] and one study with seven patients exhibited low T1 intensity.[20]

Alternative imaging modalities such as STIR imaging was examined by Kashiwagi et al. in 10 CXPA patients.[18] This identified specific radiological features that differentiated invasive and noninvasive CXPA, which were further explored by Akutsu et al.[16], namely the black ring and corona signs. Invasive CXPA was more likely to demonstrate a "corona" sign, increased tumour size on FS-T2Q1 and/or CE-FS-T1W1 compared to T1W1, reaching statistical significance (OR 14.40, p=0.001 and OR 9.31, p=0.007). The black ring sign, a hypointense ring thicker than the benign PA capsule, was also statistically more likely to be present in invasive CXPA (OR 13.11, p=0.011). In this same study, invasive CXPA was more likely to have ill-defined borders (OR 14.41, p=0.002) and no capsule (OR 38.18, p<0.001).[16] Another method of assessing tumours on MRI is the time-signal-intensity curve (TIC) based on enhancement ratio (ER), maximum time (MT), washout ratio (WR), which was performed on 8 CXPA patients and 20 PA patients. Although there was no statistical difference in TIC types between CXPA and PA, TIC with rapid uptake and a low WR was more likely to diagnose CXPA.[6]

Computed Tomography (CT)

Five studies (n=253 patients) reported on pre operative CT findings in CXPA.[5, 17, 19-21] (Table 3) All studies correlated MRI findings to CT findings, and both non-contrast and contrast-

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

enhanced CT were used. CT was used as an additional imaging modality to supplement MRI findings, identifying specific characteristics of interest, such as bony involvement. Incidence of commonly reported findings were bony involvement (n=6/22, 27.3%),[17, 19] low-attenuation indicating cystic or necrotic change (n=7/19, 36.8%),[20, 21] calcification (n=80/196, 40.8%),[5, 21] ill-defined borders (n=128/227, 56.4%),[5, 20] and lymphadenopathy ≥5mm (n=74/227, 32.6%).[5, 20] Horiuchi et al. compared CXPA to adenoid cystic carcinoma (ACC), and other malignant tumours such as salivary duct carcinoma (SDC). CXPA had less perineural invasion compared to ACC (p=0.017) and SDC (p=0.041), and lower rates of bony change compared to ACC (p=0.02).[17] Seok et al. compared CXPA to PA, demonstrating CXPA to have statistically significant difference in tumour size (p=0.01), and higher rates of lymphadenopathy ≥5mm (p=0.44). The authors also report there was deep lobe involvement on 3/15 patients, and all 15 CXPA tumours were single tumours. These two features did not achieve statistical significance.[20] The other three papers did not have a comparator group.

Ultrasound

Only one study reported on ultrasound in CXPA.[3] Ding et al. compared ultrasound findings of 11 intracapsular and 78 invasive CXPA. Three key features examined were irregular edges, ill-defined borders, and no enhancement of posterior echo. Although individual features demonstrated low sensitivity (51.3%, 51.3%, and 56.4% respectively), further analysis where the presence of any one of three features were demonstrated showed a sensitivity of 85.9% and specificity of 90.9% for predicting malignancy.[3]

Subgroup Analysis

Subgroup analysis could be performed for non/minimally invasive tumours against frankly invasive tumours in three studies.[3, 5, 16] Akutsu et al. suggest there were statistically

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

significant differences in the corona signs between invasive and non invasive CXPA ($p<0.001$ for FS-T2W1, and $p=0.001$ for CE-FS-T1W1), but not for the black ring sign ($p=0.31$).[16] Wang et al. note that radiological features such as morphology and boundary, such as uneven margins and irregularity, are more likely to predict invasive CXPA. Although the mean ADC values for non-invasive CXPA is higher than invasive CXPA, there is no statistically significant difference between the two.[5] Ding et al. similarly report ultrasound features indicating malignancy are ill-defined borders and irregularity.[3]

Risk of Bias Assessment

CEBM level of evidence was assessed. There were nine level 3 studies,[3, 5-7, 9, 15-17, 20] and three level 4 studies.[18, 19, 21] All studies were retrospective. Common issues were that most studies were local non-random sample of SGTs,[9, 15, 17] or case series,[18, 19, 21] thus reducing their level of evidence.

Risk of bias assessment was performed with the QUIPS tool,[13] and graphed with the robvis tool.[22] (Figure 3) Risk of bias was high in five studies,[9, 15, 17, 18, 21] moderate in two studies,[6, 19] and low in five studies.[3, 5, 7, 16, 20] The generally high risk of bias can be attributed to the large amount of missing data in judging bias due to outcome measurement,[3, 6, 7, 15, 17, 18, 21] and confounding.[7, 9, 15, 17] Due to the retrospective nature of the included studies, study authors were not able to control for confounders. As CXPA was frequently part of a larger cohort of salivary gland tumours,[9, 15, 17] or study authors did not clearly specify how patients were identified for inclusion,[6, 18, 21] participant selection was an area with high risk of bias. Furthermore, it was not specified if there was consecutive inclusion of CXPA patients into the study, hence increasing selection bias in the study. Prognostic factors were well reported, including details regarding radiology equipment and techniques.[3, 5-7, 9, 15-21]

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

Discussion

This is the first systematic review summarizing imaging characteristics in CXPA. In considering the three imaging modalities reported in the literature, pre-operative MRI appeared to have the highest utility in predicting for CXPA as opposed to benign tumours.[2, 6, 15] In studies reporting on CT, this was used in addition to MRI in order to supplement MRI radiological findings, and identify particular characteristics such as osseous change.[17, 19] Despite the accessibility of ultrasound as an imaging modality, only one study examined this modality, hence generalizable conclusions could not be determined.

Identifying radiological characteristics that may discriminate CXPA from PA and other benign SGTs will strengthen the body of evidence guiding resection against surveillance imaging in SGTs. This will allow for increasingly nuanced discussions, and decision-making to improve patient care. As in other salivary gland tumours, MRI appeared to be the imaging modality of greatest interest in CXPA. In the current literature, there is common consensus that CXPA demonstrates T1 and T2 heterogenous intensity,[5, 21] and lower ADC values,[23, 24] although there is yet to be a common consensus in regards to the type of MRI signal demonstrated. [23, 24] One resource suggests CXPA demonstrates low T2 intensity,[23] whilst another suggests low T1 with hyperintense foci, and high T2 intensity.[24] Results from our systematic review suggests that most CXPA demonstrate heterogenous intensity on T2 weighted MRI and lower mean ADC values on DWI than benign tumours. In addition to using ADC values for differentiating benign from malignant SGTs, Hepp et al., also indicated that ADC histograms containing ADC values may have higher levels of accuracy, and recommend using these histograms to enhance the accuracy of differentiating SGTs.[25]

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

Perineural invasion (PNI), although a known prognostic factor, was not well reported as a discrete data subset for radiological features in CXPA. Only four studies reported on clinical PNI in CXPA,[16, 17, 20, 21] wherein 14.1% (n=10/71) of patients were clinically noted to have evidence of perineural invasion (PNI) reported at presentation. Radiological evidence of this was not well reported. One of the included studies by Horiuchi et al. identified any PNI indicates higher bone involvement for a pooled group of malignant SGTs (OR 3.98, p=0.006), although only one of 15 CXPA patients were positive.[17] Inferences can be drawn from a larger group of pooled 151 parotid gland tumours, in which 26 CXPA patients (20 with facial nerve invasion, and 6 without) were included.[8] Although discrete data was not reported for CXPA, statistically significant radiological features predicting facial nerve invasion in both univariate and multivariate analysis were spiculated margins (p=0.003), larger mean tumour size (p=0.001), location in the course of the facial nerve (p=0.014), and retromandibular vein involvement (p= 0.023).[8] Future directions examining CXPA characteristics could consider exploring these features as a particular area of focus in MR characteristics of CXPA.

Radiomic analysis is another emerging element in the radiological assessment of SGTs, particularly in differentiating benign from malignant tumours preoperatively. Utilization of predictive models based on MRI characteristics are already under development.[4, 26, 27] However, due to the rarity of CXPA, the wider body of radiomic and machine learning data does not include CXPA as part of its malignant SGT subset.[4, 26, 28] Two radiomic studies have been recently published in the literature, for which three CXPA patients form part of the malignant SGT subset.[27, 29] Although discrete information pertaining to CXPA is not available, both studies compare benign and malignant parotid tumours. Piludu et al. identified a 80.4% accuracy, 85.0% sensitivity, and 94.1% specificity in differentiating 37 benign and

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

32 malignant tumours in their radiomic model. They recommend utilization of T2 weightage, ADC, and qualitative scores for tumour margins and contrast enhancements to improve accuracy.[27] Wen et al. performed a similar study comparing 88 benign and 42 malignant parotid tumours on ADC mapping with 3T scanners, demonstrating an accuracy of 73.17%, sensitivity 84.62%, and specificity 67.86%. The authors identify that the lack of T2 and contrast-enhanced T1 imaging in training their radiomic model may have affected the diagnostic accuracy.[29]

A limitation of this review is that our search strategy is limited to the English language literature. The majority of emerging data appears to be from Asian institutions (7 Japan, 3 China, 1 Korea), and CXPA has been suggested to have a geographical variation in incidence.[1] Hence, inclusion of non-English databases may identify additional articles to increase the strength of evidence. There were generally low levels of evidence (CEBM level 3 and 4), with all studies being retrospective observational studies.

One of the challenges encountered during this review related to difficulty in separating CT and MRI findings in the included studies, thus precluding calculation of modality-specific diagnostic accuracy data.[5] Additionally, there was limited synthesis of multiple features in improving diagnostic accuracy. One study demonstrated improved sensitivity of ultrasound in detecting invasive CXPA by combining three sonographic features,[3] indicating this may be an area for future research. Furthermore, it is noted that although ultrasound is a readily available modality for assessing SGTs, only one ultrasound study was identified, raising the possibility of missing data in ultrasound assessment of CXPA. Future studies could consider analysis of imaging modalities in combination, particularly as SGTs can be imaged with any of ultrasound, CT, or MRI, in routine clinical practice.[2]

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

Additionally, studies had heterogeneously defined characteristics and radiological features of interest. As such, there were insufficient radiological characteristics with comparable data for each modality, hence ROC curves to predict frankly invasive CXPA could not be calculated as planned. Similarly, although Fisher's exact test and chi-square were planned to be used in comparing poorer clinical outcomes against radiological features, there were insufficient studies with directly comparable data. Sensitivity analysis was planned to separate high and low quality studies. However, due to the low number of studies, and heterogenous reporting of radiological features, this was not possible. Given the lack of standardised radiological characteristics, a meta-analysis could not be performed. As the body of evidence surrounding CXPA develops, potential pathognomonic signs have been described in the literature, namely the corona and black ring signs,[16] which may warrant further investigation in future studies. An intrinsic limitation of systematic reviews is our findings are guided by the existing literature. There is sparse literature pertaining to T1 findings, and hence a definite conclusion cannot be inferred for T1 signal. Akutsu et al. performed an analysis comparing radiological features in invasive and non-invasive CXPA for particular radiological characteristics, identifying statistically significant relationships.[16] Prospective collection of both clinical and radiological data similar to the study methods utilized in this study may be useful in further identifying the relationship of these two components. The small sample sizes reported in the literature limit the generalizability of conclusions. However, this is the inherent challenge when dealing with a rare tumour such as CXPA. Prospective international collaborations, such as registry-based study designs could be considered for future research.

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

Conclusion

MRI has the greatest utility in preoperative prediction for CXPA. Within the limits of interpreting a heterogenous body of evidence, in addition to general radiologic features of malignancy such as irregularity and poorly demarcated borders, MRI features of lower mean ADC values and heterogenous T2 intensity are associated with, and may predict for, CXPA.

Funding

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Competing interests

The authors declare none.

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

References

1 Antony J, Gopalan V, Smith RA, Lam AKY. Carcinoma ex Pleomorphic Adenoma: A Comprehensive Review of Clinical, Pathological and Molecular Data. *Head and Neck Pathology* 2012;**6:**1-9

2 Geiger JL, Ismaila N, Beadle B, Caudell JJ, Chau N, Deschler D, et al. Management of Salivary Gland Malignancy: ASCO Guideline. *Journal of Clinical Oncology* 2021;**39:**1909-41

3 Ding A, Jia L, Xia G, Ping X, Jiang L. Gray scale and doppler ultrasonography features of the carcinoma ex pleomorphic adenoma. *Dentomaxillofac Radiol* 2018;**47:**20170268

4 Zhang R, Ai QYH, Wong LM, Green C, Qamar S, So TY, et al. Radiomics for Discriminating Benign and Malignant Salivary Gland Tumors; Which Radiomic Feature Categories and MRI Sequences Should Be Used? *Cancers (Basel)* 2022;**14**

5 Wang C, Yu Q, Li S, Sun J, Zhu L, Wang P. Carcinoma ex pleomorphic adenoma of major salivary glands: CT and MR imaging findings. *Dentomaxillofac Radiol* 2021;**50:**20200485

6 Katayama I, Eida S, Fujita S, Hotokezaka Y, Sumi M, Nakamura T. Perfusion MR imaging detection of carcinoma arising from preexisting salivary gland pleomorphic adenoma by computer-assisted analysis of time-signal intensity maps. *PLoS One* 2017;**12:**e0178002

7 Wada T, Yokota H, Horikoshi T, Starkey J, Hattori S, Hashiba J, et al. Diagnostic performance and inter-operator variability of apparent diffusion coefficient analysis for differentiating pleomorphic adenoma and carcinoma ex pleomorphic adenoma: comparing one-point measurement and whole-tumor measurement including radiomics approach. *Jpn J Radiol* 2020;**38:**207-14

8 Cho WK, Lee MK, Choi YJ, Lee YS, Choi SH, Nam SY, et al. Preoperative Magnetic Resonance Image and Computerized Tomography Findings Predictive of Facial Nerve

Invasion in Patients with Parotid Cancer without Preoperative Facial Weakness-A Retrospective Observational Study. *Cancers (Basel)* 2022;**14**

9 Sumi M, Nakamura T. Salivary gland carcinoma: Prediction of cancer death risk based on apparent diffusion coefficient histogram profiles. *PLoS One* 2018;**13:**e0200291

10 Tanaka F, Umino M, Maeda M, Nakayama R, Inoue K, Kogue R, et al. Tumor blood flow and apparent diffusion coefficient histogram analysis for differentiating malignant salivary tumors from pleomorphic adenomas and Warthin's tumors. *Sci Rep* 2022;**12:**5947

11 Pfishter DG. NCCN Guidelines: Head and neck cancers. 2019

12 Veritas Health I. Covidence Systematic Review Software, Melbourne Australia. 2020

13 Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing Bias in Studies of Prognostic Factors. *Annals of Internal Medicine* 2013;**158:**280-6

14 The Oxford 2011 Levels of Evidence. In: http://www.cebm.net/index.aspx?o=5653 [9 October 2022]

15 Abdel Razek AAK, Elkhamary SM, Nada N. Correlation of apparent diffusion coefficient with histopathological parameters of salivary gland cancer. *Int J Oral Maxillofac Surg* 2019;**48:**995-1000

16 Akutsu A, Horikoshi T, Yokota H, Wada T, Motoori K, Nasu K, et al. MR Imaging Findings of Carcinoma Ex Pleomorphic Adenoma Related to Extracapsular Invasion and Prognosis. *AJNR Am J Neuroradiol* 2022;**43:**1639-45

17 Horiuchi D, Shimono T, Tatekawa H, Tsukamoto T, Takita H, Okazaki M, et al. Frequency and imaging features of the adjacent osseous changes of salivary gland carcinomas in the head and neck region. *Neuroradiology* 2022;**64:**1869-77

18 Kashiwagi N, Murakami T, Chikugo T, Tomita Y, Kawano K, Nakanishi K, et al. Carcinoma ex pleomorphic adenoma of the parotid gland. *Acta Radiol* 2012;**53:**303-6

19 Li W, Lu H, Zhang H, Lai Y, Zhang J, Ni Y, et al. Sinonasal/nasopharyngeal pleomorphic adenoma and carcinoma ex pleomorphic adenoma: a report of 17 surgical cases combined with a literature review. *Cancer Manag Res* 2019;**11:**5545-55

20 Seok J, Hyun SJ, Jeong WJ, Ahn SH, Kim H, Jung YH. The Difference in the Clinical Features Between Carcinoma ex Pleomorphic Adenoma and Pleomorphic Adenoma. *Ear, Nose, & Throat Journal* 2019;**98:**504-9

21 Kato H, Kanematsu M, Mizuta K, Ito Y, Hirose Y. Carcinoma ex pleomorphic adenoma of the parotid gland: radiologic-pathologic correlation with MR imaging including diffusion-weighted imaging. *AJNR Am J Neuroradiol* 2008;**29:**865-7

22 McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. *Research Synthesis Methods* 2020;**n/a**

23 Friedman E, Patino MO, Abdel Razek AAK. MR Imaging of Salivary Gland Tumors. *Magn Reson Imaging Clin N Am* 2022;**30:**135-49

24 Maraghelli D, Pietragalla M, Cordopatri C, Nardi C, Peired AJ, Maggiore G, et al. Magnetic resonance imaging of salivary gland tumours: Key findings for imaging characterisation. *Eur J Radiol* 2021;**139:**109716

25 Hepp T, Wuest W, Heiss R, May MS, Kopp M, Wetzl M, et al. Apparent Diffusion Coefficient (ADC) Histogram Analysis in Parotid Gland Tumors: Evaluating a Novel Approach for Differentiation between Benign and Malignant Parotid Lesions Based on Full Histogram Distributions. *Diagnostics (Basel)* 2022;**12**

26 He Z, Mao Y, Lu S, Tan L, Xiao J, Tan P, et al. Machine learning-based radiomics for histological classification of parotid tumors using morphological MRI: a comparative study. *Eur Radiol* 2022;**32:**8099-110

27 Piludu F, Marzi S, Ravanelli M, Pellini R, Covello R, Terrenato I, et al. MRI-Based Radiomics to Differentiate between Benign and Malignant Parotid Tumors With External Validation. *Front Oncol* 2021;**11:**656918

28 Huang N, Chen Y, She D, Xing Z, Chen T, Cao D. Diffusion kurtosis imaging and dynamic contrast-enhanced MRI for the differentiation of parotid gland tumors. *Eur Radiol* 2022;**32:**2748-59

29 Wen B, Zhang Z, Zhu J, Liu L, Li Y, Huang H, et al. Apparent Diffusion Coefficient Map-Based Radiomics Features for Differential Diagnosis of Pleomorphic Adenomas and Warthin Tumors From Malignant Tumors. *Front Oncol* 2022;**12:**830496

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

This is an Accepted Manuscript for *The Journal of Laryngology & Otology*
DOI: 10.1017/S0022215124001841

Tables

Table 1: Study Characteristics

Author	Study Type	CEBM	QUIPS Overall	Country	n(CXPA)	Age	Male	Parotid	SMG	SLG / Minor	Invasiveness	Ultrasound	CT	MRI
AbdelRazek 2019[15]	Cohort	3	High	Egypt	3	N/A						0	0	1
Akutsu 2022[16]	Cohort	3	Low	Japan	37	64.7	26	25	7	5	Non/Minimally: 12 Frankly: 25	0	0	1
Ding 2018[3]	Cohort	3	Low	China	89	N/A	57	73	16	0	Non/Minimally: 11 Frankly: 78	1	0	0
Horiuchi 2022[17]	Cohort	3	High	Japan	15	62	10	13	0	2		0	1	1
Kashiwagi 2012[18]	Cohort	4	High	Japan	10	52	5	10	0	0		0	0	1

Katayama 2017[6]	Case-control	3	Moderate	Japan	8	64	5	1	1	6		0	0	1
Kato 2008[21]	Case Series	4	High	Japan	4	73	2	4	0	0		0	1	1
Li 2019[19]	Case-control	4	Moderate	China	7	58	5	0	0	7		0	1	1
Seok 2019[20]	Case-control	3	Low	Korea	15	55.1	7	9	3	3		0	1	1
Sumi 2018[9]	Cohort	3	High	Japan	4	N/A						0	0	1
Wada 2020[7]	Case-control	3	Low	Japan	22	63.9	16	18	3	1		0	0	1
Wang 2021[5]	Cohort	3	Low	China	212	57.2	144	169	36	7	Non/Minimally: 55 Frankly: 157	0	1	1

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

Center for Evidence Based Medicine (CEBM);[14] Quality in Prognostic Studies (QUIPS);[13] Submandibular gland (SMG); Sublingual (SLG); N/A = not applicable

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

Table 2: MRI Features of CXPA

	n(CXPA)	T	Modality	T1	T2	DWI	Other
AbdelRazek 2019[15]	3	1.5T	T1, T2, DWI with ADC	Not reported	Not reported	Mean ADC 0.83 ± 0.09 (0.75–0.93)	
Akutsu 2022[16]	37	1.5T	T1, T2, FS-T2W1, CE-FS-T1W1, DWI with ADC	Not well reported	Hypointense ring on T2	Not reported	Corona sign, black ring sign, capsule, and borders.
Horiuchi 2022[17]	15	1.5T or 3T	Non FS T1 and T2	Not reported	Not reported	N/A	Bone involvement (see CT section)
Kashiwagi 2012[18]	10	N/A	T1, T2, STIR	Not reported	Hypointense rim (7/10), heterogenous (10/10)	N/A	

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

Katayama 2017[6]	8	1.5T	CE-T1, FS-T2	Not reported	Heterogenous, mixed (8/8), and not different from PA.	Not reported	TIC analysis
Kato 2008[21]	4	1.5T	T1, T2, DWI	Not reported	Mild to moderate high (3/4), mixed (1/4)	Not quantified	
Li 2019[19]	7	N/A	T1, T2	Moderate signal (n=1/1)	High signal (1/1)	Not quantified	
Seok 2019[20]	15	N/A	T1, T2, DWI with ADC	Low signal (n=7/7)	High (6/7), unknown (1/7)	ADC: n=4/6 low (<1.2), n=2/6 (1.2) intermediate.	
Sumi 2018[9]	4	1.5T	T1, FS-T2, DWI with ADC	Not reported	Not reported	Mean ADC 1.23±0.19	
Wada 2020[7]	22	1.5T	T1, FS-T2, DWI with ADC	Not reported	Not reported	Not quantified – synthesized into histogram.	

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

Wang 2021[5]	212	1.5T	T1, FS-T2, DWI with ADC	Not reported	Heterogenous (173/212)	Mean ADC (Non or minimally Invasive) 1.0 (0.8–1.1) Mean ADC (Frankly invasive) 0.91 (0.6–1.5), Mean 0.93 (0.6–1.5), but not significant (p=0.455)

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

Table 3: CT Features of CXPA

Author	n(CXPA)	PNI	Bony Involvement	Low Attenuation	Calcification	Ill defined Borders	Lymph Nodes	Other Features
Horiuchi 2022[17]	15	1/15	Lytic Change (1/15)	N/A	N/A	N/A	N/A	N/A
Kato 2008[21]	4	3	Not reported	Necrosis (4/4)	4/4	N/A	N/A	N/A
Li 2019[19]	7	Not reported	Osteolysis (5/7)	N/A	N/A	N/A	N/A	N/A
Seok 2019[20]	15	Not reported	Not reported	(3/15) – not significant compared to PA (p=0.08)	N/A	5/15	7/15, **p=0.44**	Larger size (**p=0.01**), single tumour (0/15), deep lobe involvement (3/15)
Wang 2021[5]	212	N/A	N/A	N/A	76/192	123/212	67/212	

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

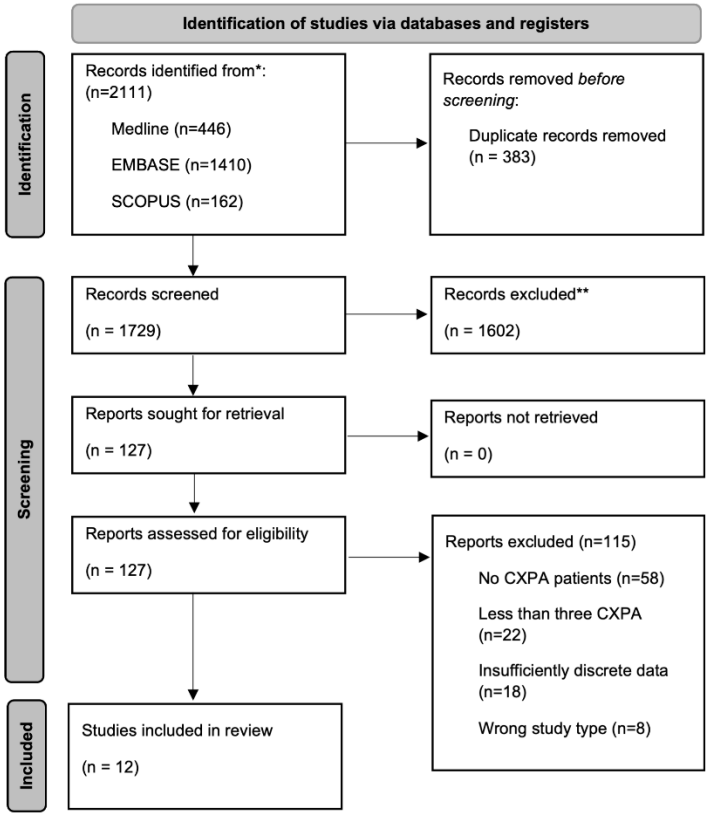

Figure 1

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press

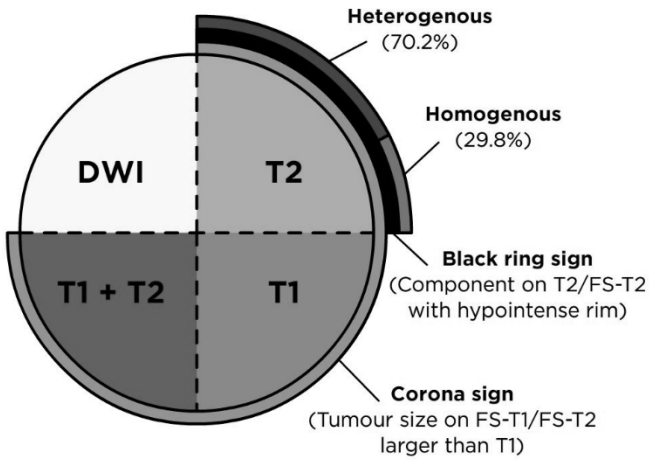

Figure 2

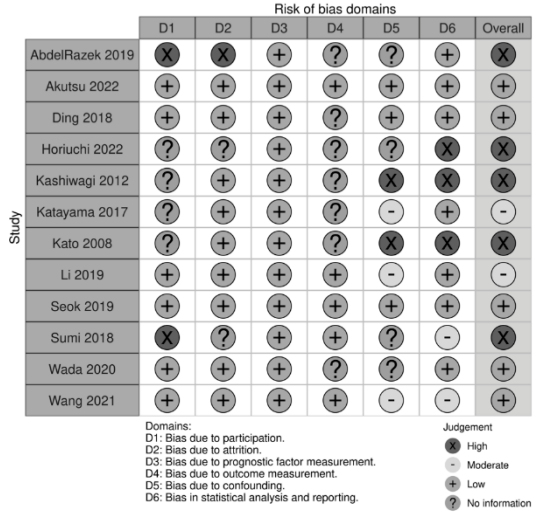

Figure 3

https://doi.org/10.1017/S0022215124001841 Published online by Cambridge University Press