This is an Accepted Manuscript for *The Journal of Laryngology & Otology*
DOI: 10.1017/S0022215124002159

Title: TP53 mutation may underlie increasing incidence of external auditory canal carcinoma

Authors:

Aashish Pandya[1] MBBCh, BSc (Anatomy), MRCS (DOHNS). ORCID ID: 0000-0003-1281-7483

Deepak Chandrasekran[1] MBBS, FRCS ORL-HNS. ORCID ID: 0000-0002-3427-3926

Krishna Suchak[1] BDS MFDS FRCPath ORCID ID: 0009-0008-6541-0963

Jagdeep S Virk[1] MA FRCS ORL-HNS PGCert MedEd ORCID ID: 0000-0001-9065-8962

[1] Otolaryngology and Pathology Department, Royal London Hospital, Barts NHS Health Trust

Authorship:

AP - Data Curation, Formal Analysis, Roles/Writing - original draft

DC – Data Curation, Formal Analysis, Roles/Writing - original draft, Writing - review and editing.

KS – Data curation, Methodology, Formal Analysis Writing - review and editing, Data curation.

JSV – Conceptualization; Data curation, Supervision, Formal Analysis Writing - review and editing.

Corresponding Author

Mr Aashish Pandya

Otolaryngology Department, Whipps Cross Hospital, Barts NHS Health Trust.

Aashish.pandya@nhs.net

07891480044

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

Abstract

Background: Primary neoplasm of the external auditory canal (EAC) has historically been documented to have a low incidence rate of between 1-6 per million internationally, with UK incidence yet to be officially cited.

Methods: Here, we report a rise in incidence at a single UK trust with seven carcinomas (six T4 EAC squamous cell, T4 basal cell) reported within an eighteen-month period. All tumours underwent next generation sequencing (NGS).

Results: The cases recorded represented a twofold rise in incidence in reference to international literature from a population-adjusted estimate of 0.5-3 cases for the catchment area to seven cases. All cases were treated with temporal bone resections (n=7) and with post-operative radiotherapy in six cases**.** Tumour analysis showed all were *TP53* mutant and HPV/*P16* negative.

Conclusion: We suggest chronic inflammation and genetic alterations as putative contributory factors in our case series and outline clinical strategies for timely detection of EAC neoplasms.

Keywords

Neoplasms, External Auditory canal, epigenetics, squamous cell carcinoma, TP53 mutations

Introduction

Malignant neoplasm of the external auditory canal (EAC) is a rare pathology with an incidence of between 1-6 per million people[1]. The most common neoplasm is squamous cell carcinoma (SCC). Less common types include basal cell carcinoma, adenoid cystic carcinoma (ACC), ceruminous adenocarcinoma and middle ear adenocarcinoma[2] . Early diagnosis can prove challenging owing to the rarity of the disease together with overlapping symptoms between EAC neoplasm and more prevalent pathologies such as chronic/necrotising otitis externa. All three can present with otalgia and discharge that are refractory to antibiotics.

Cutaneous SCC (cSCC) has known risk factors of fair skin phenotype being exposed to high UV radiation, and immunosuppression[2]. The carcinogenic risk factors for squamous carcinoma of the EAC (EACSCC) are less clear with none of the above definitively shown to be causal. Chronic inflammation leading to metaplasia is the leading theory of pathogenesis but the mechanism by which this occurs is unknown but may involve changes in pH of the EAC [3,6]. Alternative theories of pathogenesis include the association of HPV with EACSCC[4], or previous radiation[6].

The genetic basis for EACSCC remains largely unknown owing to its rarity, in contrast to the genetic mapping available for cSCC and HNSCC. Sato et al. have been the first to map genetic alterations using genome sequencing on eleven primary tumours of the EAC from ten different patients with two-third of the tumours showing *TP53* mutations[7].

https://doi.org/10.1017/S0022215124002159 Published online by Cambridge University Press

Initial management after biopsy proven diagnosis is staging by Magnetic Resonance Imaging (MRI) and Computerised Tomography (CT) (Figure 1), with subsequent Multidisciplinary Team discussion[8]. The Pittsburgh Staging System[9] is an accepted staging system in reference to cancers of the EAC. The primary treatment modality is surgery with the aim of en-bloc resection (temporal bone and parotid) with postoperative radiotherapy in advanced tumours[8]. Late stage and high-grade differentiation of SCC are associated with worse prognostic factors [8,3].

The aim of this correspondence is to highlight the increasing incidence of neoplasms affecting the EAC as documented in this regional case series with seven cases over an eighteen-month period with reference to the Hospital Episode Statistics (HES) database[10] and identify potential aetiological or mechanistic factors underlying this rise.

Methods

We analysed all (n=7) cases of primary neoplasms of the EAC diagnosed at a regional NHS trust over an eighteen-month period. All biopsy proven patients discussed at the MDT were included. Data were collected via an electronic database on patient demographics (age at diagnosis, sex); histological subtype and grade; treatment modality; marginal status (clear, involved, marginal); and recurrence. The Pittsburgh Staging System[9] was used to stage the cancers. Tumour specific analysis included histopathological characterisation using staining of tumour invasion, next generation sequencing (NGS) and HPV status using in-situ hybridisation.

Results

Table I summaries the main demographics and treatment pathways of each patient. Six were diagnosed with squamous cell carcinoma of the EAC and one with Basal Cell Carcinoma of

https://doi.org/10.1017/S0022215124002159 Published online by Cambridge University Press

the EAC, with all cases graded as T4. The male to female ratio was 2:5 and of the average age was 64.5years. Mean time (months) of follow post-surgery (correct to May 2024) is 14.7 months with one mortality and one patient with residual disease. Patient A and E were the only reported case to have nodal disease (Table II) . No cases demonstrated distant metastases.

To test whether the rise in incidence seen locally was reflected nationally we performed a search on the HES database[10], which highlighted no diagnostic code for cancers of the external auditory canal. As a control we used titles of "Carcinoma in situ: Skin of ear and external auricular canal" and "Malignant neoplasm: Middle ear". From the data available it was not possible to comment on any increase in cases of EAC malignancy over a 5 year period. Carcinoma of the external ear and EAC. There were 514 cases seen in 2022- 2023[11] compared to that of 491 in 2016-2017[12]. For carcinomas of the middle ear there were 26 cases in 2016-2017[12] rising to 50 in 2021 -2022[13], and 39 from 2022 -2023[11]. We also performed a systematic literature review with broad search terms of "neoplasm OR carcinoma OR tumour OR malignancy OR cancer" AND "External auditory OR ear canal OR EAC OR ear" and did not find any reports of rising incidence.

With regards to potential underlying risk factors, three of the seven patients had well controlled type two diabetes with all of them having a haemoglobin A1c of less than 50mmol. Patient B suffered with chronic eczema affecting her ears and swam regularly. Patient F had a previous BCC of the concha but had clear margins with excision three years prior to re-presentation. All SCC cases had prolonged antibiotic treatment in both primary and secondary care for greater than four weeks prior to diagnosis. This was either due to

https://doi.org/10.1017/S0022215124002159 Published online by Cambridge University Press

suspicion of necrotising externa or severe otitis externa. Of the four patients who had ear swabs sent for microbiology analysis, none showed any growth.

Table II summaries the tumour characteristics observed. All patients yielded negative P16/HPV analysis. All had bony involvement, with two cases having parotid involvement and the BCC case was the only example to show perineural invasion. Sequencing showed all seven cases demonstrating *TP53* mutation, with 2 cases over >50%, with *ERBB2* and *CDKN2A* mutations observed separately in one case each (Table II). Patient F (Figure 2) displayed SCC infiltration of bone and Patient D (Figure 3) demonstrated circumferential severe epithelial dysplasia of the external auditory canal epidermis with an exo-endophytic growth pattern.

All patients included in this report underwent en bloc temporal bone resection. Six patients underwent PORT with two subsequently undergoing palliative immunotherapy (Cemiplimab) due to either recurrence (patient E) or residual tumour (patient A). Patient A was noted to have residual disease on her PORT planning imaging and underwent five weeks of PORT but this was stopped after subsequent imaging showed further tumour progression.

Patient E is the only reported mortality to date of the series and had associated N3 staging. They had previous nasopharyngeal cancer (NPC) treated twenty years ago in China with wide field radiotherapy, such that adjuvant RT was not possible. Intraoperatively he had multiple frozen sections positive at the sinodural angle. His post operative pathology showed cancer involving the dura, mastoid and parotid. His recurrence occurred five months after surgery and he passed away 8 months after surgery.

https://doi.org/10.1017/S0022215124002159 Published online by Cambridge University Press

Of the seven completed operations the facial nerve was preserved in two and sacrificed in five of the resections. Neck dissections were performed in all patients with EACSCC. In this series only two patients were seen to have nodal involvement with associated extracapsular spread (ECS) (Table II).

Discussion

This report shows a rise in incidence of EACSCC with all cases showing *TP53* mutations. Given the rarity in clinical practice, and by extension in the research literature, there is currently limited understanding of underlying aetiology.

Our findings are largely comparable with other published case series. The largest case series review in Australia was of 39 patient patients collating twenty years of data from 1974 to 1995[14]. They advocated for the use of a congruous staging system to allow comparison between studies. They comment on resection margin status as a key prognostic factor and a non-significant but important role of radiotherapy, where resection margins were positive. A notable feature of their series was recurrence in the EAC from previous pinna and periauricular sites. Our smaller series only noted one recurrent BCC with previous excision from the concha three years prior to the lesion in the EAC emerging.

A review of 95 patients with both middle ear carcinomas (MESCC) and EACSCC in Japan in 2006[3] came to similar conclusions from the Australian study. They both established early surgical treatment followed by chemo/radiotherapy provided the best survival rates. Staging, clear tumour margins, recurrence, and metastasis had the greatest significance influence on survival. Of note only 12% of patients in their study had a history of recurrent otitis externa and tended to present atypically. This highlights some of the challenges faced with early

https://doi.org/10.1017/S0022215124002159 Published online by Cambridge University Press

diagnosis of the EACSCC with patients often presenting with generic non-specific symptoms, overlapping with otitis externa resulting in prolonged antibiotic treatment. This report supports a lower threshold for biopsy and imaging after a period of infective antibiotic therapy.

A more recent literature review[8] focused on SCC of the temporal bone. The study echoed findings from previous papers noting a lack of universal treatment strategy, with late stage and differentiation of cancer giving the worst prognostic factors[8]. The review also identifies the need for a more collaborative effort in producing high quality research to help overcome the rarity of this disease. The last review of EAC neoplasms based on UK practice was published in 1993, focusing on the efficacy of surgical treatments[15], highlighting the need for more up to date local guidance on the disease. Overall UK incidence is yet to be established and formalised as reflected by no specific category within HES database.

Sequencing shows TP53 mutation in all cases

The genetic analysis from our case series of patients demonstrated mutations in TP53 with one displaying an additional ERBB2 mutation. These findings are consistent with other genetic studies of EACSCC [7]. Sato et al[7] found that in their eleven sample case series, the mutations in TP53 was the most common gene mutation found in 63.3% of patients. The study also showed that the activation of apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like (APOBEC) was associated with the mutational progression, similar to other SCC subtypes. This suggests a link between chronic inflammation and tissue damage and the mutational pathway in which APOBEC is dominant[7]. APOBEC mutations have been shown to drive carcinogenesis in aggressive cSCC[16].

https://doi.org/10.1017/S0022215124002159 Published online by Cambridge University Press

Chronic inflammation may underly tumorigenesis

The implication of chronic inflammation in the metaplasia-dysplasia requires large scale cohort data collection referencing past medical history and duration of ear pathology to try and identify potential drivers of inflammation. Within our smaller sample size potential inflammatory drivers could have arisen from diabetes, skin conditions and chronic discharge. However, this sample size was too small to draw significant conclusions. Likewise whether COVID or the pandemic had any impact either in pathogenesis or clinical practice is unclear but HES data pre and post pandemic shows no obvious increase in incidence when applied to carcinomas on the ear skin and EAC[11-13]. It has been suggested that higher pH of the skin in the auditory canal results in a more severe otitis externa lending to chronicity[6]. Although the pH of the EAC was not measured in this study this could be investigated further with a hypothesis of alkaline pH being a local risk factor for progression to EACSCC.

The relevance of HPV as a risk factor for EACSCC and middle ear SCC has been shown to be less significant compared to its role in oropharyngeal SCC[7]. However HPV 16-18 have been found in MESCC[17-18] with Masterson et al also finding HPV-16 in EACSCC tumours[19]. These findings warrant further investigation with larger data samples and standardised analysis to truly clarify the role of HPV in the pathogenesis of EACSCC.

Future work

The role of epigenetics could perhaps have the largest influence in the rise in incidence of EACSCC. While the genetic basis for cancer is well understand it has been proposed that epigenetic changes can be the drivers of initiating and progression of cancer as a consequence of aberrant regulation of signalling pathways[20-21]. One such association is the disruption of progenitor cells resulting in reduced expression Wnt gene signalling and subsequent stem cell

https://doi.org/10.1017/S0022215124002159 Published online by Cambridge University Press

instability[21]. This is pertinent to colorectal cancers where 90% of early progression are linked with altered Wnt signalling[22]. In addition, epigenetic mutations in DNA methylation are widely detected in lung adenocarcinomas and are implicated in their pathogenesis, with links between environmental exposure to cigarette smoke and DNA methylation of the genome[23]. The epigenetic mutations and environmental influences in EACSCC are yet to be elucidated but warrant further investigation given the documented rise in incidence. Whether pH changes, chronic inflammation or HPV are involved in the observed TP53 mutation remains to be seen but holds major therapeutic potential given the reversibility of epigenetic changes (unlike genetic mutations). Furthermore, immunotherapy is a promising new avenue of treatment and may potentially be used in the neoadjuvant setting, and not solely in the context of palliative or unresectable cases[24].

Conclusion

Primary SCC of the external auditory canal has historically been considered a rare disease. This case series highlights a significant rise in incidence of *TP53* mutant carcinomas. This spike has highlighted the need for up-to-date guidance and pathways given the importance of early diagnosis in treatment. Further work centred around larger cohorts are required to clarify clinical traits and molecular pathophysiology specific to EACSCC. Developments can help guide local practice and also generate better insight into therapeutic interventions especially in high grade advanced disease where prognosis is particularly poor.

Acknowledgements

No further acknowledgements

Funding

No funding contributed to this report.

Competing interests:

The authors declare none.

Ethical Considerations

All data was part of routine clinical care. Patient information used in the article was anonymised to gender and age. Participants were not allocated to particular study arms and treatment was decided via Head and Neck MDT irrespective of this article. No experimental treatment was undertaken. Verbal consent was obtained from all patients during clinical follow up with the ENT team.

The data that support the findings of this study are available from the corresponding author [AP], upon reasonable request.

References

1. Oya R, Takenaka Y, Takemura K, Ashida N, Shimizu K, Kitamura T, Yamamoto Y, Uno A. Surgery With or Without Postoperative Radiation Therapy for Early-stage External Auditory Canal Squamous Cell Carcinoma: A Meta-analysis. *Otology & Neurotology* 2017;**38**:1333-1338

2. Allanson BM, Low TH, Clark JR, Gupta R. Squamous Cell Carcinoma of the External Auditory Canal and Temporal Bone: An Update. *Head Neck Pathol* 2018;**12**:407-418

3. Yin M, Ishikawa K, Honda K, et al. Analysis of 95 cases of squamous cell carcinoma of the external and middle ear. *Auris Nasus Larynx* 2006;**33**:251-257

4. Tsai ST, Li C, Jin YT, Chao WY, Su IJ. High prevalence of human papillomavirus types 16 and 18 in middle-ear carcinomas. *International journal of cancer* 1997;**71**:208-212

5. Mofat DA, Wagstaf SA, Hardy DG. The outcome of radical surgery and postoperative radiotherapy for squamous carcinoma of the temporal bone. *Laryngoscope* 2005;**115**:341–347

6. Martinez Devesa P, Willis CM, Capper JW. External auditory canal pH in chronic otitis externa. *Clin Otolaryngol Allied Sci* 2003;**28**:320-324

7. Sato K, Komune N, Hongo T, Koike K, Niida A, Uchi R, Noda T, Kogo R, Matsumoto N, Yamamoto H, Masuda M, Oda Y, Mimori K, Nakagawa T. Genetic landscape of external auditory canal squamous cell carcinoma. *Cancer Sci* 2020;**111**:3010-3019

8. Lechner, M., Sutton, L., Murkin, C. *et al.* Squamous cell cancer of the temporal bone: a review of the literature. *Eur Arch Otorhinolaryngol* 2021**;278**:2225–2228

9. Moody SA, Hirsch BE, Myers EN. Squamous cell carcinoma of the external auditory canal: an evaluation of a staging system. *Am J Otol* 2000;**21**:582–588

10. NHS Digital. Hospital Admitted Patient Care Activity. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity. Accessed 2 December 2023

11. NHS Digital. Hospital Episode Statistics, Admitted Patient Care: Diagnosis – England, 2022 – 2023 [NS]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2022-23.Accessed 2 December 2023.

12. NHS Digital. Hospital Episode Statistics, Admitted Patient Care: Diagnosis – England, 2016 – 2017 [NS].Available from https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2016-17. Accessed 2 December 2023

13. NHS Digital. Hospital Episode Statistics, Admitted Patient Care: Diagnosis – England, 2021 – 2022 [NS].Available from https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22. Accessed 2 December 2023

14. Lim, Lim LH, Goh YH, Chan YM, Chong VF, Low WK. Malignancy of the temporal bone and external auditory canal. *Otolaryngol Head Neck Surg* 2000;**122**:882-886

15. Prasad S, Janecka IP. Efficacy of surgical treatments for squamous cell carcinoma of the temporal bone: a literature review. *Otolaryngol Head Neck Surg*1994;**110**:270-280

16. Cho RJ, Alexandrov LB, den Breems NY, et al. APOBEC mutation drives early-onset squamous cell carcinomas in recessive dystrophic epidermolysis bullosa. *Sci Transl Med* 2018;**10**:aas9668

17. Tsai ST, Li C, Jin YT, Chao WY, Su IJ. High prevalence of human papillomavirus types 16 and 18 in middle-ear carcinomas. *Int J Cancer* 1997;**71**:208-212

18. Jin YT, Tsai ST, Li C, et al. Prevalence of human papillomavirus in middle ear carcinoma associated with chronic otitis media. *Am J Pathol* 1997;**150**:1327-1333

19. Masterson L, Winder D.M, Marker A, Sterling J.C, Sudhoff, H.H, Moffat D.A, Kin Cho Goon, P. Investigating the role of human papillomavirus in squamous cell carcinoma of the temporal bone. *Head Neck Oncol* 2013;**5**:22.

20. Sharma S, Kelly TK, Jones PA. Epigenetics in cancer. *Carcinogenesis* 2010;**31**:27-36

21. Feinberg A, Ohlsson R, Henikoff, S. The epigenetic progenitor origin of human cancer. *Nat Rev Genet* 2006; **7**:21–33

22. Fodde R, Smits R, Clevers, H. APC, signal transduction and genetic instability in colorectal cancer. *Nat Rev Cancer* 2001;**1**: 55–67

23. Cancer Genome Atlas Research, N. Comprehensive molecular profiling of lung adenocarcinoma. *Nature* 2014*;* **511**:543–550

24. Boutros A, Cecchi F, Tanda ET, Croce E, Gili R, Arecco L, Spagnolo F, Queirolo P. Immunotherapy for the Treatment of Cutaneous Squamous Cell Carcinoma. *Frontiers in Oncology* 2021;**11**:733917

This is an Accepted Manuscript for *The Journal of Laryngology & Otology*
DOI: 10.1017/S0022215124002159

Table I: Summary of patients included in case series highlighting key demographics, pathology, treatment and outcomes. Follow up correct to December 2023

Patient	Sex	Age	Initial complaint	Diagnosis	Staging	Past Medical History	Treatment	Facial Nerve outcome	Follow up post operatively (Months)	Outcome
A	F	61	Pain	Left EACSCC	T4N1M0	Hypertension Previous Endometrial Cancer Lymphedema	Parotidectomy Pinnectomy Petrosectomy, Partial Mandibulectomy Neck dissection PORT Current: palliative immunotherapy	Resected	17	Residual disease Noted on repeat pre-RT planning scan (delayed due to wound dehiscence)
B	F	45	Pain + Discharge	Left EACSCC	T4N0M0	Eczema	Parotidectomy, Petrosectomy, Neck dissection PORT	Preserved	17	Remission
C	F	71	Pain + Discharge	Right EACSCC	T4N0M0	T2DM- Hba1c 49 Hypertension Hypercholesterolemia	Parotidectomy, Petrosectomy, Neck dissection PORT	Resected	14	Remission
D	F	72	Pain + Bleeding	Right EACSCC	T4N0M0	Osteoarthritis	Parotidectomy Pinnectomy Temporal Bone resection Neck dissection PORT	Resected	13	Remission

https://doi.org/10.1017/S0022215124002159 Published online by Cambridge University Press

E	M	62	Discharge	Right EACSCC	T4N3M0	Previous Nasopharyngeal carcinoma requiring wide field Radiotherapy. Hypercholesterolaemia IHD CVA	Petrosectomy Pinnectomy Parotidectomy Neck dissection (Prior wide field RT for NPC) Palliative Immunotherapy	Resected	8	Out of field recurrence at 5 months post op. RIP at 8 months
F	F	75	Pain + Discharge	Left EACSCC	T4N0M0	HTN T2DM – Hba1c 49 in July 2023 Polymyalgia rheumatica	Lateral temporal bone resection, Pinnectomy, Petrosectomy, Parotidectomy, Neck Dissection PORT	Resected	9	Remission
G	M	76	Stenosis + Discharge	Left EACBCC	T4NxM0	Previous BCC of the concha 3 years prior to presentation. Treated by excision and reported clear margins	Sleeve resection mastoidectomy, Temporal bone dissection, Petrosectomy PORT	Preserved	18	Remission

https://doi.org/10.1017/S0022215124002159 Published online by Cambridge University Press

Table II: Tumour Characteristics. ECS - Extracapsular spread. LVI -Lymphovascular Invasion. NGS – Next Generation sequencing

Patient	Staging	LN	Bone Invasion	Parotid invasion	LVI	Perineural	HPV status	Staging	NGS
A	Well to moderately diff SCC	1/32 with ECS	Yes with Mandible	Yes and + intraparotid node	Suspicious	Not seen	P16/HPV neg	pT4a pN1	TP53 33%
B	Mod diff SCC	0/29	Yes	No	Not seen	Not seen	P16/HPV neg	pT4a pN0	TP53 71% and ERBB2 34%
C	Mod to poor diff SCC	0/35	Yes with skull base	No	Suspicious	Not seen	P16/HPV neg	pT4b pN0	TP53 8% and CDKN2A 20%
D	Mod to poor diff SCC	0/40	Yes	No	Not seen	Not seen	P16/HPV neg	pT4a pN0	TP53 56%
E	Poorly differentiated SCC (involving dura, parotid and mastoid)	8 LN positive for SCC and 1 ECS	Yes	Yes	Yes	Not seen	P16/HPV neg	pT4pN3	TP53 38 %
F	Mod to poor diff SCC	0/22	Yes	No	Not seen	Not seen	p16/HPV neg	pT4a pN0	TP53 32%
G	Basosquamous BCC	0/2	Yes	No	Yes	Yes	p16/HPV neg	pT4a pNx	TP53 16%

https://doi.org/10.1017/S0022215124002159 Published online by Cambridge University Press

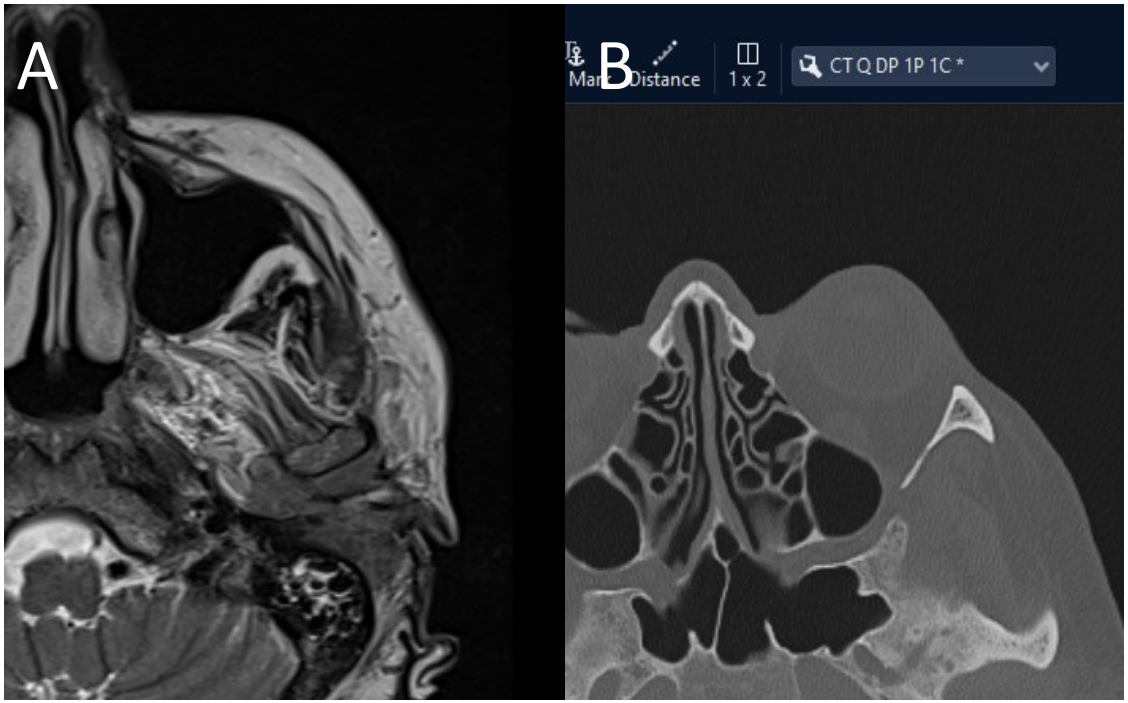

Figure 1: A) MRI Left Internal acoustic meatus showing increased soft tissue in the left external auditory canal and in the surrounding regions B) CT Left Petrous bone demonstrating soft-tissue thickening in the left external auditory canal.

https://doi.org/10.1017/S0022215124002159 Published online by Cambridge University Press

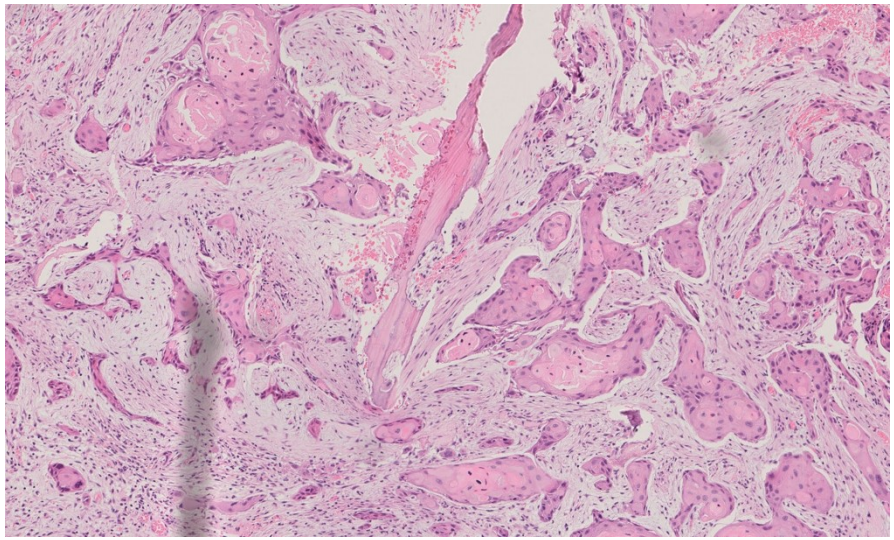

Figure 2: High power image to show moderate to poorly differentiated squamous cell carcinoma infiltrating bone and associated with a fibromyxoid stromal reaction. Hematoxylin and eosin staining of tissue and cell sections.

https://doi.org/10.1017/S0022215124002159 Published online by Cambridge University Press

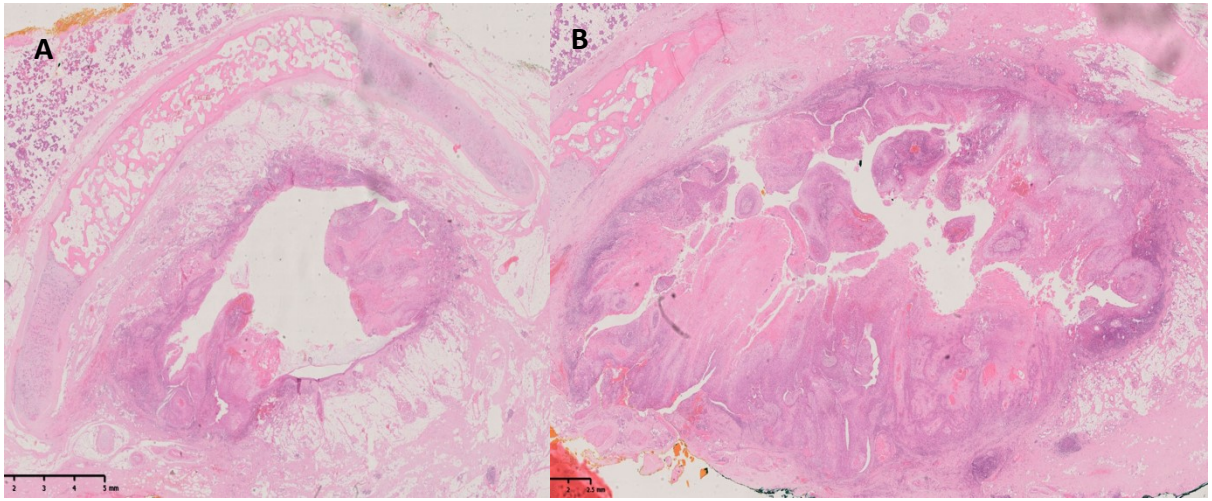

*Figure 3: **A**:Low power image of squamous cell carcinoma arising from widespread circumferential severe epithelial dysplasia of the external auditory canal epidermis with an exo-endophytic growth pattern. In image **B** the severe epithelial dysplasia is discontinuous with polypoid tumour protruding into the canal lumen. Hematoxylin and eosin staining of tissue and cell sections.*

https://doi.org/10.1017/S0022215124002159 Published online by Cambridge University Press