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# MR Imaging of Perineural Spread from Retrieved Clinico-Radio-Pathological Archives of "Asymptomatic" Patients with Head and Neck Malignancies: Constellation of Diagnostic Findings by Conventional and Diffusion Techniques

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## Abstract

*Background:* Conventional MRI has been working horse for diagnosis of perineural spread in head and neck cancer, either symptomatic or not. The purpose of this retrospective research is to collect data of asymptomatic patients to reveal conventional MRI signs with additional data on diffusion of primary tumor and perineural tissues.

*Aim of study:* The aim of the current research is to evaluate MRI findings in exclusively "asymptomatic" patients with Pathologic-Radiologic proof of PNTS in head and neck malignancies.

*Patients and Methods:* This retrospectively approached research aimed to collect patients' data from the clinico-radio-pathologic Archives of Radiology department in our tertiary institution. These were collected from June 2021 to June 2023 staring by clinical archives.

*Results:* Conventional signs included "nerve enhancement"(100%), "foraminal enlargement" (93.3%), "obliteration of foraminal fat"(93.3%),"foraminal destruction" (13.3%), intracranial extension (73.3%), muscular atrophy (20%). Diffusion was restricted at main tumor sites and inside foraminal nerve soft tissue of perineural invasion with low ADC $<1 \times 10^{-3}$ $cm^2$/sec.

*Conclusions:* MRI, including DWI, is essential in the evaluation of perineural spread in head and neck cancer. The combination of conventional MRI sequences and DWI provides comprehensive information on the extent of tumoral spread, aiding in diagnosis, treatment planning, and prognosis.

***Key Words:*** *MRI – Perineural spread – Carcinoma.*

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## Introduction

**PERINEURAL** tumor spread (PNS) of head & neck malignancies is a form of metastatic disease and defined by direct continuous extension of tumour along perineural space for some distance from primary lesion **[1,2,3]**. Although PNS has a low overall incidence, 2.5 to 5%, it is considered of high clinical importance, carrying poor prognosis, upstaging & upgrading tumors, with additionally increased local recurrence risk up-to 45% **[4,5,6]**. Any nerve may serve as a conduit for spread of head & neck tumours. Also, any segment can be affected by PNTS whole way from nerve exit/entry zone (NEZ), either intra-and extra-cranial course, with bi-directional mode of spread, being ante-grade and retro-grade. Centripetal extension along branches of trigeminal nerve may lead to tumour infiltration of Gasserian nucleus (GN) in Meckel's cave, and less frequently cisternal segment **[7,8,9]**.

The road of spread can also be in direct contiguity or with skip pattern. This explains for why it is essential to conduct scanning that covers whole different zones of the related sensory supply. The maxillary & mandibular divisions of trigeminal

***List of Abbreviations:***

PNS : Perineural Spread.
PNTS : Perineural Spread.
MRI : Magnetic resonance imaging
ADC : Apparent Diffusion Co-efficient.
NPC : Nasopharyngeal carcinoma.
HN : Head And Neck.
SCC : Squamous Cell Carcinoma.
ACC : Adenoid Cystic Carcinoma.
PPF : Pterygopalatine fossa.
SOF : Superior Orbital Fissure.

nerve & facial nerve are most commonly implicated. The ophthalmic division of trigeminal nerve and hypoglossal nerve are less frequently involved. Still, any cranial nerve can be implicated by PNTS, even olfactory, optic, Vagus- & Hypoglossal nerves **[10,11,12].** Multiple neuronal connections are described between nerves in dissections & noticed in imaging practice. There are multiple connections between divisions of trigeminal nerves. Also facial & trigeminal nerves are inter-connecting at multiple sites, & between branches of extra parotid segment of VII nerve. Details are beyond scope of article **[13,14,15,16].**

Imaging of PNS in HN malignancies is readily accomplished by MRI, CT & PET/CECT. MRI is main and best tool, due to its superior soft tissue contrast & less susceptibility to artifacts from any hardware compared with (CT) **[17,18,19,20]**. Still, we are witnessing increasing use of FDG positron emission tomography with contrast-enhanced CT (PET/CECT) in evaluation of HN malignancy for staging, re-staging, & response evaluation. The accuracy of PET/CT is detection of PNS is notably lower than MRI due to its lower anatomical resolution, image artifacts, and higher incidence of false positive/false negative interpretations. A false negative scan is attributable to tumor biology, commonly exampled by slow-growing adenoid cystic carcinoma. False negative can also be created by improper PET/CT co-registration, partial volume avreaging of subcentemtric lesions or high adjacent background activity. False positive scans can be seen in non-neoplastic hyper-metabolic pathologies **[21,22]**. Careful assessment of clinical history and correlative imaging should be highly considered to avoid pitfalls. Albeit afore-mentioned role of PET/CT, MRI is yet still commonest modality serving many wonderful merits; showing high sensitivity of 96-100% for detection of PNTS; graded "excellent". Furthermore, it has high accuracy in predicting entire extent of disease, including intra cranial extension **[23,24].**

A constellation of MR diagnostic of spread has been widely discussed in literature, either for symptomatic or asymptomatic patients. These included nerve enlargement, enhancement-usually first sign and could be only one in early stages-foraminal enlargement, obliteration of fat planes and foraminal destruction, a delayed finding and neuropathic denervation atrophy **[21]**. The mechanism of nerve enhancement in PNTS was explained by disruption of blood-nerve barrier with raised permeability of endo-neurial capillaries.

## Patients and Methods

*Patients:* This retrospectively approached research aimed to collect patients' data from the clinico-radio-pathologic Archives of Radiology department in our tertiary institution. These were collected from June 2021 to June 2023 staring by clinical archives. The "Ethics Committee" of our medical institution had approved the proposed protocol. An informed consent was not necessarily obtained from patients or relevant since it is a retrospective study. Inclusion criteria: a) adults >18 years, c) Asymptomatic c) pathology proven perineural spread by dedicated immuno-histo-chemistry, d) Any type of head and neck malignancy known by PNS, including carcinomas, sarcomas and lymphomas. The exclusion criteria included a) patients with prior surgeries that alters the morphological signal and perineural lymphatics, d) symptomatic tumor, c) Children, d) Usual contra-indication to MRI.

*MRI imaging protocol adopted in our imaging center for head and neck:* MRI examinations had been conducted on a closed 1.5-Tesla machine (Avanto, Germany) by a dedicated 16-channel SENSE "head-&-neck" coil): Conventional MRI-protocol covered skull base & upper neck with parameters: a) Scout images, b) Multi-planar axial, coronal, & sagittal T2-W with: FSE: TR=6000ms, TE=103ms, NA-averages=4, matrix=256 x 245mm, section thickness=3.5mm, gap=3.5mm), d) axial T1-WI: TR, 673ms, TE=8ms, NA=averages= 4, section thickness=5.0mm, gap=2.5mm, matrix=256 x 256). DWI as done in our center (If available in examination)had been obtained using single shot spin echo planar in axial plane with (TR=1760ms, echo time TE=120ms, slice thickness=3.5mm; gap=4mm, Number of averages (NA)=6. Three b-factors: 0, 500 & 1000 sec/mm$^2$, 5mm section thickness, FOV =245mm. Contrast-enhanced sequence made by manual injection of GAD (Gadopentetate-Dimeglumine); using dose=0.1mmol/kg) followed by 25ml saline flush. Enhanced images are obtained through lesion in axial plane and at different time intervals. For CT imaging (If available), non-contrast scans were performed on 160-MSCT (AquillionToshiba, Canon; Japan). Spiral scanning was performed at 120 kVp and 70 mAs. IV) Image analysis: The entire course of each nerve traversing primary tumor site was evaluated both intra-& extra-cranial segments. Sites of whole course of nerve & branches are scrutinized, with foramina and fissures, e.g. PPF, vidian canal, f. rotundum & palatine canals for V2, f. ovale & inferior alveolar canal for V3. The examination must be ante-grade & retrograde for each nerve, and for any division of Trigeminal nerve, while V1, V2, and V3 must be also scrutinized. Neuronal inter-connections must be examined between V & VII at 3 sites: Parapharyngeal space, peri-/retro-auricular area & petrous apex. Perineural tumor spread was considered positive by signs of PNTS: a) foraminal enhancement: subjectively by hyper-enhanced as compared to normal contra-lateral side, or segment of nerve, b) foraminal enlargement: asymmetric widening of canal as compared to expected normal anatomy known by experience of normal subjects, or by comparison to other side, c) obliteration of perineural fat pad, or obliteration of CSF signal at f. ovale when occupied

by fluid signal of Meckel's cave, d) On CT, foraminal margins are reported as "remodeling" shown as smooth expansion, or "Permeative" meaning aggressive destruction, e) Intracranial extension: intracranial enhancement +/- obliteration of Meckel's cave, lateral bulging or enlargement of CS or dural thickening, f) Neuropathic atrophy of muscles: either acute by increased size, T2 signal intensity / GAD incremental enhancement, or chronic shown ass decreased size, T2 signal/enhancement, +/- fat replacement. 7) Analysis of diffusion: ADC calculated by Workstation, from ROIs placed on solid portions of primary tumor and course of PNTS (Intra-foraminal or adjacent cord thickening along nerve). Three ADC values were got, and mean ADC was used in statistical analysis.

*Statistical analysis of the data:* Data were analyzed using IBM SPSS software package version 20.0 (Armonk, NY: IBM Corporation). Qualitative data were described using number and percent. The used tests were: 1) Chi-square test For categorical variables, to compare between different groups, $x^2$) Fisher's Exact / Monte Carlo Correction for chi-square if >20% of cells have expected count <5.

## Results

Our retrospective research enrolled 45 cases PNS with head and neck malignancies were evaluated in this study; 36 patients (80%) were male, 9 patients (20%) were female. The mean age (± SD) was 42.27 (±16.31). Thirty nine presented as primary malignancy (86.6%), compared to only 6 (13.3%) who had recurrent disease. Regarding pathology type: Squamous cell carcinoma (SCC) was most common encountered primary tumour; (n=21, 46.7%), followed by muco-epidermoid (MEC) in 15 (33.3%), adenoid cystic carcinoma-ACC in 6 (13.3%) & lymphoma in 3 (6.7%). Out of 21 SCCs, 18 had NPC & 3 had oropharyngeal carcinoma. SCCs showed PNTS mostly along V3 (100%) followed by V2 (37%) & hypoglossal nerve (12%). Muco-epidermoid mainly spread was along facial & V3 nerves (60%) followed by V2 &Vidian nerves (33%). Adenoid cystic carcinoma showed equal percentage spread along V1, V3 and Vidian nerves (33%). Only one case of lymphoma showed spread along V2, V3 &Vidian nerves. The primary sites involved by tumour and PNTS distributed as: Nasopharynx in 18 (40%), hard palate in 3 (=13%), parotid gland in 15 (26%), lacrimal gland in 3 (=7%), oropharynx in 3 (7%) & lymphoid tissue (lymphoma) also as primary site in 3 cases; = 7% of patients (Fig. 1).

Revealing relation between primary tumour site & nerve affection by PNTS; In our study all cases with primary tumour arising from parotid gland showed PNTS along corresponding facial nerve with significant *p*-value of 0.001. No significant relation between other primary sites & corresponding nerve affected was noted. The lacrimal gland tumors showed exclusive spread along V1 ophthalmic division of CNV (=3), while parotid neoplasm spread along VII (=15) & V3 (n=9), Nasopharynx (NPC) spread along V3 (n=3), hypoglossal (n=3) & V2 nerve (n=12), while palatal tumors exclusively spread along V2 (lesser & greater palatine canals), three lymphomas spread along Vidian-V2. As for "foraminal involvement", PNTS was noted in f. Ovale (n=30; 60%), foramen rotundum (n=15; 33%), Vidian nerve (n=18; =46%), PPF (n=18;46%), SOF (n=9; 20%), mandibular (n=9;13%), stylomastoid (n=15;33.3%), Hypoglossal (n=3; 6%) & f. lacerum (n=3; 6%). Bilateral affection (n=15; 33.3%); illustrated in Fig. (2-A). While distribution of cranial nerves affected was noted as: mandibular (V3) was most commonly involved (n=36; 80%), maxillary (n=15; 33%).Three (6.7%) showed PNTS along ophthalmic (V1), 18 (40%) along Vidian, 15 (33.3%) along (CNVII) & 3 showed spread along hypoglossal nerve. Multiple nerve affection was noted in 18 cases (40%); illustrated in Fig. (2-B).

As for signs of perineural spread, all 45 cases (n=100) included in this study showed nerve enhancement of the corresponding nerve(s) affected. Foraminal enlargement was noted in 42 cases (93.3%). Obliteration of fat planes of the foramina involved was also noted in 42 cases (93.3%). Foraminal destruction was noted in only 6 (13.3%),33 showed intracranial extension (73.3%); 30 of which showed cavernous sinus (CS) involvement. Six (20%) showed neuropathic muscular atrophy. A significant relation was noted between NPC & intracranial extension of PNTS with significant *p*-value of <0.001. No other sites showed significantly related signs; shown in Table (1).

Evaluation ofeffect of PNTS of radiological TNM staging: The T1 and overall local staging of lesions with proven associated PNTS compared to counterparts excluding PNTS: Without PNTS; 46% of cases were T3, 20% were T2, 20% were T4 and 13% were T1. The presence of perineural spread increased T staging in all 45 cases into T4. Presence of PNTS increased radiological TNM staging of the lesions by 21 in 46% of cases, by 9 in 20% of cases & by 6 in 13% of cases, while TNM staging was not increased in 20% of cases.

Diffusion had been made in 30 cases only out of 45. Revealing the relation between diffusion restriction of the primary tumour and presence of concomitant diffusion restriction of the correspond foramina affected by perineural spread; in 24 out of 30 cases (=88%) where primary tumour showed diffusion restriction (18 SCCs, 9 MEC & 3 ACC), showing mean ADC of $1.03 \times 10^{-3}$ $cm^2$/sec. The PNTS along corresponding foraminal showed concomitant diffusion restriction, associated with whole 18 SCCs, 6 of 9 MEC and none with 3 ACCs; shown in Tables (2,3).

Table (1): Distribution of different conventional MRI signs of PNTS.

| MRI signs | Pathology | | | | | | | | $\chi 2$ | MCp |
|---|---|---|---|---|---|---|---|---|---|---|
| | Adenoid cystic carcinoma (n = 6) | | Mucoepidermoid carcinoma (n = 15) | | SCC (n = 21) | | Lymphoma (n = 3) | | | |
| | No. | % | No. | % | No. | % | No. | % | | |
| Nerve enhancement | 6 | 13.3 | 15 | 33.3 | 21 | 46.7 | 3 | 6.7 | – | – |
| Foraminal enlargement | 3 | 6.7 | 15 | 33.3 | 21 | 46.7 | 3 | 6.7 | 11.110* | 0.003* |
| Obliteration of fat planes | 3 | 6.7 | 15 | 33.3 | 21 | 46.7 | 3 | 6.7 | 11.110* | 0.003* |
| Foraminal destruction | 0 | 0.0 | 3 | 6.7 | 3 | 6.7 | 0 | 0.0 | 1.323 | 0.816 |
| Intracranial extension | 3 | 6.7 | 9 | 20.0 | 18 | 40.0 | 3 | 6.7 | 5.297 | 0.127 |
| Neuropathic atrophy | 3 | 6.7 | 3 | 6.7 | 6 | 13.3 | 0 | 0.0 | 2.675 | 0.473 |
| Nerves communication | 3 | 6.7 | 3 | 6.7 | 0 | 0.0 | 0 | 0.0 | 9.718* | 0.008* |
| Cavernous sinus involvement | 0 | 0.0 | 6 | 13.3 | 18 | 40.0 | 3 | 6.7 | 18.851* | <0.001* |

Table (2): Relation between final diagnoses with diffusion and ADC values (n=33).

| Prumary path. | Diffusion restriction of primary tumour | | Diffusion restriction of corresponding formatina with perinerural spread | | Mean ADC |
|---|---|---|---|---|---|
| | Positive | Negative | Positive | Negative | |
| SCC | 18 | 0 | 18 | 0 | 1.04 |
| Mucoepidermoid carcinoma | 9 | 3 | 6 | 3 | 1.03 |
| Adenoid cystic carcinoma | 0 | 3 | – | – | – |

Table (3): The relation between diffusion restriction of the primary tumour and presence of concomitant diffusion restriction of the correspond foramina affected by perineural spread PNTS (n=27).

| | Restricted corresponding foramina | | $\chi 2$ | EFp |
|---|---|---|---|---|
| | Positive | Negative | | |
| | No. % | No. % | | |
| Restricted primary tumour | 3 12.0 | 24 88.0 | 16.333* | <0.001* |

$\chi 2$: Chi square test. MC: Monte Carlo.
*p*: *p*-value for association between different categories.
*: Statistically significant at $p \leq 0.05$.

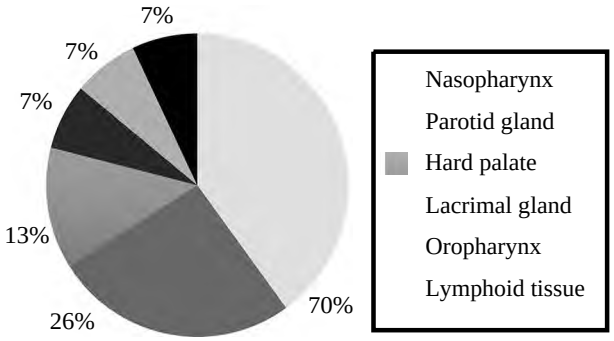



Fig. (1): Distribution of primary tumor sites involved by PNTS in current study.

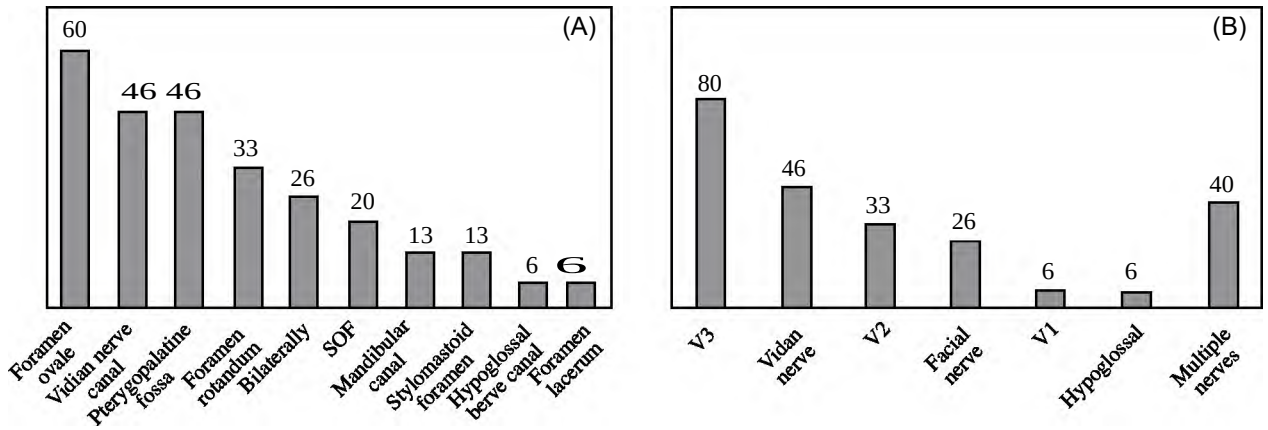



Fig. (2): Distribution and incidence rate of involvement of nerves (a) and foramina (b) in current study.

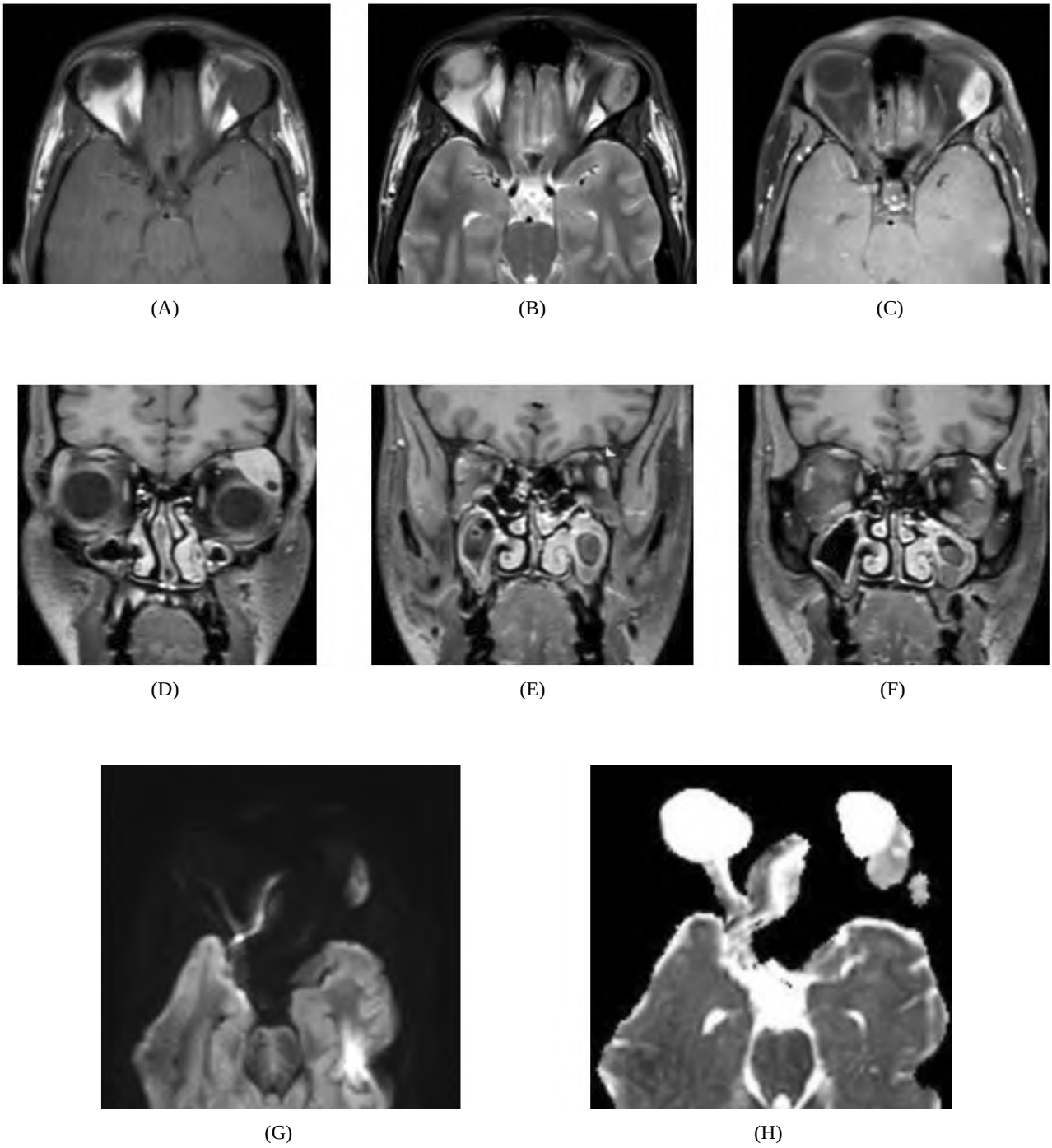


Fig. (3): A patient with lacrimal gland adenoid cystic carcinoma (ACC) & PNS; (A&B) Axial pre-contrast T1WI and T2WI show a lesion involving left lacrimal gland (straight arrow), (C) Axial T1WI contrast with fat suppression showing heterogeneous enhancement of the lesion with cystic areas with enhancing left lacrimal nerve (curved arrow) (D), (E&F) Coronal T1 post contrast with fat sat suppression showing abnormal enhancement along lacrimal nerve from lesion till SOF (arrow head) denoting PNTS (G&H) diffusion weighted sequence and its corresponding ADC map showing no diffusion restriction of the main lesion nor the lacrimal nerve.

A 44 years old male diagnosed with NPC and PNTS along CNV (V3 and V2). Images (A,B) and (C) Axial T1WI, T1WI with fat sat suppression and T2WI showing wide bilateral foramen ovale(long straight arrow heads), thickening of the roof of the nasopharynx and soft tissue sheet involving right masticator muscles(short straight arrow head), (D&E) Axial & coronal T1 post GAD with fat suppression showing PNTS along bilateral foramen ovale(notched arrows), with wide enhancing foramina, obliterated fat planes &minor bony erosions, (F) Axial T1WI post contrast fat suppression showing perineural spread along Vidian nerve canal on both sides(striped arrows) which are seen widened with bony erosions. (G) Axial T1WI post contrast perineural spread along. (F) rotundum bilaterally reaching peri-cavernous regions (curved arrows), (H,I&J) Coronal & axial CT confirming bony erosions of bilateral foramen ovale, foramen rotundum and Vidian nerve canal.

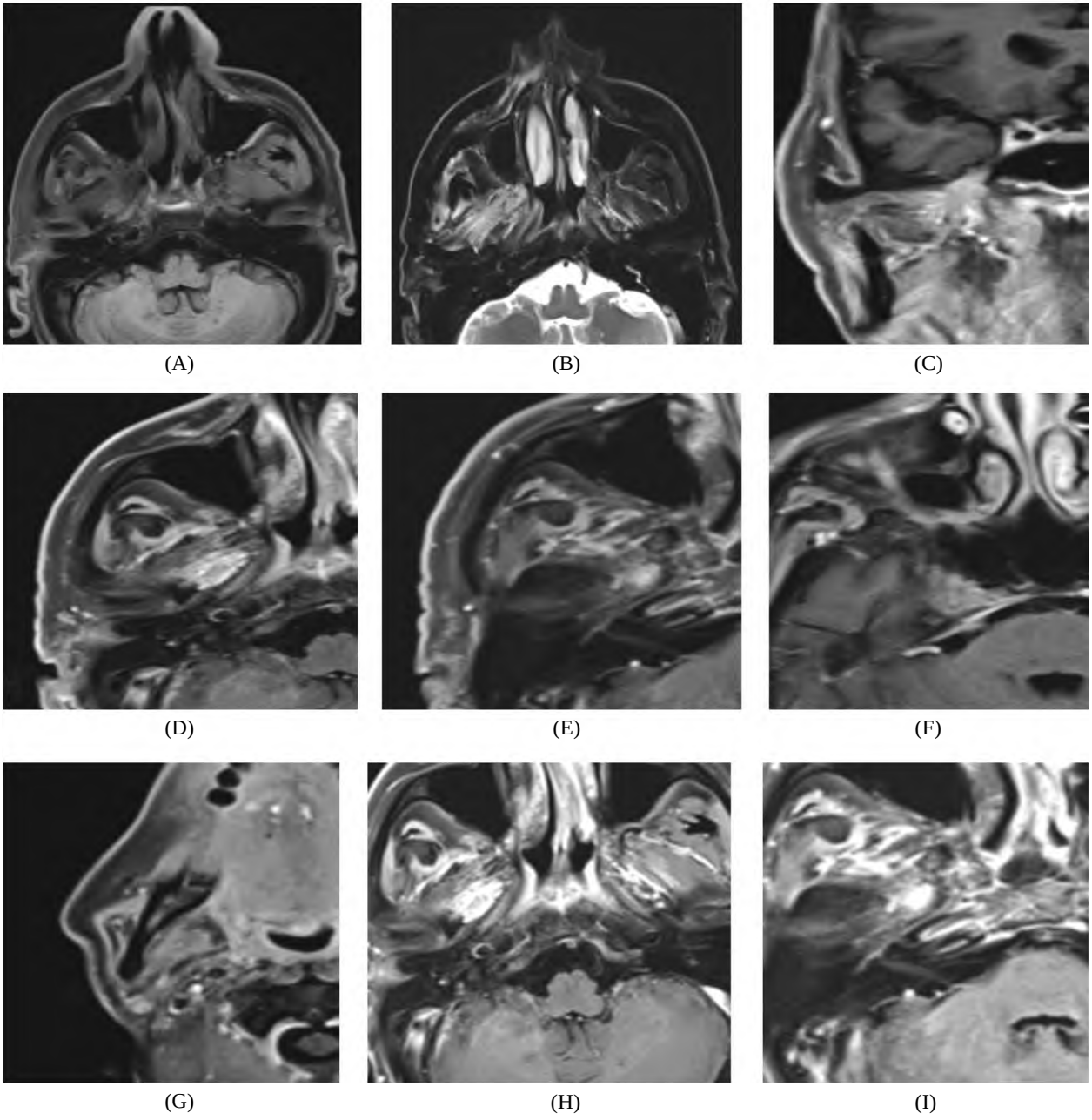



Fig. (4): An example of PNTS along inter-connections V-VII; A 37 years old male with known parotidectomy for MEC with recurrence and PNTS along V-VII interconnections (a)&(b) Axial pre-contrast T1WI with fat suppression and T2WI showing wide right foramen oval(long straight arrow), also noted hyperintense signal of masticator muscles (short straight arrow) denoting denervation atrophy. c, d, e & f. post GAD coronal and axial T1WI with fat suppression showing linear soft tissue enhancement parallel to medial border of pterygoid muscle suggesting PNTS along the auriculo-temporal nerve, widening & enhancement of the foramen ovale with soft tissue obliteration(curved arrow), suggesting PNTS along V3, CS involvement. More posterior proximal extension is seen through porus trigeminus reaching pre-pontine segment of trigeminal nerve (arrowhead). g, h & i. showing clear parotidectomy surgical bed, hyper-enhancement of mastoid portion of facial nerve(notched arrow) as compared to mild enhancement on left side, abnormal enhancement of labyrinthine portion of Facial nerve(striped arrow) denoting PNTS along facial nerve.

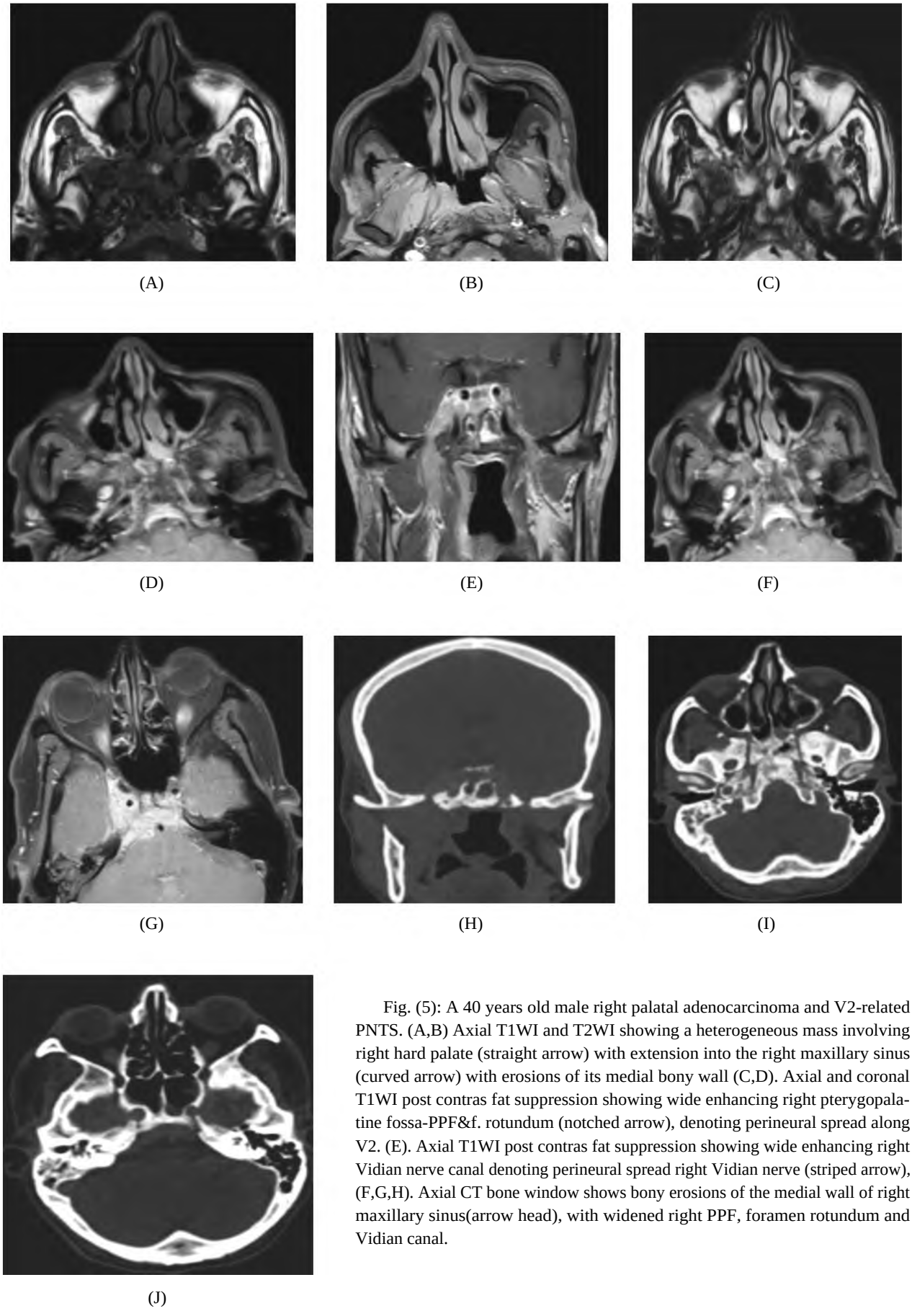
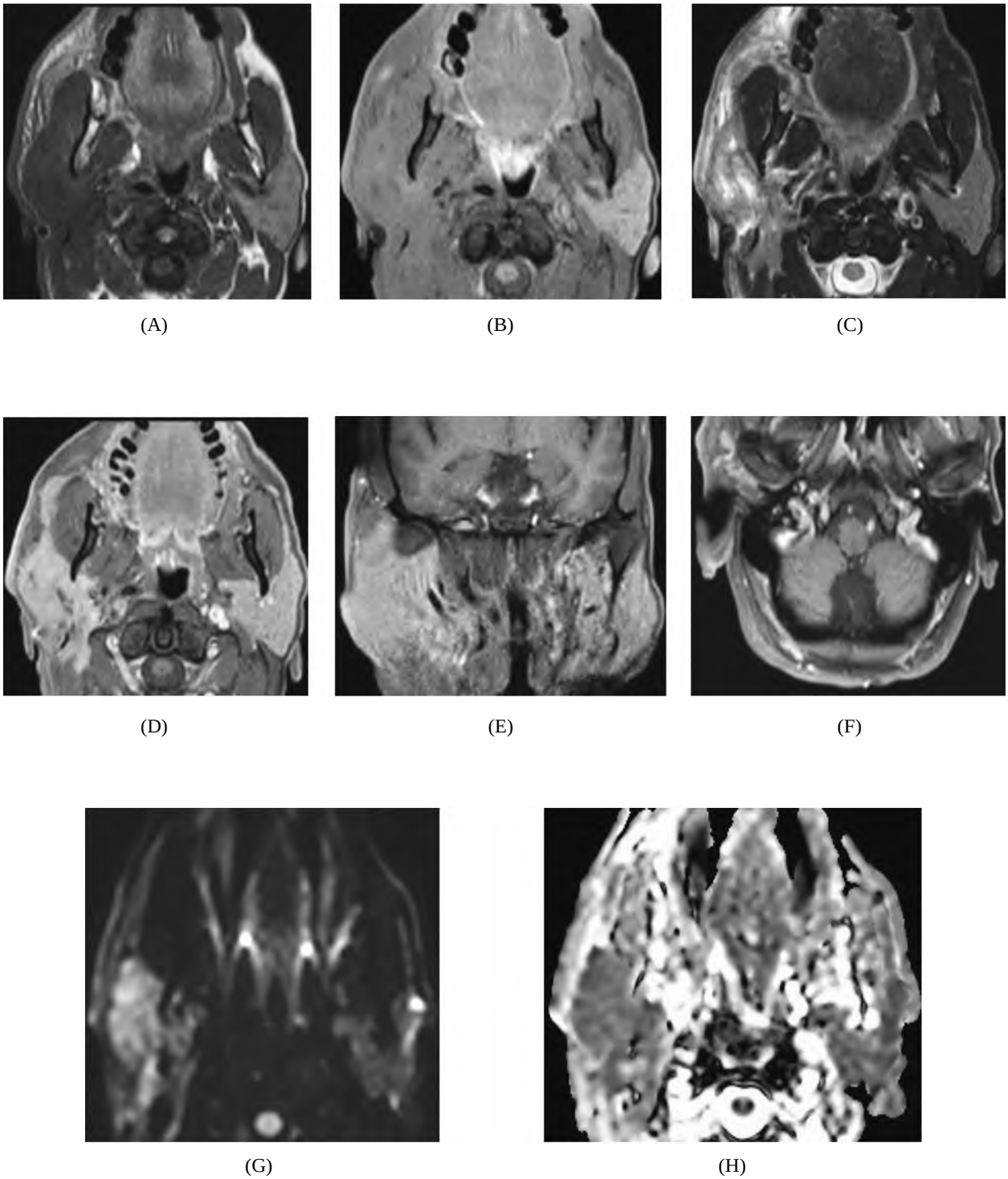



Fig. (5): A 40 years old male right palatal adenocarcinoma and V2-related PNTS. (A,B) Axial T1WI and T2WI showing a heterogeneous mass involving right hard palate (straight arrow) with extension into the right maxillary sinus (curved arrow) with erosions of its medial bony wall (C,D). Axial and coronal T1WI post contras fat suppression showing wide enhancing right pterygopalatine fossa-PPF&f. rotundum (notched arrow), denoting perineural spread along V2. (E). Axial T1WI post contras fat suppression showing wide enhancing right Vidian nerve canal denoting perineural spread right Vidian nerve (striped arrow), (F,G,H). Axial CT bone window shows bony erosions of the medial wall of right maxillary sinus(arrow head), with widened right PPF, foramen rotundum and Vidian canal.



(A) (B) (C)

(D) (E) (F)

(G) (H)

Fig. (6): A 65 years old male diagnosed with mucoepidermoid carcinoma of the right parotid gland. (A,B&C) Axial T1WI, T1WI with fat suppression and axial T2WI, showing heterogeneous right parotid mass (curved arrows) (D)&(E) Axial and coronal T1WI post contrast with fat suppression showing heterogeneously enhancing right parotid mass(notched arrow) (F) Axial T1WI post contrast fat suppression showing hyper enhancement of the mastoid segment of the right facial nerve denoting perineural tumour spread(striped arrow). (G&H) Axial diffusion weighted image and ADC map showing diffusion restriction of the main tumour.

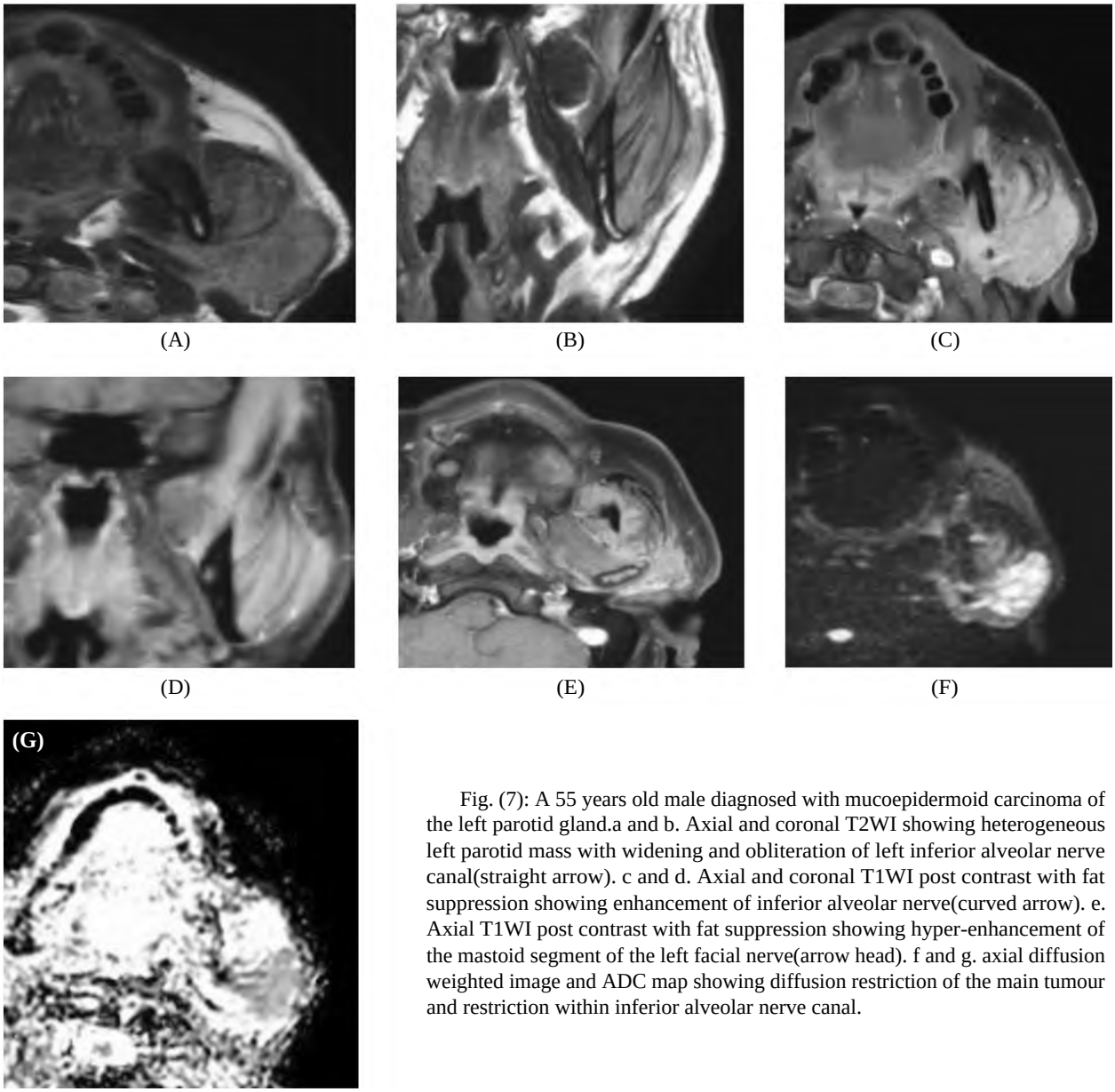



Fig. (7): A 55 years old male diagnosed with mucoepidermoid carcinoma of the left parotid gland.a and b. Axial and coronal T2WI showing heterogeneous left parotid mass with widening and obliteration of left inferior alveolar nerve canal(straight arrow). c and d. Axial and coronal T1WI post contrast with fat suppression showing enhancement of inferior alveolar nerve(curved arrow). e. Axial T1WI post contrast with fat suppression showing hyper-enhancement of the mastoid segment of the left facial nerve(arrow head). f and g. axial diffusion weighted image and ADC map showing diffusion restriction of the main tumour and restriction within inferior alveolar nerve canal.

## Discussion

Perineural tumor spread of HN tumors has been considered a well-known clinical, pathological and radiological phenomenon; with low incidence ranging from 2.5-5% **[1,2].** MRI is considered the main imaging modality for its diagnosis. MRI can't only diagnose presence of perineural spread; it can also accurately delineate the extent of the primary disease, identify spread through nerve communications and detect intracranial extension. Nemzek WR et al., **[25]** in his study conducted on 19 patients reported MRI diagnostic sensitivity reaching up to 95%. The aim of our study was to evaluate MRI findings. We included pre and post contrast T1WI with fat suppression, revealing it to be very beneficial, particularly in diagnosis of PNTS in fat containing spaces and foramina. Though it is suggested by many literatures ath fat suppression is very essential to elucidate nerve enhancement of PNTS, Nemzek WR et al., **[25]** mentioned that, though fat saturation sequence enhances detection of subtle nerve enhancement, usage of fat suppression on T1WI must be judicious, may it augment or introduce magnetic susceptibility artifacts at air/soft-tissue interfaces, thus obscuring disease. He also suggested that very high doses of contrast material could overcome it.

We retrospective collected "asymptomatic" patients as documented in their clinical archives. Those constituted 34% of the whole total caseload in Archives. This comes in agreement with most English literatures, reporting asymptomatic rate 30-45%. As for demographics, the current study enrolled 45 patients, as collected from Archives, included: 38 (87%) males and only 6 (13%) females

with peak incidence 56-60 years of age. The mean age was 43.93 years (SD=17.1). Such findings could be anticipated consideration the common pathologies encountered in our study; NPC, being most common pathology seen in our sample, known to have strong male predilection with male to female ratio seen nearly 2-3:1.

It is well agreed that any cranial nerve could serve as a conduit for PNTS, yet trigeminal nerve was the most involved cranial nerve in our patient group, in 42 patients, followed by "Vidian nerve-V2" in 18 & facial nerve in 15. The 3rd division of trigeminal nerve in particular was most affected in 36 (=80%) of patients. Nemzek WR et al., **[25]** described similar finding in his study with PNTS along trigeminal nerve seen in 16 out of 19 patients, and facial nerve involvement in 2 patients. This can be explained as both trigeminal and facial nerves have the most extensive & complex distributions in head and neck region. PNTS from parotid gland tumors is usually escalated through CNV & CNVII nerves. The study in hand showed that facial nerve was most commonly affected in parotid gland tumours; being involved in parotid tumour irrespectively of pathological type, while concomitant involvement of the mandibular nerve was found in 9 cases.

Mandibular nerve was most commonly involved in NPC; involved in all 18 NPCs, & oropharyngeal cancers. The maxillary nerve (V2) was involved in 9 NPCs, 3 palatal adenocarcinoma, & 3 lymphomas. This is in agreement with Amit M et al, **[26]** in his review, found that VII nerve was most commonly affected in parotid tumours. Maxillary nerve was involved commonly in oral, paranasal & palatal tumours. Mandibular nerve was most commonly involved in tumours of mandible and NPCs.

The study in hand showed that diagnostic MRI signs of PNTS in order of frequency were; nerve enhancement in 45 cases (100%), obliteration of foraminal fat planes in 42 cases, foraminal widening in 42, intracranial extension in 33, latest had high peri-cavernous involvement (30 out of 33) & denervation atrophy in 9, as well as foraminal destruction in 6. Therefore, Nerve enhancement was the most constant finding seen in all cases. This well agrees with Blandino A et al., **[32]** who conducted imaging of 98 candidatesdescribed nerve enhancement as the most constant findingin 13 cases showing PNTS along V2 nerve, 13 showed nerve enhancement.

Nevertheless, Blandino A. et al., **[27]** described nerve enhancement as nonspecific finding occurring in varices inflammatory diseases; yet in clinical setting of HN detected nerve enhancement is considered significant. Giensberg LE et al., **[28]** also described isolated nerve enhancement to be a non-specific finding as it can occur, infrequently, in infections and may extend along cranial nerves in a perineural way. Even more, post maxillectomy might have long-term abnormal enhancement in PPF, which should not be considered as PNTS or tumor recurrence in absence of other more definite signs. We conclude that although nerve enhancement is earliest & most constant finding in PNS, isolated enhancement without other definitive signs is not yet specific, however it should be highly considered as PNTS in appropriate clinical and radiological context. Caldemeyer KS et al., **[29]** described foraminal enlargement as delayed finding; because normal nerve size is small relative to foraminal size; allowing for considerable tumour proliferation without foraminal enlargement or erosions, thus taking some time. He also describes obliteration of fat planes to be a reliable indicator of PNTS. In our study denervation atrophy was less commonly seen & one of the most late signs. It was noted in 9 (20%), involving masticatory muscles, shown asedematous changes with T2 hyper-intense signals reflecting recent phase. Dercle L et al., **[30]** described presence of acute or chronic denervation atrophy to be non-specific. The sign of intracranial extension and manifestation of cranial neuropathy was noted.

The value of diagnosis of PNTS is best demonstrated by its prognostic importance. As by the latest TNM staging perineural spread is considered as an independent prognostic factor associated with increase in loco-regional recurrences & reduction in survival rates. In head and neck tumours it is incorporated in TNM staging in some instances; skin tumours with PNTS reaching skull base can be classified as T4 (apart from eyelid tumours classified as T3), lip & oral cavity tumours with PNTS classified as T4, major salivary glands tumours classified as T3 (upstaged to T4 if facial nerve involved), while NPC with cranial nerve involvement classified as T4 **[42,43]**. In our study presence of PNTS greatly impacted local staging of the tumour; all patients in their latest study staged as T4 with presence of PNS upstaging the local stagingof approached cases. Amit M et al., **[38]** described that although most literature agreed that PNTS increase local recurrence rate, yet evidence regarding prognostic value of PNTS on survival and disease control is still contradictory **[38]**. Caldemeyer KS et al., **[29]** mentioned that prognosis is not badly affected if neural spread involves only the extra cranial nerves; in whom curative treatment is yet eligible though aggressive surgery with radical nerve dissection are needed to achieve clear surgical histological margins.

Diffusion had been made in 30 cases only out of 45 cases. Revealing the relation between diffusion restriction of the primary tumour and presence of concomitant diffusion restriction of the correspond foramina affected by perineural spread; in 24 out of 30 cases (=88%) where primary tumour showed diffusion restriction (18 SCCs, 9 MEC, and 3 ACCs), showing mean ADC of $1.03x10^{-3}$ $cm^2$/sec. This was in agreement with extensive researches on head and neck carcinomas, which concluded that lower ADC

values (<1.0x10$^{-3}$ mm$^2$/s) are often associated with malignant tumours like ACC and SCC. The PNTS along corresponding foraminal showed concomitant diffusion restriction, associated with whole 18 SCCs, 6 of 9 MEC & none with 3 ACCs. In context of PNS, affected nerves are expected to exhibit restricted diffusion due to increased cellularity and reduced extracellular space. However, few English literatures discussed diffusion within foraminal nerve tumoral tissue. In a study by Christophe Schroeder et al. **[30]** involving 25 patients, MRI with diffusion-(DWI) identified nerve infiltration in 5 out of 7 with PNTS confirmed on histopathology, although two showed false positive results. However, these differences did not reach statistical significance ($p$>0.05), likely due to limited sample size. Still, lower ADC values along affected nerves would be indicative of tumoral infiltration. The study had limitations. First, small sample size and this is explained by the low frequency of PNTS. Secondly, diffusion and CT weren't part of all cases and couldn't be correlated with already available pathology.

*Conclusions:* In conclusion, our study on asymptomatic patients matched descriptive studies of mixed subjects including symptomatic and asymptomatic. Our study revealed that even with inter-connections of VII and V, as well as cavernous sinus and intracranial involvement, patient can be still asymptomatic while MRI is marvelous in revealing the whole course of long branching peri-neural spread. MRI, including DWI, is essential in the evaluation of perineural spread in head and neck cancer. The combination of conventional MRI sequences and DWI provides comprehensive information on the extent of tumor spread, aiding in diagnosis, treatment planning, and prognosis.

*Ethics Approval and Consent to Participate:* All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Institutional Review Board (IRB)" of Alexandria General Hospital on 14th February 2023) and with the Helsinki Declaration of 1964 and later versions. Committee's reference number is unavailable (NOT applicable). No consent was obtained from the patients since it was a retrospective study.

*Consent for publication:* All patients included in this research gave written informed consent to publish the data contained within this study.

*Availability of data and materials:* The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

*Competing interests:* The authors declare that they have no competing interests.

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*Authors' contributions:* AO provided the cases and final diagnoses, with detaileddescription of results. LE gave the idea,wrote the section of introduction and provided the whole references for introduction and discussion with making of figure legends. AM made the whole final supervision on conducted research and on the written consent.

"All authors read and approved the final manuscript".

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# التصوير بالرنين المغناطيسي لانتشار حول الأعصاب من الأرشيفات السريرية والشعاعية والمرضية المسترجعة لمرضى «بدون أعراض» مصابين بأورام خبيثة فى الرأس والرقبة: مجموعة من النتائج التشخيصية باستخدام التقنيات التقليدية والانتشارية

الخلفية: كان التصوير بالرنين المغناطيسى التقليدى بمثابة الحصان العامل لتشخيص انتشار حول الأعصاب فى سرطان الرأس والرقبة، سواء كان مصحوبًا بأعراض أم لا. والغرض من هذا البحث الاستعادى هو جمع بيانات المرضى بدون أعراض للكشف عن علامات التصوير بالرنين المغناطيسى التقليدى مع بيانات إضافية حول انتشار الورم الأولى والأنسجة حول الأعصاب.

النتائج: تضمنت العلامات التقليدية «تعزيز الأعصاب» (١٠٠٪)، «تضخم الثقبة» (٣, ٩٣٪)، «إزالة الدهون الثقبة» (٣, ٩٣٪)، «تدمير الثقبة» (٣, ١٣٪)، التمدد داخل الجمجمة (٣, ٧٣٪)، ضمور العضلات (٢٠٪). كان الانتشار مقيدًا فى مواقع الورم الرئيسية وداخل الأنسجة الرخوة للأعصاب الثقبية للغزو العصبى مع انخفاض ADC <١×١٠-٣ سم٢/ ثانية.

الاستنتاجات: التصوير بالرنين المغناطيسى، بما فى ذلك DWI، ضرورى فى تقييم انتشار الورم العصبى فى سرطان الرأس والرقبة. يوفر الجمع بين تسلسلات التصوير بالرنين المغناطيسى التقليدية وDWI معلومات شاملة عن مدى انتشار الورم، مما يساعد فى التشخيص وتخطيط العلاج والتنبؤ.