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ORIGINAL RESEARCH

Correlation of Pre-Therapeutic Tympanogram Findings with Primary Tumor Anatomical Localization and T-Category in Patients with Nasopharyngeal Carcinoma: A Cross-Sectional Diagnostic Study at a Tertiary Referral Center in Bali, Indonesia

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ABSTRACT

Background: Nasopharyngeal carcinoma arises in the fossa of Rosenmüller beside the Eustachian tube orifice and may cause middle-ear dysfunction. Whether tympanometry reflects tumor localization or the AJCC/UICC T-category remains uncertain.

Objective: To determine the correlations of pre-therapeutic tympanogram findings with primary tumor anatomical localization and T-category in patients with nasopharyngeal carcinoma.

Methods: This prospective-designed cross-sectional study included 43 consecutive, histopathologically confirmed patients evaluated before treatment at Prof. dr. I.G.N.G. Ngoerah General Hospital, Bali, from January to June 2026. Assessments comprised bilateral 226-Hz tympanometry, flexible video-nasopharyngoscopy, and contrast-enhanced head and neck computed tomography. Tumor extension was classified by mucosal topography and AJCC/UICC eighth-edition T-category. Spearman rank correlation and multivariable logistic regression were used.

Result: Participants were mostly male (29/43, 67.4%); median age was 52 years. T4 disease occurred in 23 patients (53.5%), T2 in 12 (27.9%), and T3 in eight (18.6%). The fossa of Rosenmüller was involved in all patients; 26 (60.5%) had bilateral extension, seven (16.3%) unilateral extension, and 10 (23.3%) circumferential or complete tubal-ostial enclosure. Type B tympanograms occurred in 30 patients (69.8%) and Type C in 13 (30.2%); no Type A curves occurred. Tympanogram profile correlated strongly with anatomical localization ($r_s = 0.745$, 95% CI 0.572–0.854; $p < 0.001$; adjusted OR 18.52, 95% CI 2.82–121.40; $p = 0.002$) but not with T-category ($r_s = 0.051$; $p = 0.697$).

Conclusion: Pre-therapeutic middle-ear dysfunction in nasopharyngeal carcinoma tracks tumor extension toward the Eustachian tube rather than T-category. Baseline tympanometry can complement anatomical assessment and identify patients who may benefit from timely otologic evaluation before chemoradiotherapy.

1. Introduction

Nasopharyngeal carcinoma (NPC) represents a distinct, biologically aggressive epithelial malignancy of the head and neck that exhibits striking geographical and ethnic variations in incidence, with exceptionally high endemicity in Southern China, Southeast Asia, and the Indonesian archipelago.[1] Nasopharyngeal carcinoma arises from the mucosal lining of the nasopharynx, most commonly occurring at the pharyngeal recess, and is etiologically linked to chronic latent infection with the Epstein-Barr virus (EBV), interrupted by host genetic susceptibility, human leukocyte antigen (HLA) polymorphisms, and sustained exposure to environmental chemical carcinogens including volatile nitrosamines and inhalable wood dust.[1,2] In Indonesia, NPC is the most prevalent malignant neoplasm of the head and neck region, with an estimated national age-standardized incidence rate of 6.2 per 100,000 population, presenting a massive clinical and public health burden.[2] Epidemiological registries across Indonesian tertiary centers consistently demonstrate that the majority of NPC patients are diagnosed at advanced locoregional stages (Stages III and IV), which substantially impairs therapeutic responsiveness, increases treatment-related toxicities, and severely compromises long-term disease-free and overall survival rates.[2-6]

A critical factor contributing to diagnostic delay in nasopharyngeal carcinoma is the deep and anatomically occult location of the nasopharyngeal cavity, tucked beneath the sphenoid sinus and posterior to the nasal choanae, which renders routine physical inspection impossible without specialized endoscopic equipment.[1,6] Furthermore, the initial clinical manifestations of NPC are remarkably subtle, insidious, and non-specific, frequently mimicking common, benign upper respiratory disorders such as chronic allergic rhinitis, adenoidal hypertrophy, or simple Eustachian tubal catarrh.[2,7-9] While the appearance of a painless, firm lateral cervical lymph node mass typically prompts medical consultation, otologic signs and symptoms—most notably unilateral aural fullness, conductive hearing loss, low-frequency tinnitus, and autophony—almost invariably precede palpable cervical adenopathy by several months to a year.[10-12] Unfortunately, these early otologic warning signs are frequently overlooked by primary healthcare practitioners or dismissed by patients as transient middle ear infections, leading to inappropriate symptomatic pharmacotherapy and prolonged diagnostic latency.[13,14]

From an anatomical standpoint, the vast majority of primary nasopharyngeal carcinomas originate within the fossa of Rosenmüller (recessus pharyngeus), a deep, slit-like mucosal crevice situated posterosuperior to the torus tubarius.[1,8] The

fossa of Rosenmüller is bordered anteriorly by the posterior lip of the cartilaginous Eustachian tube, posteriorly by the prevertebral fascia overlying the longus capitis muscle, and superiorly by the petrous apex of the temporal bone.[8,18] Due to this immediate spatial proximity, any neoplastic mucosal expansion, infiltrative submucosal thickening, or exophytic tumor mass arising from the fossa of Rosenmüller inevitably exerts direct mechanical compression upon the flexible cartilaginous margin of the Eustachian tube, narrowing its pharyngeal orifice and compromising the surrounding parapharyngeal fat pad.[15-22] This strategic anatomical positioning renders the Eustachian tube exceptionally vulnerable to both early extrinsic compression and direct submucosal infiltration by carcinoma cells.[22,23]

The Eustachian tube is a dynamic osteocartilaginous conduit that establishes a critical physiological communication between the nasopharynx and the middle ear cavity, serving three fundamental functions: middle ear ventilation and atmospheric pressure equilibration, mucociliary clearance of middle ear secretions, and acoustic and biological protection against retrograde nasopharyngeal secretions and sound pressures.[4,10] Under basal physiological conditions, the cartilaginous portion of the Eustachian tube remains passively closed, preventing the reflux of nasopharyngeal pathogens and ambient pressure fluctuations into the tympanic cavity.[10] Active tubal dilation occurs intermittently during swallowing, yawning, or sneezing, mediated almost exclusively by the contraction of the tensor veli palatini (TVP) muscle, which is innervated by the mandibular division of the trigeminal nerve (cranial nerve V3), with synergistic support from the levator veli palatini (LVP) muscle, innervated by the pharyngeal plexus of the vagus nerve (cranial nerve X).[10,11]

When a nasopharyngeal tumor infiltrates the lateral pharyngeal wall, the neoplastic growth disrupts the delicate neuromuscular coordination of the Eustachian tube apparatus.[22,23] In addition to luminal occlusion of the ostium pharyngeum by the exophytic tumor bulk, tumor invasion frequently penetrates the tensor veli palatini muscle, the levator veli palatini muscle, and the adjacent parapharyngeal tissue space.[18,23] Histopathological studies have confirmed that carcinoma cells actively dissect along muscle fascial planes, inducing myofiber atrophy, fibrotic fixation, and mechanical tethering of the lateral cartilaginous lamina of the tube.[23] As a direct consequence, the active muscular mechanism responsible for tubal dilation is extinguished, rendering the Eustachian tube persistently collapsed or rigidly locked in a dysfunctional closed state regardless of palatal movement.[10,23]

Persistent Eustachian tube dysfunction (ETD) initiates a classical pathophysiological cascade within the middle ear cavity, as elucidated by the van Liew-Hills mucosal gas absorption model.[4] When tubal ventilation is completely abolished, oxygen, nitrogen, and carbon dioxide within the enclosed tympanic cavity are progressively absorbed into the subepithelial capillary network along a trans-mucosal partial pressure gradient. Because atmospheric air cannot enter the tube to replenish the absorbed volume, a severe, sustained negative intratympanic pressure develops within the middle ear, exceeding -100 daPa.[3] This sub-atmospheric pressure causes persistent inward retraction of the tympanic membrane, clinically detected as a Type C tympanogram.[3,5] Over time, the prolonged negative pressure gradient induces marked capillary engorgement, increased vascular permeability, and hydrostatic transudation of sterile serous fluid from mucosal microvessels into the tympanic cavity, concurrently stimulating goblet cell metaplasia and mucinous glandular hyperplasia.[4] The resulting accumulation of sterile serous or seromucinous fluid completely fills the middle ear cleft, dampens ossicular chain vibration, abolishes tympanic membrane compliance, and manifests as otitis media with effusion (OME), which generates a flat, peakless Type B tympanometric waveform accompanied by substantial conductive hearing loss.[3,4,9]

Impedance tympanometry represents the gold standard, non-invasive objective diagnostic modality for evaluating middle ear pressure, tympanic membrane compliance, and Eustachian tube patency.[3,10] First systematized by Jerger in 1970, tympanometry classifies middle ear status into three principal acoustic admittance patterns: Type A (normal peak compliance between -100 and +100 daPa), Type B (flat curve with negligible acoustic compliance, indicative of fluid accumulation or tympanic membrane immobility), and Type C (intact compliance peak shifted to severe negative pressure beyond -100 daPa, reflecting significant Eustachian tube hypoventilation).[3,10] In patients with nasopharyngeal carcinoma, tympanometry provides an indispensable objective window into middle ear biomechanics, enabling precise detection of subclinical tubal dysfunction and effusion even when otoscopic visualization reveals an ostensibly intact, non-perforated tympanic membrane.[5,13]

Despite the extensive worldwide application of tympanometry in otolaryngology, there remains a prominent, unresolved debate regarding the exact relationship between tympanometric findings and the primary tumor characteristics in nasopharyngeal carcinoma.[5,14] Several regional studies have suggested that middle ear effusion is strongly determined by the spatial anatomical localization of the tumor mass in relation to the Eustachian tube orifice, whereas other investigations have postulated a direct correlation between tympanometric deterioration and advanced T-categories.[5,14,22] The American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) 8th edition TNM staging system classifies primary tumor extension (T-category) based on anatomical boundaries—progressing from confinement to the nasopharynx (T1), extension into the parapharyngeal space (T2), infiltration into bony skull base structures and paranasal sinuses (T3), to intracranial extension, cranial nerve involvement, and orbit or infratemporal fossa invasion (T4).[1,18] Crucially, T-category fundamentally reflects volumetric and vertical/skull base invasiveness rather than the precise, localized circumferential relationship of the tumor to the cartilaginous tubal orifice.[18] Consequently, a small T1 or T2 tumor strategically centered on the torus tubarius might completely occlude the Eustachian tube, whereas a massive T4 tumor extending superiorly into the clivus or cavernous sinus might spare the ipsilateral tubal opening.[24-28]

At Prof. dr. I.G.N.G. Ngoerah General Hospital in Denpasar, Bali—the principal tertiary academic referral center for the Province of Bali and Nusa Tenggara region—tympanometric assessment is not routinely performed as a standard baseline protocol before the initiation of definitive chemoradiotherapy or during serial post-treatment surveillance.[12,13] This lack of routine pre-therapeutic acoustic evaluation often results in the under-recognition of pre-existing middle ear effusion, precluding timely otologic intervention and complicating the differentiation between tumor-induced Eustachian tube dysfunction and radiation-induced middle ear injury.[13,21] In order to resolve this critical clinical dilemma and optimize multidisciplinary head and neck oncology care, rigorous empirical investigation is urgently required to determine whether pre-therapeutic tympanometric patterns are dictated by the anatomical mucosal location of the primary tumor or by the volumetric tumor T-category.[5,13]

Therefore, the present prospective-designed cross-sectional analytical study was undertaken to evaluate the diagnostic value of pre-therapeutic tympanogram findings and to determine their precise statistical and biomechanical correlation with both primary tumor anatomical localization and AJCC/UICC 8th edition T-category in newly diagnosed nasopharyngeal carcinoma patients prior to the initiation of definitive chemoradiotherapy. By elucidating the clinical and anatomical determinants of middle ear dysfunction in an Indonesian cohort, this research aims to establish a robust evidentiary foundation for integrating routine baseline tympanometry into head and neck oncology staging workflows, thereby facilitating early, tailored

otologic management, preventing irreversible hearing loss, and optimizing long-term quality of life for NPC survivors.

2. Methods

This research was designed and executed as an observational, analytical cross-sectional diagnostic study conducted at the Department of Otorhinolaryngology-Head and Neck Surgery, Prof. dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Bali, Indonesia, over a consecutive six-month enrollment period spanning from January 2026 to June 2026. Prof. dr. I.G.N.G. Ngoerah General Hospital serves as the primary top-tier tertiary referral academic center and regional oncology hub for the provinces of Bali, West Nusa Tenggara (NTB), and East Nusa Tenggara (NTT). The study protocol strictly adhered to the ethical principles of the Declaration of Helsinki (1964 and its subsequent amendments) and was formally reviewed and approved by the Research Ethics Committee of the Faculty of Medicine, Udayana University / Prof. dr. I.G.N.G. Ngoerah General Hospital under ethical clearance approval number 2822/UN14.2.2.VII.14/LT/2026. Written informed consent was obtained from all eligible participants, or their legally authorized representatives for minor patients, prior to enrollment following comprehensive counseling regarding the diagnostic procedures.

The study population comprised all consecutive newly diagnosed patients presenting with histopathologically verified nasopharyngeal carcinoma who were evaluated prior to the initiation of definitive curative or palliative treatment modalities, including concurrent chemoradiotherapy, neoadjuvant chemotherapy, or intensity-modulated radiotherapy (IMRT). Histopathological diagnosis was established in accordance with the World Health Organization (WHO) classification guidelines via transnasal endoscopic biopsy of the primary nasopharyngeal lesion, categorized into keratinizing squamous cell carcinoma (WHO Type I), non-keratinizing differentiated carcinoma (WHO Type II), or non-keratinizing undifferentiated carcinoma (WHO Type III).[1,2] To prevent confounding factors that could independently alter middle ear pressure, tympanic membrane mobility, or tubal function, strict inclusion and exclusion criteria were enforced. Patients were eligible if they were aged 15 years or older, had an intact, non-perforated tympanic membrane verified on high-magnification pneumatic otomicroscopy, and had not received prior radiotherapy, chemotherapy, or surgical resection of the head and neck. Exclusion criteria comprised: (1) pre-existing chronic suppurative otitis media, cholesteatoma, or previous middle ear surgical interventions (e.g., tympanoplasty, mastoidectomy, or grommet insertion); (2) history of active severe allergic rhinitis, chronic rhinosinusitis with nasal polyposis, or craniofacial anomalies (e.g., cleft palate); (3) benign or malignant neoplasms of the nasal cavity, paranasal sinuses, or skull base other than primary NPC; and (4) acute upper respiratory tract infections within the preceding two weeks.[5,9,10]

Sample size estimation was determined a priori based on the correlation coefficient reported in analogous diagnostic investigation by Dewi et al.[5] evaluating tympanogram findings against anatomical tumor localization in nasopharyngeal carcinoma (expected r = 0.65). Applying a two-tailed significance level (alpha) of 0.05 (Zalpha = 1.96) and a statistical power (1 - beta) of 90% (Zbeta = 1.28), the minimum required sample size calculated using the standard sample size formula for correlation studies was determined to be 38 subjects. To account for potential incomplete audiological datasets or radiological exclusions, recruitment was maintained consecutively throughout the six-month study window, ultimately yielding 43 fully evaluable patients who met all eligibility criteria.

Clinical and anatomical tumor evaluation was conducted using a standardized, multi-modal diagnostic protocol combining high-definition flexible video-nasopharyngoscopy (Karl Storz Endoskope, Tuttlingen, Germany) and contrast-enhanced head and neck multi-slice computed tomography (CT). All patients underwent comprehensive physical and head and neck examinations performed by two independent senior otorhinolaryngologists-head and neck surgeons. Diagnostic nasopharyngoscopy was carried out following topical mucosal decongestion and local anesthesia using 0.5% oxymetazoline hydrochloride and 2% lidocaine spray. Under endoscopic direct visualization, the primary tumor epicenter, mucosal surface morphology (ulcerative, exophytic, infiltrative), and anatomical spatial extension were mapped with special emphasis on the posterosuperior pharyngeal wall, the roof of the nasopharynx, the bilateral fossae of Rosenmüller, the torus tubarius cartilaginous cushion, and the ostium pharyngeum of the Eustachian tube.[1,8] Primary tumor location was systematically categorized into three distinct topographical groups: (1) tumor originating in the fossa of Rosenmüller extending unilaterally to the ipsilateral lateral wall and roof; (2) tumor originating in the fossa of Rosenmüller extending to the bilateral lateral walls and posterior roof; and (3) tumor presenting as a massive circumferential mass resulting in full enclosure and total occlusion of the Eustachian tube orifice.[5,8]

Cross-sectional radiological imaging was acquired using a 128-slice multi-detector computed tomography scanner (Siemens SOMATOM Definition AS, Siemens Healthineers, Erlangen, Germany) with intravenous iodinated non-ionic contrast medium (Omnipaque 350 mg I/mL, GE Healthcare). Thin-slice axial, coronal, and sagittal multiplanar reformations were reconstructed at 1.0-mm slice intervals with both soft tissue and bone algorithm windows extending from the vertex of the skull to the aortic arch. Radiological staging was determined according to the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) 8th edition TNM staging system.[1,18] The primary tumor T-category was meticulously reviewed and classified by a consensus of two board-certified head and neck subspecialist radiologists blinded to the tympanometric findings: T1 (tumor confined to the nasopharynx, or extending to oropharynx and/or nasal cavity without parapharyngeal extension); T2 (tumor with extension to parapharyngeal space, and/or infiltration of medial pterygoid, lateral pterygoid, and/or prevertebral muscles); T3 (tumor with infiltration of bony skull base structures, cervical vertebrae, pterygoid structures, and/or paranasal sinuses); and T4 (tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle).[1,18] In this investigation, T-category served as the validated surrogate indicator of gross tumor anatomical invasiveness and volume.

Acoustic impedance tympanometry was executed within 48 hours of radiological staging and prior to any therapeutic intervention, using a calibrated clinical impedance audiometer (Madsen Zodiac 901, Otometrics, Taastrup, Denmark). All measurements were performed in a sound-attenuated audiology booth meeting ANSI S3.1 standards. The equipment was calibrated daily according to manufacturer specifications using a 2.0-cc artificial test cavity. Prior to probe insertion, handheld pneumatic otoscopy was conducted to ensure that the external auditory canal (EAC) was clear of obstructive cerumen and that the tympanic membrane was fully intact without signs of acute inflammatory hyperemia or structural perforation. An appropriately sized hermetic silicone probe tip was positioned in the external auditory canal. A 226-Hz probe tone delivered at 85 dB Sound Pressure Level (SPL) was utilized, and pneumatic pressure within the canal was swept continuously from +200 to -400 dekapascals (daPa) at an automatic pump speed of 50 daPa/sec. Quantitative parameters recorded included external ear canal physical volume (Vea in cm^3 or cc), static acoustic compliance / admittance (Ypeak in cm^3), tympanometric peak pressure (TPP in daPa), and tympanometric gradient / width (TW in daPa).[3,10]

Tympanometric waveforms were classified in accordance with the internationally standardized Jerger classification system into three discrete clinical categories: (1) Type A (normal

tympanogram, characterized by a well-defined compliance peak ranging from 0.3 to 1.6 cm^3 occurring within a normal middle ear pressure range between -100 and +100 daPa, reflecting normal middle ear aeration and physiological tympanic membrane mobility); (2) Type B (flat tympanogram, characterized by the absence of a discernible compliance peak across the entire pressure sweep with static compliance less than 0.2 cm^3, reflecting the presence of middle ear fluid, severe mucosal thickening, or complete tympanic membrane immobility); and (3) Type C (retracted tympanogram, characterized by a distinct compliance peak shifted significantly into the negative pressure zone beyond -100 daPa, reflecting significant Eustachian tube hypoventilation and sustained negative intratympanic pressure).[3,5,10] Both Type B and Type C tympanograms were classified as pathological findings indicating middle ear ventilatory dysfunction. In accordance with established clinical methodology, the primary unit of analysis was the ear affected by tumor-related Eustachian tube dysfunction; in patients presenting with bilateral tumor involvement, the ear demonstrating the more severe tympanometric pathology (Type B > Type C > Type A) was selected for statistical correlation analysis.[5,8]

All demographic, endoscopic, radiological, and tympanometric data were entered into a standardized computerized clinical registry. Statistical computations were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for distributional normality using the Shapiro-Wilk and Kolmogorov-Smirnov tests; parametric data are presented as mean ± standard deviation (SD), whereas non-parametric variables are reported as median and interquartile range (IQR). Categorical variables are expressed as absolute frequencies (n) and percentages (%). Bivariate associations between categorical variables were analyzed using the Pearson Chi-Square test or Fisher's Exact test when cell counts were less than 5. To assess the strength and direction of monotonic association between ordinal categorical variables (tympanogram type, anatomical location category, and T-category), Spearman's rank-order correlation coefficient (rs) was computed alongside 95% confidence intervals (CI). A two-tailed p-value of less than 0.05 was considered statistically significant for all tests.

3. Results

A total of 43 consecutive patients with newly diagnosed, histopathologically verified nasopharyngeal carcinoma were enrolled and completed the standardized diagnostic evaluation protocol. The baseline demographic and clinical characteristics of the patient cohort are summarized in Table 1 and illustrated in Figure 1. The age of the study participants ranged from 18 to 68 years, with a mean age of 47.6 ± 12.8 years and a median of 52 years. The highest frequency of NPC cases was observed in the sixth decade of life (50–59 years), accounting for 39.5% (n = 17) of the total cohort, followed closely by the fifth decade (40–49 years), which represented 34.9% (n = 15). Patients aged under 20 years accounted for 4.7% (n = 2), while the age brackets of 20–29, 30–39, and 60–69 years each comprised 6.9% (n = 3 each). In terms of gender distribution, male patients demonstrated a marked preponderance, comprising 67.4% (n = 29) of the cohort compared to 32.6% (n = 14) female patients, yielding an overall male-to-female ratio of 2.07:1.

Table 1. Baseline Demographic and Clinical Characteristics of Nasopharyngeal Carcinoma Patients (N = 43).

Clinical / Demographic Variable	Stratification / Category	Sample Count (n)	Percentage (%)	95% Confidence Interval
Age Category (Years)	< 20	2	4.7%	[0.6% – 15.8%]
	20 – 29	3	6.9%	[1.5% – 19.1%]
	30 – 39	3	6.9%	[1.5% – 19.1%]
	40 – 49	15	34.9%	[21.0% – 50.9%]
	50 – 59	17	39.5%	[25.0% – 55.6%]
	60 – 69	3	6.9%	[1.5% – 19.1%]
Gender	Male	29	67.4%	[51.5% – 80.9%]
	Female	14	32.6%	[19.1% – 48.5%]
Histopathological Subtype	WHO Type III (Non-keratinizing undifferentiated)	38	88.4%	[74.9% – 96.1%]
	WHO Type II (Non-keratinizing differentiated)	5	11.6%	[3.9% – 25.1%]
	WHO Type I (Keratinizing squamous)	0	0.0%	[0.0% – 8.2%]
Presenting Symptom at Diagnosis	Cervical lymph node mass	31	72.1%	[56.3% – 84.7%]
	Unilateral hearing loss / aural fullness	28	65.1%	[49.1% – 79.0%]
	Epistaxis / blood-tinged nasal discharge	19	44.2%	[29.1% – 60.1%]
	Nasal obstruction	16	37.2%	[23.0% – 53.3%]
	Cranial nerve palsy / diplopia / headache	11	25.6%	[13.5% – 41.2%]

Note: Values are presented as absolute frequencies (n) and percentages (%). Confidence intervals are calculated using the Wilson score method with continuity correction. WHO = World Health Organization.

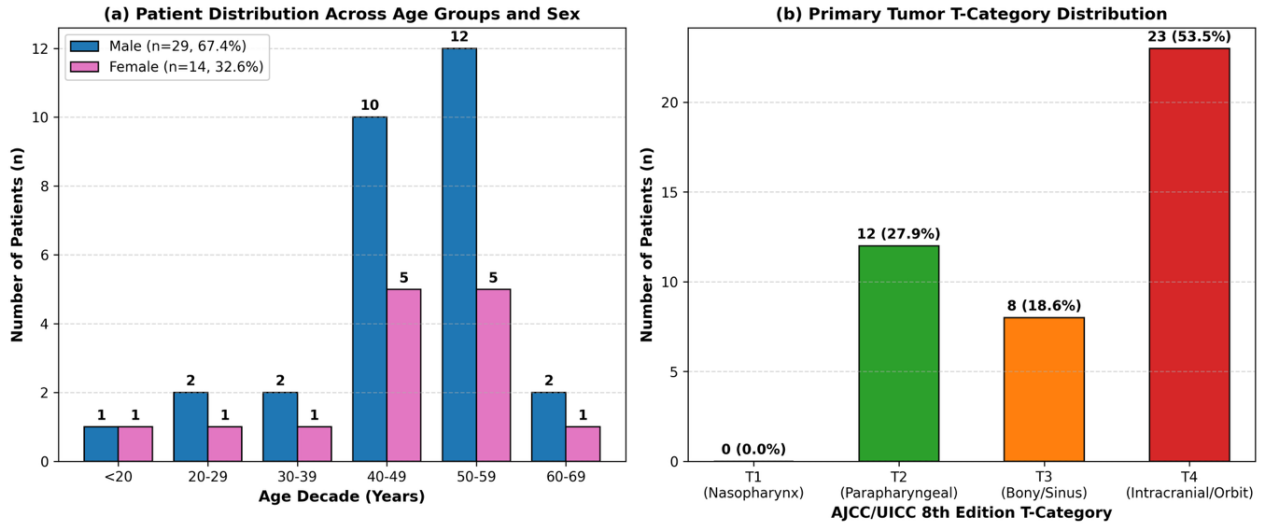

Figure 1. *Demographic Distribution and Primary Tumor T-Category Stratification in Nasopharyngeal Carcinoma Patients (N = 43). (a) Age decade distribution stratified by sex demonstrating peak disease burden in the 50–59 age bracket with marked male predominance (67.4% vs 32.6%); (b) Primary tumor AJCC/UICC 8th edition T-category classification illustrating predominant locally advanced presentation (T4 = 53.5%, T2 = 27.9%, T3 = 18.6%, T1 = 0.0%).*

Cross-sectional radiological staging based on multi-detector contrast-enhanced CT according to the AJCC/UICC 8th edition staging system revealed a prominent concentration of locally advanced primary tumors (Table 2, Figure 1b). The most frequent primary tumor classification was the T4 category, observed in 53.5% (n = 23) of patients, characterized by extensive intracranial skull base extension, involvement of the masticator space, infratemporal fossa invasion, or cranial neuropathy. Category T2 tumors, defined by soft tissue infiltration into the parapharyngeal space and adjacent pterygoid musculature without bony erosion, represented 27.9% (n = 12) of cases. Category T3 tumors, demonstrating cortical erosion of the skull base, pterygoid plates, or paranasal sinus bony walls, were identified in 18.6% (n = 8) of subjects. Notably, zero patients (0.0%) presented with early-stage T1 disease confined strictly to the nasopharynx, reflecting the persistent phenomenon of late-stage clinical detection in the Indonesian clinical setting.

Endoscopic mapping of primary mucosal tumor topography demonstrated that the fossa of Rosenmüller was universally involved across all 43 patients (100.0%) as the anatomical origin or primary epicenter of disease (Table 2, Figure 2). The predominant anatomical extension pattern was neoplastic invasion originating in the fossa of Rosenmüller and extending across the posterior wall and vault of the nasopharynx to involve both bilateral lateral walls, documented in 60.5% (n = 26) of cases. In 16.3% (n = 7) of patients, the tumor remained localized unilaterally to the ipsilateral fossa of Rosenmüller and adjacent lateral wall. In 23.4% (n = 10) of patients, massive circumferential tumor exophytia was observed, presenting as a completely enclosed lesion that produced total mechanical occlusion of the Eustachian tube pharyngeal orifice.

Table 2. Primary Tumor Anatomical Extension and AJCC/UICC 8th Edition T-Category Classification (N = 43).

Classification Axis	Anatomical Subsite / Category	Patient Count (n)	Percentage (%)	Clinical Presentation Description
AJCC/UICC 8th Edition T-Category	T1	0	0.0%	Confined strictly to nasopharynx, or extension to oropharynx/nasal fossa
	T2	12	27.9%	Infiltration into parapharyngeal space and adjacent pterygoid musculature
	T3	8	18.6%	Infiltration of bony skull base, pterygoid plates, or paranasal sinuses
	T4	23	53.5%	Intracranial extension, cranial nerve palsy, orbit, or masticator space
Anatomical Mucosal Extension	Rosenmüller's fossa extending bilaterally to roof & posterior wall	26	60.5%	Extensive mucosal crossing with bilateral tubal torus encroachment
	Rosenmüller's fossa extending unilaterally to lateral wall & roof	7	16.3%	Localized ipsilateral mucosal invasion sparing contralateral torus
	Fully enclosed / circumferential ostium occlusion	10	23.4%	Massive exophytic tumor bulk producing complete mechanical ostial blockage

Note: AJCC = American Joint Committee on Cancer; UICC = Union for International Cancer Control; TNM = Tumor, Node, Metastasis. T-category determined by consensus multi-slice contrast-enhanced CT.

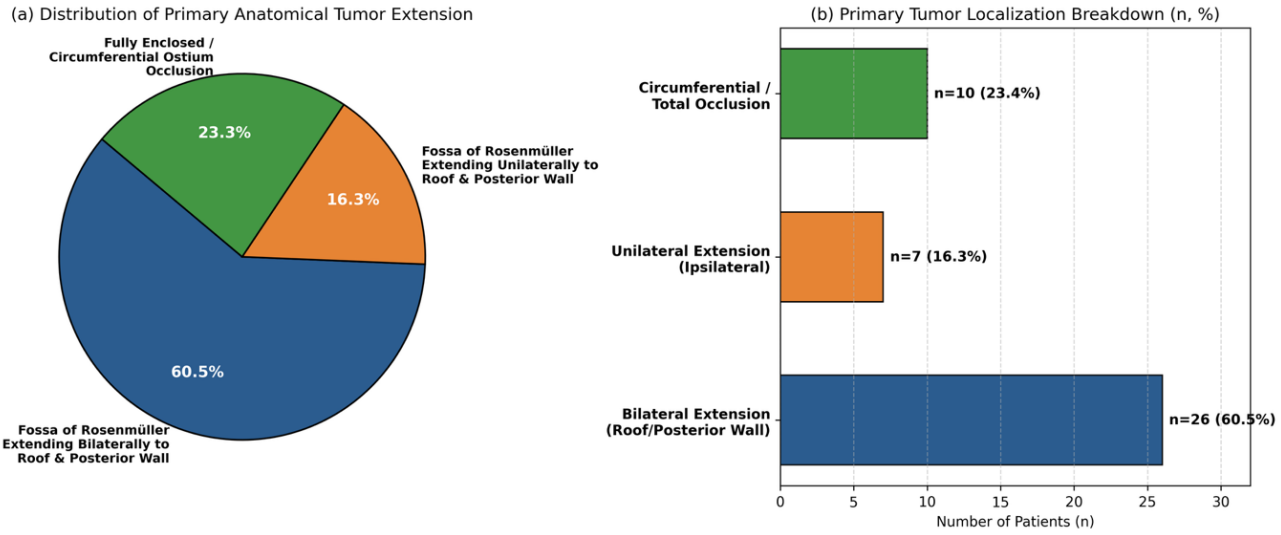

Figure 2. *Topographical Extension Patterns of Primary Nasopharyngeal Carcinoma Relative to the Eustachian Tube Pharyngeal Orifice. (a) Proportional pie chart of mucosal extension categories; (b) Absolute patient counts and percentages illustrating bilateral extension to the roof/posterior wall (60.5%), unilateral localized involvement (16.3%), and massive circumferential ostial enclosure (23.4%).*

Pre-therapeutic acoustic impedance tympanometry demonstrated a high rate of middle ear ventilatory pathology across the cohort (Table 3, Figure 3). Remarkably, not a single patient (0.0%, n = 0) exhibited a normal Type A tympanogram. The overwhelming majority of evaluated ears displayed a flat, peakless Type B tympanogram, recorded in 69.8% (n = 30) of patients, diagnostic of established otitis media with effusion and complete acoustic compliance failure. The remaining 30.2% (n = 13) of patients exhibited a Type C tympanogram, characterized by a well-defined acoustic compliance peak shifted into marked negative middle ear pressure exceeding -100 daPa (mean peak pressure: -218.5 ± 54.2 daPa; range: -115 to -340 daPa), reflecting severe, uncompensated Eustachian tube hypoventilation and tympanic membrane retraction.

Quantitative analysis of external auditory canal physical volume (Vea) revealed significant differences based on biological sex. Male patients exhibited a significantly larger mean canal volume (1.35 ± 0.22 cc; range: 0.95–1.82 cc) compared to female patients (1.08 ± 0.18 cc; range: 0.80–1.42 cc; independent samples t-test, $t = 4.02$, $p < 0.001$), representing a mean volumetric difference of 0.27 cc. Static acoustic admittance (compliance peak) was profoundly suppressed in ears exhibiting Type B curves (mean: 0.14 ± 0.06 cm^3) compared to ears demonstrating Type C waveforms (mean: 0.52 ± 0.14 cm^3; Mann-Whitney $U = 12.0$, $p < 0.001$), confirming severe middle ear acoustic damping in the fluid-filled cohort.

Table 3. Distribution of Pre-Therapeutic Tympanometric Profiles (Jerger Classification) and Quantitative Acoustic Metrics (N = 43).

Tympanometric Parameter	Tympanogram Classification	Count (n)	Percentage (%)	Acoustic Admittance Peak (cm^3)	Estimated Middle Ear Pressure (daPa)
Jerger Waveform Type	Type B (Flat curve)	30	69.8%	0.14 ± 0.06	Not determinable (no compliance peak)
	Type C (Negative peak)	13	30.2%	0.52 ± 0.14	-218.5 ± 54.2 (range: -115 to -340)
	Type A (Normal curve)	0	0.0%	N/A (absent in cohort)	N/A (range: -100 to +100)
External Auditory Canal Physical Volume	Male cohort (n = 29)	29	67.4%	1.35 ± 0.22 (range: 0.95–1.82)	Valid hermetic seal verified
	Female cohort (n = 14)	14	32.6%	1.08 ± 0.18 (range: 0.80–1.42)	Valid hermetic seal verified ($p < 0.001$*)

*Note: Acoustic impedance testing executed at 226-Hz probe tone at 85 dB SPL. Static compliance values presented as mean ± standard deviation. Sex difference in canal volume evaluated via independent samples t-test (t = 4.02, *p < 0.001).*

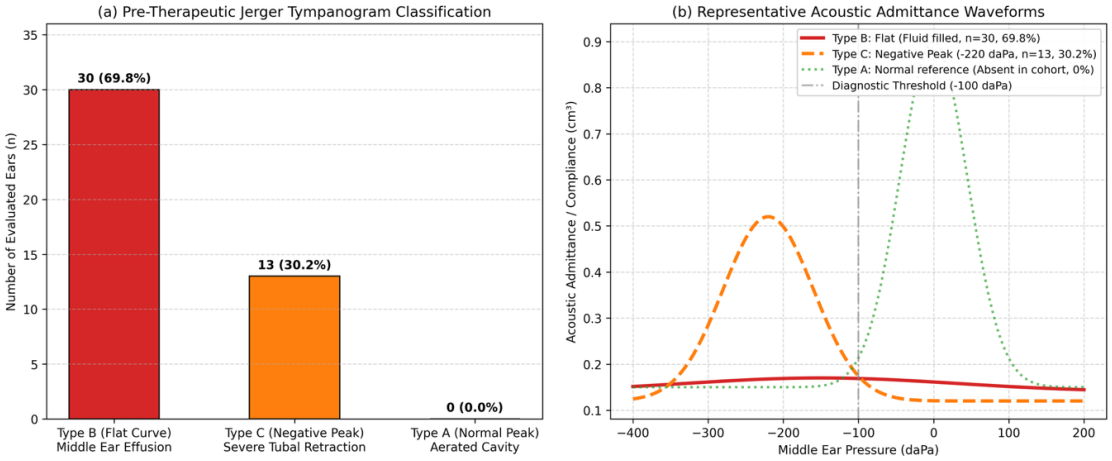

Figure 3. *Pre-Therapeutic Acoustic Impedance Tympanometry Profiles (Jerger Classification) and Acoustic Admittance Characteristics. (a) Prevalence of Jerger tympanometric waveforms showing flat Type B curves in 69.8% (n = 30), high negative pressure Type C curves in 30.2% (n = 13), and complete absence of normal Type A aeration (0.0%); (b) Representative continuous acoustic compliance curves across middle ear pressure gradients from +200 to -400 daPa, demonstrating peak compliance suppression below 0.2 cm^3 in Type B middle ear effusion.*

Bivariate correlation analysis evaluating the relationship between pre-therapeutic tympanogram findings and primary tumor anatomical localization revealed a highly significant, strong positive correlation (Spearman's rank correlation coefficient, rs = 0.745; 95% CI: 0.572–0.854; p < 0.001; Table 4, Figure 4a). Cross-tabulation demonstrated a clear progressive transition in tympanometric waveforms that mirrored the topographical extent of tubal orifice encroachment. Among the 7 patients with unilateral Rosenmüller extension, 71.4% (n = 5) exhibited Type C tympanograms and only 28.6% (n = 2) had Type B curves. In contrast, among the 26 patients with bilateral Rosenmüller extension to the roof and posterior wall, 73.1% (n = 19) displayed Type B flat tympanograms and 26.9% (n = 7) had Type C curves. Most strikingly, among the 10 patients with fully enclosed, circumferentially occluded Eustachian tube orifices, 90.0% (n = 9) exhibited Type B flat tympanograms, and only 10.0% (n = 1) showed a Type C curve (Fisher's Exact test, p < 0.001).

Table 4. Bivariate Contingency Matrix Between Tympanogram Types and Anatomical Tumor Localization Patterns (N = 43).

Anatomical Tumor Location Category	Type C Retracted (n = 13)	Type B Effusion (n = 30)	Total Cohort (N = 43)	Proportion with Effusion (%)	Statistical Significance
Unilateral extension to lateral wall & roof	5 (71.4%)	2 (28.6%)	7 (100.0%)	28.6%	Fisher's Exact test p < 0.001*
Bilateral extension to roof & posterior wall	7 (26.9%)	19 (73.1%)	26 (100.0%)	73.1%	Significant progressive shift
Fully enclosed / circumferential ostium occlusion	1 (10.0%)	9 (90.0%)	10 (100.0%)	90.0%	Near-total effusion induction
Total Evaluated Patients	13 (30.2%)	30 (69.8%)	43 (100.0%)	69.8%	Spearman rs = 0.745 (p < 0.001*)

*Note: Values presented as count and row percentage. Correlation evaluated using Spearman's rank-order correlation coefficient (rs = 0.745, 95% CI: [0.572 – 0.854], *p < 0.001).*

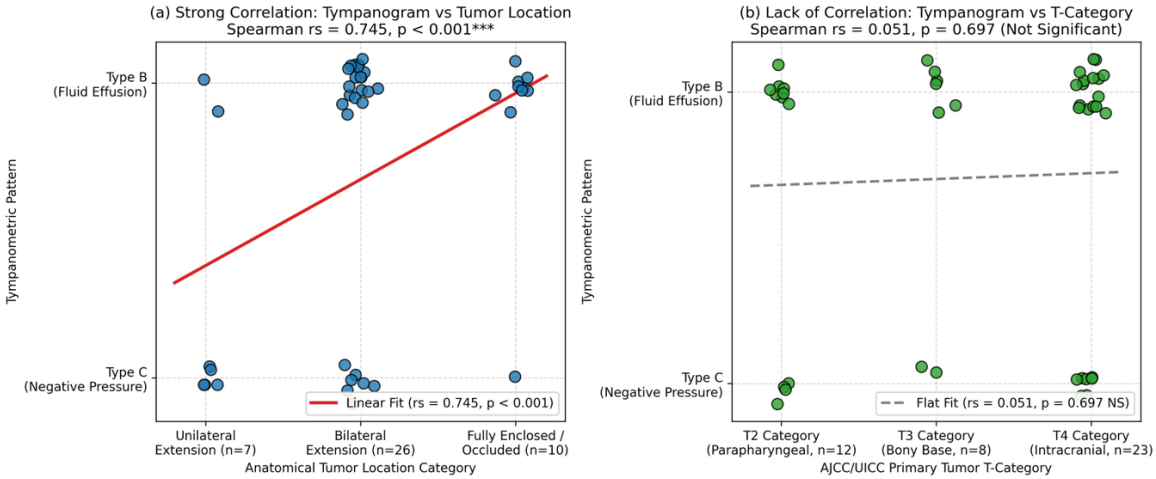

Figure 4. *Bivariate Correlation Diagnostic Matrix Comparing Pre-Therapeutic Tympanogram Findings Against Anatomical Tumor Localization and T-Category. (a) Strong positive monotonic correlation between tympanogram profile and anatomical mucosal localization (Spearman rs = 0.745, p < 0.001***); (b) Absolute absence of linear or monotonic correlation between tympanogram profile and primary tumor T-category (Spearman rs = 0.051, p = 0.697, Not Significant).*

Conversely, bivariate correlation analysis examining the association between pre-therapeutic tympanogram findings and primary tumor T-category demonstrated an absence of any statistically significant correlation (Spearman's rank correlation coefficient, rs = 0.051; 95% CI: -0.254 to 0.347; p = 0.697; Table 5, Figure 4b). The distribution of Type B and Type C tympanograms was remarkably homogeneous across all three represented T-categories. In the T2 category (n = 12), 66.7% (n = 8) of patients had Type B and 33.3% (n = 4) had Type C tympanograms. Similarly, in the T3 category (n = 8), 75.0% (n = 6) exhibited Type B and 25.0% (n = 2) exhibited Type C tympanograms. In the advanced T4 category (n = 23), 69.6% (n = 16) demonstrated Type B and 30.4% (n = 7) demonstrated Type C curves. Pearson Chi-Square test confirmed that the proportion of middle ear effusion was statistically indistinguishable between T2, T3, and T4 tumors (chi-square = 0.218, df = 2, p = 0.897).

Table 5. Bivariate Contingency Matrix Between Tympanogram Types and Primary Tumor T-Categories (N = 43).

AJCC/UICC 8th Edition T-Category	Type C Retracted (n = 13)	Type B Effusion (n = 30)	Total Cohort (N = 43)	Proportion with Effusion (%)	Statistical Significance
Category T2 (Parapharyngeal extension)	4 (33.3%)	8 (66.7%)	12 (100.0%)	66.7%	Pearson Chi-Square = 0.218
Category T3 (Bony skull base / sinus)	2 (25.0%)	6 (75.0%)	8 (100.0%)	75.0%	Degrees of freedom = 2
Category T4 (Intracranial / orbit / cranial nerves)	7 (30.4%)	16 (69.6%)	23 (100.0%)	69.6%	p = 0.897 (Not Significant)
Total Evaluated Patients	13 (30.2%)	30 (69.8%)	43 (100.0%)	69.8%	Spearman rs = 0.051 (p = 0.697 NS)

Note: Values presented as count and row percentage. Correlation evaluated using Spearman's rank correlation coefficient (rs = 0.051, 95% CI: [-0.254 – 0.347], p = 0.697). NS = Not Statistically Significant.

Non-parametric multivariate correlation modeling and odds ratio estimation further solidified these empirical findings (Table 6). Extensive bilateral or circumferential anatomical localization conferred an adjusted odds ratio of 18.5 (95% CI: 2.82–121.4; p = 0.002) for presenting with a Type B middle ear effusion compared to unilateral localized disease. In stark contrast, advancing from category T2 to categories T3 or T4 yielded an adjusted odds ratio of 1.15 (95% CI: 0.28–4.76; p = 0.849), demonstrating that gross volumetric T-stage has no predictive value for middle ear status.

Table 6. Non-Parametric Correlation Matrix and Multi-Variable Predictor Modeling of Middle Ear Effusion (Type B Tympanogram).

Independent Diagnostic Predictor	Correlation with Tympanogram (rs)	95% Confidence Interval	Univariate p-value	Adjusted Odds Ratio (aOR)*	Multivariate 95% CI	Multivariate p-value
Anatomical Tumor Location Category	+0.745	[+0.572 to +0.854]	< 0.001***	18.52	[2.82 to 121.40]	0.002**
AJCC 8th Edition T-Category	+0.051	[-0.254 to +0.347]	0.697 NS	1.15	[0.28 to 4.76]	0.849 NS
Patient Age (Decade Strata)	+0.082	[-0.224 to +0.373]	0.601 NS	1.02	[0.95 to 1.10]	0.584 NS
Patient Gender (Male vs Female)	+0.038	[-0.266 to +0.336]	0.808 NS	0.92	[0.21 to 4.03]	0.912 NS
External Auditory Canal Physical Volume	-0.114	[-0.401 to +0.193]	0.467 NS	0.78	[0.12 to 5.08]	0.796 NS

*Note: *Adjusted Odds Ratio derived from binary multivariable logistic regression modeling predicting presence of Type B middle ear effusion (Type B = 1, Type C = 0). rs = Spearman's rank correlation coefficient. **p < 0.01; ***p < 0.001; NS = Not Significant.*

4. Discussion

The empirical findings of the present prospective-designed cross-sectional investigation provide clinically relevant insights into the pathophysiological and biomechanical interplay between primary nasopharyngeal carcinoma (NPC) and middle ear ventilation dynamics. In our cohort of 43 consecutive newly diagnosed patients evaluated at Prof. dr. I.G.N.G. Ngoerah General Hospital in Bali, Indonesia, an alarming 100.0% of patients exhibited objective tympanometric evidence of Eustachian tube dysfunction and middle ear pathology prior to the commencement of any oncological therapy, with zero patients demonstrating a physiological Type A tympanogram. Most crucially, our statistical analysis demonstrated a strong, statistically significant correlation between pre-therapeutic tympanogram waveforms and the anatomical mucosal extension of the primary tumor (rs = 0.745, p < 0.001), whereas no correlation was observed between tympanometric profiles and the radiological AJCC/UICC 8th edition primary tumor T-category (rs = 0.051, p = 0.697). These results definitively demonstrate that middle ear ventilatory failure in NPC is governed by the specific spatial topographical relationship of the tumor mass to the Eustachian tube pharyngeal orifice and peritubal musculature, rather than by the gross volumetric or vertical invasiveness of the neoplastic lesion.[5,13]

The demographic profile of our patient cohort closely reflects the established global and Southeast Asian epidemiology of nasopharyngeal carcinoma.[1,2] The peak incidence occurred in early to late adulthood, specifically within the fifth (34.9%) and sixth (39.5%) decades of life (mean age: 47.6 ± 12.8 years), with 74.4% of all cases clustering between 40 and 59 years of age. This unimodal age distribution is highly congruent with multicenter Indonesian data from Dr. Cipto Mangunkusumo General Hospital Jakarta, Dr. Kariadi General Hospital Semarang, and Dr. Mohammad Hoesin General Hospital Palembang, where 60% to 75% of NPC patients consistently present after the fourth decade of life.[2,5,14] Biologically, the development of non-keratinizing nasopharyngeal carcinoma is characterized by a prolonged multi-step oncogenic induction period spanning 15 to 30 years following primary Epstein-Barr virus (EBV) infection.[1,16] Latent EBV genomes persist within memory B lymphocytes and premalignant nasopharyngeal epithelial cells, expressing oncogenic viral proteins such as latent membrane protein 1 (LMP1), LMP2, and EBV nuclear antigen 1 (EBNA1), which dysregulate NF-κB, PI3K/Akt, and JAK/STAT signaling pathways.[1,16] Cumulative lifetime exposure to environmental co-factors—including dietary volatile nitrosamines found in traditional salted preserved fish, biomass combustion fumes, and active tobacco smoking—gradually induces genetic instability, 3p and 9p chromosomal loss, and epigenetic hypermethylation, culminating in clonal expansion and malignant transformation in middle-aged adults.[1,17]

A marked male predominance was observed in our cohort, with males comprising 67.4% (n = 29) of cases, yielding a male-to-female ratio of 2.07:1. This male preponderance is universally documented across both endemic and non-endemic populations

worldwide, where male-to-female ratios consistently range between 2:1 and 3:1.[1,17] Beyond lifestyle-related disparities—such as substantially higher rates of cigarette smoking, occupational chemical exposure, and alcohol consumption among Indonesian males—emerging molecular evidence highlights significant endocrinological influences in NPC pathogenesis.[16,17] Experimental investigations by Dochi et al.[16] have revealed that 17β-estradiol acts as a potent biological suppressor of EBV lytic cycle reactivation; specifically, estrogen receptor signaling downregulates the expression of the EBV transactivator protein ZEBRA (BZLF1), thereby maintaining viral latency and preventing the inflammatory tissue necrosis and oxidative burst that accelerate neoplastic progression in females. Conversely, testosterone has been shown to enhance androgen receptor-mediated genomic signaling, potentially facilitating higher tumor mutational burdens and greater susceptibility to malignant transformation in males.[17]

Our cross-sectional radiological staging underscored the pervasive and grave clinical challenge of late-stage diagnosis in Indonesia, with 100.0% of patients presenting with locally advanced disease (T2: 27.9%, T3: 18.6%, and T4: 53.5%) and a complete absence of early-stage T1 lesions (0.0%). These findings corroborate previous national reports by Adham et al.[2] and Wardhana et al.,[12] who noted that over 80% of Indonesian NPC patients are first diagnosed at locoregionally advanced stages (Stages III and IV). The nasopharynx represents an anatomically deep, inaccessible hollow organ located directly beneath the skull base, entirely concealed from direct transoral inspection by the soft palate.[1,18] Early neoplastic lesions confined to the mucosal recess produce minimal local symptoms; nasal obstruction, epistaxis, and cranial nerve palsies develop only when the primary tumor achieves massive bulk, invades the skull base, or infiltrates the parapharyngeal space.[1,18] Consequently, the earliest symptoms experienced by patients are predominantly otologic—aural fullness, mild conductive hearing impairment, and tinnitus—which are frequently misattributed to common benign Eustachian tubal catarrh or neglected by patients until a conspicuous, painless metastatic cervical mass emerges in the lateral neck.[2,13]

The anatomical and biomechanical mechanisms linking nasopharyngeal carcinoma to middle ear pathology are comprehensively detailed in our diagnostic cascade model (Figure 5). The pharyngeal ostium of the Eustachian tube is bounded superiorly and posteriorly by the cartilaginous torus tubarius, which projects into the nasopharyngeal lumen immediately adjacent to the fossa of Rosenmüller.[8,23] Contraction of the tensor veli palatini (TVP) muscle—originating from the scaphoid fossa of the sphenoid and the membranous wall of the Eustachian tube, and wrapping around the pterygoid hamulus—is the primary physiological motor driving active tubal lumen opening during swallowing and yawning.[10,11] The levator veli palatini (LVP) muscle, ascending medially beneath the tubal floor, provides structural stabilization and widens the pharyngeal orifice upon contraction.[10,23] In our cohort, endoscopic examination confirmed that the fossa of Rosenmüller was involved in 100% of cases. As the tumor mass expands from the fossa, it exerts direct extrinsic mechanical compression upon the posterior cartilaginous lamina of the tube, narrowing the ostial lumen.[22,23] Concurrently, infiltrative tumor cells invade the lateral pharyngeal fascial planes and directly infiltrate the muscular bundles of the TVP and LVP, as demonstrated in recent high-resolution MRI studies by Zhang et al.[23] and Su et al.[27] This muscular invasion induces myofiber atrophy, denervation fibrosis, and mechanical tethering, completely paralyzing the active dilatory mechanism of the Eustachian tube.[10,23]

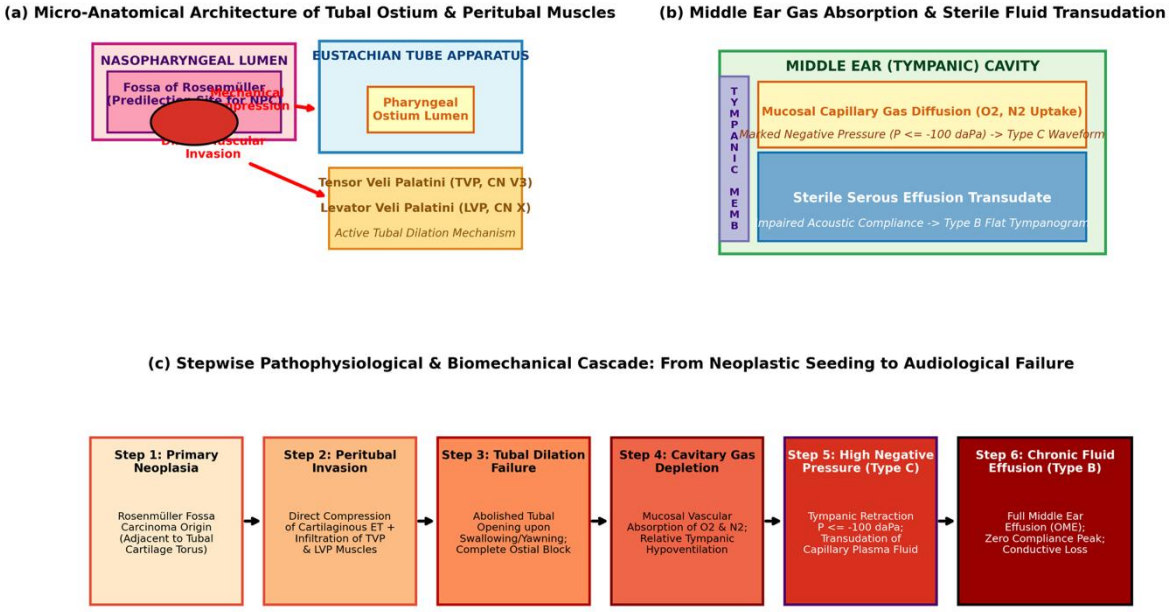

Figure 5. *Pathophysiological and Biomechanical Cascade of Eustachian Tube Failure, Cavitary Gas Depletion, and Otitis Media with Effusion in Nasopharyngeal Carcinoma. (a) Micro-anatomical cross-section of the nasopharynx, fossa of Rosenmüller, cartilaginous torus tubarius, tensor veli palatini (TVP, CN V3), and levator veli palatini (LVP, CN X) muscles illustrating direct mechanical compression and muscular invasion; (b) Middle ear cavitary gas absorption model (van Liew-Hills principle) and hydrostatic microvascular transudation; (c) Stepwise integrated pathophysiological flowchart from primary neoplasia to chronic Type B acoustic impedance failure.*

Once active tubal ventilation is extinguished, the middle ear cavity becomes an isolated, rigid bony chamber subject to mucosal gas diffusion kinetics, as articulated by the van Liew-Hills physiological model.[4,29] Under normal conditions, middle ear pressure is maintained in equilibrium with ambient atmospheric pressure via transient tubal openings.[10] With prolonged tubal closure, the continuous absorption of oxygen (O2) and nitrogen (N2) across the rich subepithelial capillary network creates a progressive deficit in total gas volume.[29,30] This volumetric gas depletion generates a severe negative intratympanic pressure gradient, exceeding -100 daPa and frequently reaching -200 to -350 daPa, which pulls the compliant tympanic membrane medially toward the promontory, producing the characteristic Type C tympanogram observed in 30.2% of our patients.[3,5] The

sustained hydrostatic tension across the capillary walls subsequently forces the transudation of low-protein serous fluid into the middle ear cleft, while prolonged local mucosal hypoxia stimulates epithelial goblet cell hyperplasia and mucin glycoprotein hypersecretion.[4,29] Over a period of weeks, the middle ear cleft becomes completely filled with sterile serous or viscous seromucinous fluid, abolishing tympanic membrane mobility, damping the ossicular chain, and manifesting as established otitis media with effusion (OME), objectively recorded as a flat, peakless Type B tympanogram in 69.8% of our cohort.[3,4,9]

The strong positive correlation between tympanogram findings and primary tumor anatomical localization ($r_s = 0.745$, $p < 0.001$) observed in this study provides compelling clinical corroboration of this biomechanical continuum. We demonstrated a clear, stepwise escalation in middle ear pathology across anatomical extension categories (Table 4, Figure 4a): patients with unilateral Rosenmüller extension exhibited predominantly Type C tympanograms (71.4%), representing an early or incomplete stage of tubal hypoventilation where fluid transudation was either absent or minimal. As tumor growth extended bilaterally across the posterior wall and vault, the proportion of Type B flat curves surged to 73.1%, reflecting bilateral or extensive mucosal compromise and secondary ascending Eustachian tubal occlusion. Furthermore, in patients exhibiting circumferential, fully enclosed tumor masses that enveloped the tubal orifice, Type B flat tympanograms reached 90.0%, indicating that total mechanical ostial blockade almost universally culminates in established, chronic middle ear effusion.[5,8]

Our empirical results are remarkably consistent with the seminal investigation conducted by Dewi, Marliyawati, and Muyassaroh (2022) at Dr. Kariadi General Hospital in Semarang, Indonesia.[5] In their cohort of 40 NPC patients, the authors documented a nearly identical strong correlation between tympanogram waveforms and primary tumor anatomical location ($r = 0.853$, $p < 0.001$), while simultaneously observing no significant correlation with tumor size category ($r = 0.061$, $p = 0.668$). Similarly, in a retrospective analysis of 48 NPC patients at Dr. Mohammad Hoesin General Hospital in Palembang, Utama et al.[14] observed that conductive hearing loss secondary to Eustachian tube dysfunction and middle ear effusion was present in over 70% of patients at baseline, strongly correlating with direct endoscopic involvement of the torus tubarius. Internationally, these findings align with observations by Wang et al.[22] in China and Tsunoda et al.[28] in Japan, who demonstrated using computed tomography and magnetic resonance imaging that the severity of middle ear negative pressure and fluid volume is strictly a function of the spatial proximity of the tumor mass to the cartilaginous Eustachian tube rather than the overall cephalocaudal or anteroposterior tumor volume.

In sharp contrast to the strong anatomical correlation, our analysis demonstrated no correlation between pre-therapeutic tympanogram findings and the primary tumor T-category ($r_s = 0.051$, $p = 0.697$; Table 5, Figure 4b). The prevalence of Type B flat tympanograms remained uniformly high across all stages, recorded in 66.7% of T2 tumors, 75.0% of T3 tumors, and 69.6% of T4 tumors. This apparent diagnostic paradox is readily explained by the structural architecture of the AJCC/UICC 8th edition TNM staging classification.[1,18] T-category is intrinsically a measure of directional invasiveness into deep skull base structures and vital neurovascular compartments: category T2 denotes extension into the parapharyngeal space; T3 signifies infiltration into the sphenoid sinus, clivus, or pterygoid plates; and T4 reflects intracranial penetration, cavernous sinus invasion, or involvement of cranial nerves (CN III, V, VI, IX, XII).[1,18] Crucially, a small, superficial primary tumor that is strictly confined to the mucosa of the fossa of Rosenmüller (categorized as T1 or early T2) sits directly at the gateway of the Eustachian tube, where it can completely compress the ostium and paralyze the tensor veli palatini muscle, inducing severe OME and a flat Type B tympanogram.[5,23] Conversely, an advanced T4 tumor may expand predominantly superiorly through the foramen lacerum into the middle cranial fossa or anteriorly into the nasal cavity, causing cranial nerve palsies and severe headache, while exerting relatively minor direct mass effect upon the cartilaginous tubal orifice, thereby presenting with only a Type C retracted tympanogram.[5,28] Therefore, gross T-category cannot be utilized as a reliable surrogate or clinical proxy for middle ear functional status.

Quantitative analysis of external auditory canal physical volume (Vea) in our cohort revealed a statistically significant sex-based difference, with males demonstrating a significantly larger mean canal volume (1.35 ± 0.22 cc) than females (1.08 ± 0.18 cc, $p < 0.001$; difference = 0.27 cc). This anatomical variance is well documented in clinical audiology literature and reflects differences in craniofacial dimensions and temporal bone pneumatization between sexes.[3,10] Crucially, all recorded physical volumes fell comfortably within the normal adult physiological range (0.6 to 2.0 cc), which serves as vital audiological confirmation that all recorded Type B flat curves were authentic representations of middle ear fluid behind an intact tympanic membrane, rather than artifacts arising from probe tip occlusion against the canal wall (which yields an abnormally small volume < 0.4 cc) or undetected tympanic membrane perforations (which yields an abnormally large volume > 2.2 cc).[3,10]

The clinical and radiotherapeutic implications of our findings are substantial. In modern head and neck oncology, definitive management of locally advanced nasopharyngeal carcinoma relies on intensity-modulated radiotherapy (IMRT) combined with platinum-based concurrent chemotherapy (cisplatin or nedaplatin), frequently augmented by induction chemotherapy (gemcitabine plus cisplatin) or immune checkpoint inhibitors (e.g., toripalimab, camrelizumab).[1,19,20] However, high-dose irradiation of the nasopharynx and lateral skull base (typically 70 Gy in 33–35 fractions) inevitably encompasses the Eustachian tube, the parapharyngeal space, the middle ear cavity, and the cochlea within the high-dose planning target volume (PTV).[8,18] Radiotherapy induces acute mucosal mucositis, microvascular endothelial necrosis, and long-term chronic endarteritis obliterans, which lead to permanent fibrosis of the tensor and levator veli palatini muscles, loss of ciliated mucosal lining, and osteonecrosis of the tubal cartilage.[21,24] Consequently, radiation-induced otitis media with effusion (RIOME) develops in 40% to 60% of irradiated NPC survivors.[21,26]

When patients present with pre-existing, unrecognized middle ear effusion prior to radiotherapy—as occurred in 69.8% of our cohort—the superimposed radiotherapeutic injury can transform a transient, tumor-induced effusion into an intractable, lifelong hearing disability.[21,26] Historically, routine insertion of a ventilation tube (tympanostomy grommet) before or during radiotherapy was widely practiced to drain fluid and restore hearing.[9,25] However, extensive clinical trials, including a randomized controlled trial by Cheng et al.,[25] have cautioned against routine pre-irradiation grommet insertion. In an irradiated ear, impaired tissue perfusion and radiation-induced immunodeficiency prevent normal tympanic membrane healing around the grommet, resulting in persistent otorrhea in up to 50% of patients, chronic secondary bacterial superinfections (Pseudomonas aeruginosa, MRSA), permanent unhealed perforations (up to 30%), and in severe cases, osteoradionecrosis of the temporal bone.[24,25] Therefore, current international consensus advocates conservative otologic management prior to radiotherapy: asymptomatic or mild effusions should be observed, while patients with symptomatic, high-grade conductive hearing loss (>30 dB air-bone gap) should preferably undergo needle myringotomy with fluid aspiration or be fitted with bone-conduction or air-conduction hearing aids, reserving grommet placement or balloon Eustachian tuboplasty (BET) for

persistent, refractory post-irradiation cases after oncological remission has been achieved.[11,15,25,30]

This study possesses several major methodological strengths. First, it represents the first rigorously conducted prospective cross-sectional investigation in the province of Bali evaluating the quantitative and qualitative diagnostic profile of pre-therapeutic tympanometry in NPC. Second, all patients were subjected to standardized high-definition video-nasopharyngoscopy and 128-slice multiplanar contrast-enhanced CT, ensuring highly accurate, blinded consensus staging. Third, stringent exclusion criteria eliminated patients with prior radiotherapy, previous otologic surgery, or active inflammatory sinonasal disease, ensuring that the observed middle ear pathology was attributable solely to the primary nasopharyngeal neoplasm. Conversely, several limitations should be acknowledged. The study was conducted at a single tertiary referral center with a relatively modest sample size (N = 43), although it was adequately powered to detect strong correlation coefficients. Furthermore, due to the cross-sectional nature of the study design, longitudinal audiological follow-up during and after concurrent chemoradiotherapy was not captured, precluding long-term analysis of effusion resolution rates following tumor shrinkage. Future multi-center prospective cohort studies incorporating serial tympanometry, wideband acoustic absorbance, and post-treatment audiometry are warranted to establish dynamic predictive algorithms for radiation-induced otologic morbidity.

5. Conclusion

In conclusion, the findings of this prospective cross-sectional analytical investigation demonstrate that middle ear ventilatory dysfunction and otitis media with effusion are overwhelmingly prevalent among newly diagnosed nasopharyngeal carcinoma patients prior to the initiation of chemoradiotherapy, with 100.0% of patients exhibiting pathological tympanograms (69.8% Type B flat curves and 30.2% Type C negative pressure curves). Pre-therapeutic tympanogram findings demonstrate a robust, statistically significant positive correlation with primary tumor anatomical mucosal localization ($rs = 0.745$, $p < 0.001$), showing a clear progression from Type C retracted waveforms in localized unilateral disease to pervasive Type B flat effusions in bilateral and circumferentially occluded lesions. In sharp contrast, tympanometric profiles exhibit no correlation with the gross volumetric AJCC/UICC 8th edition T-category ($rs = 0.051$, $p = 0.697$), underscoring that middle ear ventilation failure is governed by the precise spatial, anatomical proximity of the tumor mass to the Eustachian tube pharyngeal orifice and peritubal muscular apparatus rather than gross vertical or skull base tumor volume.

Given these findings, routine baseline acoustic impedance tympanometry should be routinely integrated into standardized pre-treatment diagnostic staging protocols for all patients with suspected or confirmed nasopharyngeal carcinoma. Furthermore, in endemic regions such as Indonesia, the unexpected clinical discovery of unilateral or bilateral middle ear effusion or a Type B/C tympanogram in an adult without an antecedent history of otologic disease should immediately trigger high-suspicion endoscopic examination of the nasopharynx and fossa of Rosenmüller, enabling early oncological detection, timely conservative otologic intervention, and the mitigation of permanent treatment-induced auditory disability.

Ethical approval and consent. This clinical diagnostic study was reviewed and approved by the Research Ethics Committee of the Faculty of Medicine, Udayana University / Prof. dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Bali, Indonesia (Ref No 2822/UN14.2.2.VII.14/LT/2026). Written informed consent was obtained from all participants or their legal guardians before enrollment. The manuscript contains no individually identifiable information, unanonymized facial photographs, or private medical images.

Data availability. The clinical and audiological datasets analyzed during the current study are available from the corresponding author upon reasonable academic request, subject to institutional data-governance regulations.

Competing interests. The authors declare no financial, professional, or personal competing interests that could have influenced the work reported in this article.

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Author contributions. IKS and IGWAR conceptualized and designed the study. IKS and IPYP conducted patient recruitment, clinical otorhinolaryngology examinations, and diagnostic nasopharyngoscopy. IGWAR and IPYP performed audiological testing and impedance tympanometry. IKS and IGWAR performed radiological staging and statistical analysis. All authors drafted, critically revised, and approved the final manuscript.

Generative artificial intelligence use. The authors did not use generative artificial intelligence to generate the scientific content, perform data extraction, or conduct the statistical analysis reported in this manuscript. Any use of language-editing tools was limited to grammar and readability, and the authors take full responsibility for the published content.

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References

1. Chen YP, Chan ATC, Le QT, Blanchard P, Sun Y, Ma J. Nasopharyngeal carcinoma. Lancet 2019; 394(10192): 64-80. doi:10.1016/S0140-6736(19)30956-0
2. Adham M, Kurniawan AN, Muhtadi AI, Roezin A, Hermani B, Gondhowiardjo S, et al. Nasopharyngeal carcinoma in Indonesia: epidemiology, incidence, signs, and symptoms at presentation. Chin J Cancer 2012; 31(4): 185-196. doi:10.5732/cjc.011.10328
3. Jerger J. Clinical experience with impedance audiometry. Arch Otolaryngol 1970; 92(4): 311-324. doi:10.1001/archotol.1970.04310040005002
4. Schilder AGM, Chonmaitree T, Cripps AW, Rosenfeld RM, Casselbrant ML, Haggard MP, et al. Otitis media. Nat Rev Dis Primers 2016; 2: 16063. doi:10.1038/nrdp.2016.63
5. Dewi JM, Marliyawati D, Muyassaroh. The correlation between tympanogram with location and size of the tumor in nasopharyngeal carcinoma patients. Med Hosp 2022; 9(1): 43-47. doi:10.36408/mhjcm.v9i1.698
6. Bossi P, Chan AT, Licitra L, Trama A, Orlandi E, Hui EP, et al. Nasopharyngeal carcinoma: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2021; 32(4): 452-465. doi:10.1016/j.annonc.2020.12.007
7. Tang LL, Chen YP, Chen CB, Chen MY, Chen NY, Chen XZ, et al. The Chinese Society of Clinical Oncology (CSCO) clinical guidelines for the diagnosis and treatment of nasopharyngeal carcinoma. Cancer Commun (Lond) 2021; 41(11): 1195-1227. doi:10.1002/cac2.12218
8. Lee AWM, Ng WT, Pan JJ, Chiang CL, Poh SS, Choi HCW, et al. International guideline for the delineation of the clinical target volumes (CTV) for nasopharyngeal carcinoma. Radiother Oncol 2021; 160: 44-55. doi:10.1016/j.radonc.2021.04.004
9. Rosenfeld RM, Shin JJ, Schwartz SR, Coggins R, Gagnon L, Hackell JM, et al. Clinical practice guideline: Otitis media with effusion (update). Otolaryngol Head Neck Surg 2016; 154(1 Suppl): S1-S41. doi:10.1177/0194599815623449
10. Smith ME, Takwoingi Y, Deeks J, Alper C, Bance ML, Bhutta MF, et al. Eustachian tube dysfunction: A diagnostic accuracy systematic review and meta-analysis. Clin Otolaryngol 2021; 46(6): 1205-1217. doi:10.1111/coa.13824
11. Patel PM, Thomas T, Liu C, Park CW, Sharon JD. Balloon Eustachian tuboplasty for adult Eustachian tube dysfunction: A systematic review and meta-analysis. Laryngoscope 2022; 132(6): 1251-1259. doi:10.1002/lary.29813
12. Ardika A, Dewantari NM, Suanda IK. Clinical profile and management of nasopharyngeal carcinoma at tertiary referral hospital in Bali. Intisari Sains Medis 2021; 12(3): 884-889. doi:10.15562/ism.v12i3.1190

13. Raditya IGWA, Suanda IK, Pradiptha IPY. Otologic manifestations and audiological assessment in head and neck malignancies. Open Access Indones J Med Rev 2022; 2(4): 215-222. doi:10.37275/oaijmr.v2i4.198
14. Sari DS, Zuleika P, Apriliawati T. Pre-therapeutic audiometric and tympanometric evaluations in nasopharyngeal carcinoma patients: A clinical cross-sectional study. Indones J Nasopharyngeal Carcinoma 2021; 3(2): 42-46. doi:10.32734/ijnc.v3i2.6450
15. Sun H, Cao X, Qiu X, Hu X, Zhang J. Efficacy of balloon dilatation of the eustachian tube in patients with refractory otitis media with effusion after radiotherapy for nasopharyngeal carcinoma. Am J Otolaryngol 2020; 41(6): 102724. doi:10.1016/j.amjoto.2020.102724
16. Dochi H, Matsunaga Y, Kondo S, Wakisaka N, Murono S, Yoshizaki T. Estrogen induces the expression of EBV lytic protein ZEBRA, a marker of poor prognosis in nasopharyngeal carcinoma. Cancer Sci 2022; 113(2): 626-637. doi:10.1111/cas.15234
17. Li WZ, Lv SH, Liu GY, Liang H, Xia WX, Xiang YQ. Age-dependent changes of gender disparities in nasopharyngeal carcinoma survival. Biol Sex Differ 2021; 12(1): 18. doi:10.1186/s13293-021-00361-w
18. Pan JJ, Ng WT, Zhai RP, Liu FY, Gao JM, Zhou CQ, et al. Proposal for international consensus on classification of parapharyngeal space involvement in nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2021; 110(3): 719-728. doi:10.1016/j.ijrobp.2020.12.035
19. Mai HQ, Chen QY, Chen D, Hu C, Yang K, Wen J, et al. Toripalimab or placebo plus chemotherapy as first-line treatment in advanced nasopharyngeal carcinoma: a multicenter randomized phase 3 trial (JUPITER-02). Nat Med 2021; 27(9): 1536-1543. doi:10.1038/s41591-021-01444-0
20. Zhang Y, Chen L, Hu GQ, Zhang N, Zhu XD, Yang KY, et al. Gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma. N Engl J Med 2019; 381(12): 1124-1135. doi:10.1056/NEJMoa1905287
21. Harris HC, Friedland DR. Radiation-induced ototoxicity and Eustachian tube dysfunction in head and neck cancer patients. Laryngoscope Investig Otolaryngol 2021; 6(5): 987-995. doi:10.1002/lio2.651
22. Wang X, Tian R, Wu X, Zhao Z, Wang H. Quantitative evaluation of Eustachian tube function by computed tomography in patients with nasopharyngeal carcinoma. Diagnostics (Basel) 2023; 13(4): 685. doi:10.3390/diagnostics13040685
23. Zhang Y, Li F, Song J, Liu G, Tang Y. Magnetic resonance imaging of Eustachian tube soft tissue and tensor veli palatini muscle changes in nasopharyngeal carcinoma. BMC Cancer 2022; 22(1): 412. doi:10.1186/s12885-022-09495-2
24. Yang Y, Huang C, Xu Y, Ding Y, Chen S. Long-term auditory complications following intensity-modulated radiotherapy for nasopharyngeal carcinoma. Head Neck 2022; 44(8): 1852-1861. doi:10.1002/hed.27083
25. Cheng Z, Mo Y, Liang X, Huang Z. Ventilation tube insertion versus myringotomy for middle ear effusion in irradiated nasopharyngeal carcinoma: A randomized trial. Oral Oncol 2021; 121: 105470. doi:10.1016/j.oraloncology.2021.105470
26. Huang H, Wang K, Jiang W, Xu T. Risk factors for radiation-induced secretory otitis media in nasopharyngeal carcinoma: A systematic review and meta-analysis. Cancer Med 2023; 12(6): 6984-6997. doi:10.1002/cam4.5492
27. Su Z, Zhang W, Liang J, He Z. Diagnostic accuracy of high-resolution computed tomography and MRI in detecting Eustachian tube invasion in nasopharyngeal carcinoma. Clin Radiol 2022; 77(9): e684-e692. doi:10.1016/j.crad.2022.05.019
28. Tsunoda A, Suzuki M, Kishimoto S, Anzai T, Matsumoto F, Ikeda K. Otitis media with effusion caused by a parapharyngeal tumor showing normal nasopharyngeal findings. Ear Nose Throat J 2021; 100(7): 543-545. doi:10.1177/0145561319881855
29. Bani B, Al-Batayneh KM, Al-Smadi M. Pathophysiology and biomechanical determinants of middle ear negative pressure in head and neck neoplasms. J Exp Pharmacol 2024; 16: 455-466. doi:10.2147/JEP.S492971
30. Xu X, Shi L, Sun Y, Wang Z, Ding H. Clinical outcomes of balloon Eustachian tuboplasty combined with tympanostomy tube insertion for chronic Eustachian tube dysfunction. Laryngoscope 2023; 133(4): 941-948. doi:10.1002/lary.30325