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ORIGINAL RESEARCH

Histopathological Spectrum and Reported Carcinogen Exposure Profile of Parotid Tumours in Bali, Indonesia: A Retrospective Cross-Sectional Study

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ABSTRACT

Background: Parotid tumours account for most salivary gland neoplasms, yet their histopathological distribution has never been characterised in Bali, and exposures common in Balinese households are undescribed in salivary gland series.

Objective: To characterise the histopathological spectrum of parotid tumours and the reported carcinogen exposure profile at a tertiary referral centre in Bali.

Methods: This retrospective cross-sectional study included all 20 patients with a parotid mass and a reportable histopathological diagnosis from January 2020 to December 2024. Proportions were reported with 95% Wilson score confidence intervals and compared with published reference values using exact binomial tests.

Result: Patients were predominantly male (14/20, 70.0%), and 18/20 (90.0%) were aged 41–70 years. Eighteen patients carried two or more exposure classes. Benign lesions predominated (12/20, 60.0%), with pleomorphic adenoma the commonest diagnosis (10/20, 50.0%). High-grade mucoepidermoid carcinoma comprised 6/7 malignancies (85.7%) against an expected 30% (p=0.004), while no Warthin tumour was identified among 18 neoplasms against an expected 30% (p=0.003). Exhaustive bounds analysis showed that no association between patient characteristics and malignancy was identifiable from the available marginal data.

Conclusion: When malignancy occurred in this series it was almost always high-grade, so diagnostic delay carries greater consequence than the malignancy rate alone suggests.

1. Introduction

Salivary gland neoplasms are uncommon, and the parotid gland accounts for the large majority of them, accounting for roughly 70 to 80% of salivary gland neoplasms. Contemporary population data place *malignant* parotid tumours at fewer than one case per 100,000 people, with benign lesions forming the bulk of surgical and outpatient caseloads.[1] The regional picture in Southeast Asia is not a scaled version of the global one. A population-based analysis of 2022 Global Cancer Observatory data across eleven Southeast Asian countries identified elevated salivary gland cancer incidence specifically in Indonesia, the Philippines and Singapore, and recorded a regional age-standardised mortality rate for head and neck cancer of 9.5 against a global 5.3 — an excess not accounted for by incidence differences alone and consistent with late presentation and constrained diagnostic capacity.[2] Series from other low- and middle-income settings frame the expected distribution: a Nigerian tertiary centre documented an incidence and clinicopathological pattern diverging from Western norms,[3] while a Tanzanian review found pleomorphic adenoma accounted for approximately 80% of benign salivary tumours.[4] Salivary gland tumours are rare in children, in whom the malignant fraction is proportionally higher,[5] as confirmed by an international paediatric series spanning three continents,[6] so the adult distribution is not simply extrapolable across age.

The molecular architecture underlying these tumours is now highly tumour-type specific and explains why histopathological classification carries prognostic weight. Pleomorphic adenoma is defined by PLAG1 and HMGA2 rearrangement,[7] and transcriptomic mapping confirms a fusion-driven phenotype that is proliferation-competent but non-invasive.[8] Mucoepidermoid carcinoma is characterised by CRTC1/3::MAML2 fusion, present in 84% of one 128-case head and neck series in which the parotid was the commonest site; fusion presence was strongly associated with low histological grade and independently predicted overall survival.[9] Warthin tumour, by contrast, is increasingly understood through mitochondrial dysfunction, chronic inflammation and cellular senescence driven by smoking, ageing and radiation exposure — the mechanistic bridge between inhaled carcinogens and salivary gland tumour development.[10]

The diagnostic pathway preceding histopathology was standardised by the Milan System in 2018, with a second edition in 2023. Fine-needle aspiration achieves sensitivity of approximately 85% and specificity above 96% in parotid masses,[11] and frozen section outperforms it substantially, proving actionable in 98% and accurate in 98% of 626 patients against 80% and 92.5% for aspiration.[12] The Milan System now attaches explicit malignancy risks to each cytological category, with the largest Indian validation of 793 aspirates reporting a 60% risk of malignancy for atypia of undetermined significance.[13] The fifth-edition World Health Organization classification has simultaneously redrawn the taxonomy, adding entities and folding recurrent fusions into tumour definitions, which makes the classification version used an essential methodological disclosure.[14]

Against this background, the exposures carried by patients in Bali are distinctive and uncharacterised. Daily household incense burning is routine in Balinese Hindu practice, and a population-based case–control study of 2,533 nasopharyngeal carcinoma cases found daily incense burning — a routine element of

household religious observance in Bali — carried an odds ratio of 1.59 (95% CI 1.31–1.95).[15] Incense smoke is a substantial physical exposure rather than a nominal one: 67 organic compounds have been quantified in its emissions, including 17 polycyclic aromatic hydrocarbons, with particulate emission factors exceeding charcoal, wood and cigarette combustion.[16] Tobacco is separately implicated in salivary tumour development, with more than ten pack-years documented in 85.3% (95% CI 76.9–93.7) of Warthin tumour cases against 51.4% of comparators in one cohort.[17] Clinical cancer research is conducted in Bali,[18] but we identified no published study addressing salivary gland disease on the island. Indonesian salivary gland data more broadly are confined to hospital series from Java and Sumatra and to national registry summaries, none of which covers the eastern provinces. Prof. dr. I.G.N.G. Ngoerah General Hospital is the tertiary referral centre for the province and participates in national multicentre oncology research,[19] yet no parotid tumour series has been reported from the island.

This study aimed to characterise the histopathological spectrum of parotid tumours at a tertiary referral centre in Bali over five years, to describe the reported carcinogen exposure profile of those patients, and to determine which features of that spectrum diverge from published reference proportions. The histopathological component is the primary objective. The exposure component is descriptive and hypothesis-generating by design: it is reported because household incense exposure has not previously been characterised in a salivary gland cohort, and no causal inference is intended or attempted.

2. Methods

Study design

This was a retrospective, descriptive cross-sectional study conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cross-sectional studies. The study used secondary data from medical records and archived anatomical pathology reports; no intervention was applied and no patient was contacted. A completed STROBE checklist is provided as supplementary material.

Ethical exemption

The study protocol was reviewed by the Research Ethics Committee of the Faculty of Medicine, Universitas Udayana, Denpasar, Indonesia, which granted an ethical exemption (No. 0659/UN14.2.2.VII.14/LT/2026; protocol number 2026.02.1.0286, issued 13 February 2026) on the grounds that the research used archived records and materials rather than prospective intervention or identifiable human subjects. Individual informed consent was therefore not required. Patient identifiers were replaced by study codes before analysis and no identifying information appears in this report. The study was conducted in accordance with the Declaration of Helsinki.

Setting and participants

The study was conducted at the Otorhinolaryngology–Head and Neck Surgery Outpatient Clinic of Prof. dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Bali, Indonesia, the tertiary referral centre for the province. Records covering January 2020 to December 2024 were retrieved and analysed in 2026.

Total sampling of eligible records was applied: every record meeting the eligibility criteria across the five-year window was included, and no sampling fraction was used. The sampling frame was therefore the set of archived records meeting those criteria, not the full population of patients presenting with a parotid mass; the number of records screened to reach that set could not be reconstructed from the clinic register. Patients were eligible if they had a clinical diagnosis of a parotid tumour recorded in the medical record, had undergone histopathological examination of tumour tissue obtained by biopsy or at operation, had a complete and legible histopathology report available, defined as a report carrying a stated diagnosis rather than a non-diagnostic or insufficient-specimen conclusion, and presented within the study window. Patients were excluded if the medical record was incomplete or the histopathology report was unavailable, if the clinical and histopathological diagnoses were contradictory, if the specimen was damaged, non-representative or non-interpretable, or if histopathological examination had been performed at another institution and the report was not held in the hospital archive. Twenty patients met the criteria; no patient contributed more than one analysed specimen, and all twenty records were complete for every analysed variable, so no missing-data handling was required. Where the presenting mass was bilateral, histopathological sampling was performed on the clinically dominant side only, so contralateral lesions in those patients are not characterised here. Participant flow is shown in Figure 1.

Variables and definitions

The primary variable was the histopathological diagnosis, recorded verbatim from the anatomical pathology report issued by a consultant pathologist of the institution's Department of Anatomical Pathology as part of routine clinical care. Slides were not re-reviewed for this study and interobserver agreement was therefore not assessed. The edition of the World Health Organization classification applied was not recorded in the archived reports; because the study period spans publication of the fifth edition in 2022,[14] diagnoses were not recoded to a single standard and are reported as issued. Diagnoses were aggregated into benign, malignant and indeterminate categories; chronic sialadenitis was classified as benign by biological behaviour but excluded from neoplasm denominators, and atypia of undetermined significance, corresponding to category III of the Milan System,[13] was treated as indeterminate and excluded from benign-versus-malignant comparisons.

One malignant lesion was reported as papillary carcinoma without further subtyping. This term does not designate a primary salivary gland entity in the current classification, and metastatic papillary thyroid carcinoma within an intraparotid lymph node, secretory carcinoma and papillary cystadenocarcinoma could not be excluded from the archived report. The case was retained in the malignant category for the primary analysis, and a prespecified sensitivity analysis excluding it is reported alongside the primary result.

Secondary variables were age at diagnosis, recorded in ten-year bands; sex; laterality of the presenting mass; and carcinogen exposure. Exposures were recorded in the medical record as four mutually exclusive and strictly nested combinations, which were recoded as an ordinal cumulative exposure burden score: 1, consumption of salted food; 2, consumption of salted and grilled food; 3, the preceding plus tobacco smoking; 4, the preceding plus household incense smoke exposure. Exposures were documented in routine clinical notes without a validated instrument and without dose, duration or intensity; no operational thresholds for consumption frequency, pack-year exposure or incense exposure intensity were prespecified, and the nested category structure was imposed by the collection instrument rather than observed independently. The recoding to an ordinal score was performed for this analysis and was not the form in which exposure was originally recorded. Data were abstracted by a single investigator onto a structured collection sheet designed for the study, without duplicate abstraction, and each histopathology result was reconciled against the clinical record and patient identifiers before entry.

Statistical analysis

Study size was determined by case availability across the fixed five-year window rather than by calculation, and no target was set. The resulting precision is stated here so that every subsequent estimate may be read against it: at n=20, a proportion near 0.50 is estimated with a 95% confidence interval half-width of approximately 20 percentage points. Categorical variables are summarised as counts and percentages with 95% Wilson score

confidence intervals computed without continuity correction, which retain nominal coverage at small sample sizes and near the distribution boundaries where the Wald interval fails. The sex and laterality distributions were tested against an equal distribution using exact binomial tests, with Cohen's h as the effect size. Observed proportions were compared with reference proportions drawn from the published literature using one-sample exact binomial tests, again with Cohen's h; the reference proportions and their reported ranges are given in the Table 3 footnote. Four such comparisons were prespecified and no formal multiplicity correction was applied, although both significant results clear a Bonferroni threshold of 0.0125. Because each reference proportion is itself an estimate carrying sampling error and between-study heterogeneity, treating it as a fixed constant makes these tests anticonservative; the sensitivity of each p-value across the reported reference range is therefore also given. Cohen's h benchmarks were derived for two-sample comparisons and are used here only as an approximate guide to magnitude. Because age was recorded only in ten-year bands, a band-midpoint reconstruction of the mean is reported and is explicitly identified as an approximation rather than a measured value.

Patient-level cross-classification of diagnosis against sex, age, laterality and exposure was not available from the archived records, so conventional bivariate and multivariable estimates could not be computed. In their place, a sensitivity analysis was performed over the complete space of patient-level datasets consistent with the observed marginal distributions. For each bivariate relationship, every non-negative integer contingency table compatible with the observed margins was enumerated exhaustively, and the odds ratio, Fisher exact p-value, Cramér's V and risk difference were computed for each; the attainable minimum and maximum of each measure are reported, with the Haldane–Anscombe correction of 0.5 applied to zero cells and all Fisher tests two-sided. The proportion of admissible tables reaching statistical significance is also reported; this quantity describes the enumerated space under uniform weighting and is not a posterior probability that an association exists, since admissible tables are not equally probable a priori. For the ordinal exposure variable the Cochran–Armitage trend statistic was computed across all admissible tables. At the multivariable level, Firth-penalised logistic regression of malignancy on sex, age group and exposure burden was fitted to 25,000 admissible datasets generated by independent label permutation, which preserves every marginal distribution exactly but also imposes mutual independence, so the resulting coefficient distribution is a null reference distribution rather than a distribution over plausible truths; the attainable coefficient bounds were obtained separately by hill-climbing and are the assumption-free quantity. Firth penalisation was used because complete separation is near-certain at this sample size, and its shrinkage combined with small-sample standard errors makes the procedure conservative. The approach is assumption-free with respect to the joint distribution, conditional on the marginal counts being accurately recorded and the variables measured without error: whatever the true unobserved joint distribution may be, it lies within the enumerated space, so any conclusion holding across the entire attainable range holds for the real data.

Statistical significance was set at α=0.05, two-tailed, and all p-values are reported exactly to three decimal places. Analyses were performed in Python 3.13 using NumPy, SciPy 1.18.1 and statsmodels 0.15.0. The permutation procedure used a fixed random seed and the hill-climbing search used ten restarts of five hundred steps per coefficient bound; the analysis code is available from the corresponding author and is provided as supplementary material.

3. Results

Participant characteristics

Twenty patients met the eligibility criteria across the five-year study window, distributed as three, two, five, six and four cases from 2020 to 2024 respectively; participant flow is detailed in Figure 1. Records were complete for every analysed variable in all twenty patients. Demographic, clinical and exposure characteristics are presented in Table 1. Men accounted for 14 of 20 patients (70.0%, 95% CI 48.1–85.5), giving a male-to-female ratio of 2.33:1; this excess did not reach statistical significance against an equal distribution (exact binomial p=0.115, Cohen's h=0.412), as shown in Figure 3B. Patients were concentrated in later adulthood: 18 of 20 (90.0%, 95% CI 69.9–97.2) fell within the 41 to 70 year bands, with the 61 to 70 year band the most frequent at 7 of 20 (35.0%, 95% CI 18.1–56.7), and only one patient each in the youngest and oldest bands (5.0%, 95% CI 0.9–23.6), as shown in Figure 3A. Age was recorded only in ten-year bands, inherited from the source records; reconstruction from band midpoints, which assumes a uniform distribution within each band, gives an approximate mean of 55.0±12.3 years. The observed range spans the 21–30 to 71–80 bands.

Clinical presentation

All 20 patients (100.0%, 95% CI 83.9–100.0) presented with a parotid or cheek mass, and no other presenting complaint was documented in the records, although absence of documentation cannot be equated with absence of symptoms in a retrospective series. Unilateral disease was more frequent, at 13 of 20 (65.0%, 95% CI 43.3–81.9) against 7 of 20 bilateral (35.0%, 95% CI 18.1–56.7), but the difference did not reach significance (exact binomial p=0.263).

Carcinogen exposure profile

The exposure profile is presented in Table 1 and Figure 4. Every patient (20/20, 100.0%, 95% CI 83.9–100.0) reported dietary exposure to salted or grilled food. Tobacco smoking was recorded in 14 patients (70.0%, 95% CI 48.1–85.5) and household incense smoke exposure in 11 (55.0%, 95% CI 34.2–74.2). The most frequent single pattern was the maximal exposure burden score of 4, combining salted and grilled food, tobacco smoking and incense smoke, recorded in 11 patients (55.0%, 95% CI 34.2–74.2); burden scores of 1, 2 and 3 were recorded in 2 (10.0%), 4 (20.0%) and 3 patients (15.0%) respectively, as shown in Figure 4A. The mean exposure burden score was 3.15±1.09 with a median of 4 (IQR 2–4). Eighteen patients (90.0%, 95% CI 69.9–97.2) carried two or more concurrent exposure classes, as shown in Figure 4B.

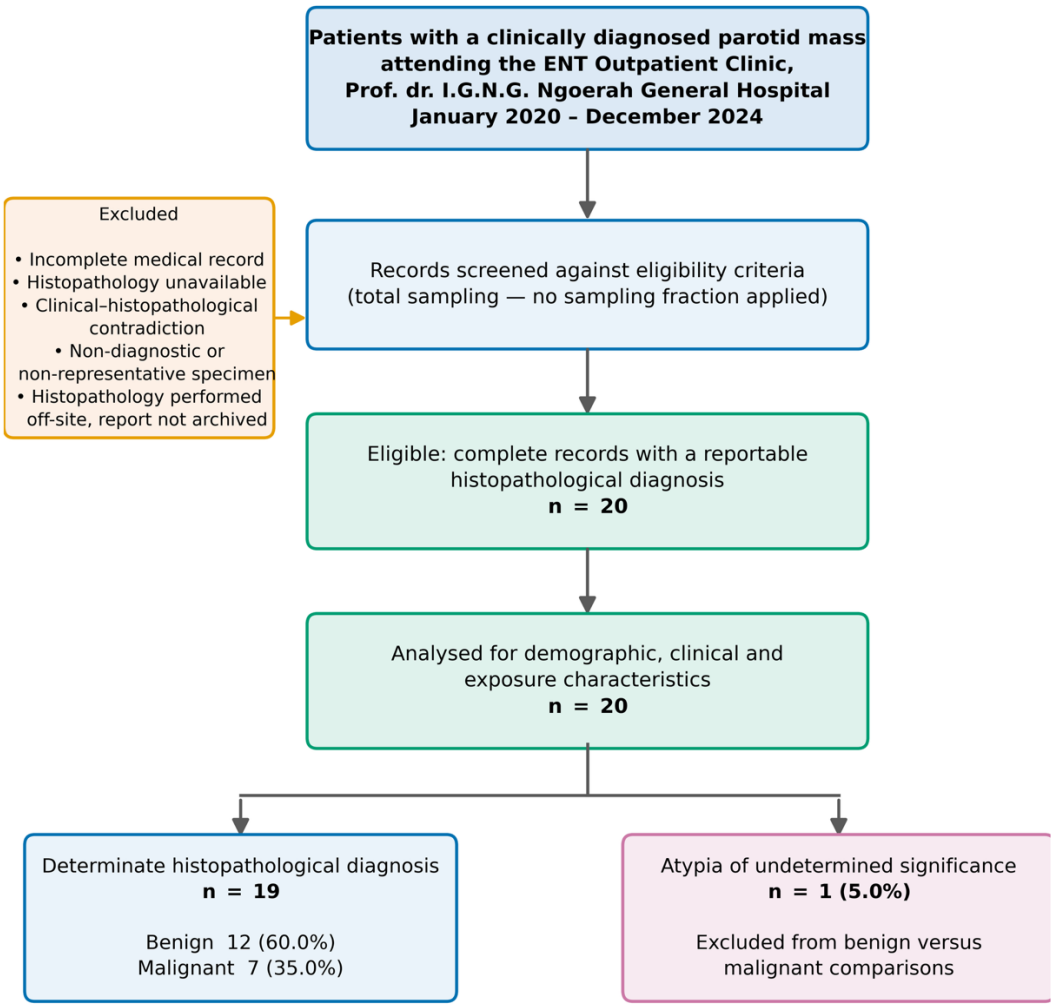

Figure 1. *Participant flow through the study, reported in accordance with STROBE. Numbers analysed are given at each stage. The denominator for the screening step was not retrievable from the clinic register and is shown as a structural stage without a count, so the eligibility fraction cannot be quantified.*

Table 1. *Demographic, clinical and cumulative carcinogen exposure characteristics of patients with a parotid mass, Prof. dr. I.G.N.G. Ngoerah General Hospital, January 2020 – December 2024 (n = 20).*

Characteristic	Category	n	% [95% CI]
Age group (years)	21–30	1	5.0 [0.9–23.6]
	31–40	1	5.0 [0.9–23.6]
	41–50	5	25.0 [11.2–46.9]
	51–60	5	25.0 [11.2–46.9]
	61–70	7	35.0 [18.1–56.7]
	71–80	1	5.0 [0.9–23.6]
Sex	Male	14	70.0 [48.1–85.5]
	Female	6	30.0 [14.5–51.9]
Presenting sign	Parotid or cheek mass	20	100.0 [83.9–100.0]
Laterality	Unilateral	13	65.0 [43.3–81.9]
	Bilateral	7	35.0 [18.1–56.7]
Cumulative carcinogen exposure	Salted food only (burden score 1)	2	10.0 [2.8–30.1]

Characteristic	Category	n	% [95% CI]
	Salted and grilled food (burden score 2)	4	20.0 [8.1–41.6]
	Salted and grilled food, tobacco smoking (burden score 3)	3	15.0 [5.2–36.0]
	Salted and grilled food, tobacco smoking, household incense smoke (burden score 4)	11	55.0 [34.2–74.2]
Individual exposure class	Any dietary exposure (salted and/or grilled food)	20	100.0 [83.9–100.0]
	Tobacco smoking	14	70.0 [48.1–85.5]
	Household incense smoke	11	55.0 [34.2–74.2]
	Two or more concurrent exposure classes	18	90.0 [69.9–97.2]

CI, confidence interval. Percentages are of the full series (n = 20). The four cumulative exposure burden categories are mutually exclusive and strictly nested; the individual exposure classes are NOT mutually exclusive and therefore sum to more than 100%. Age was recorded in ten-year bands only.

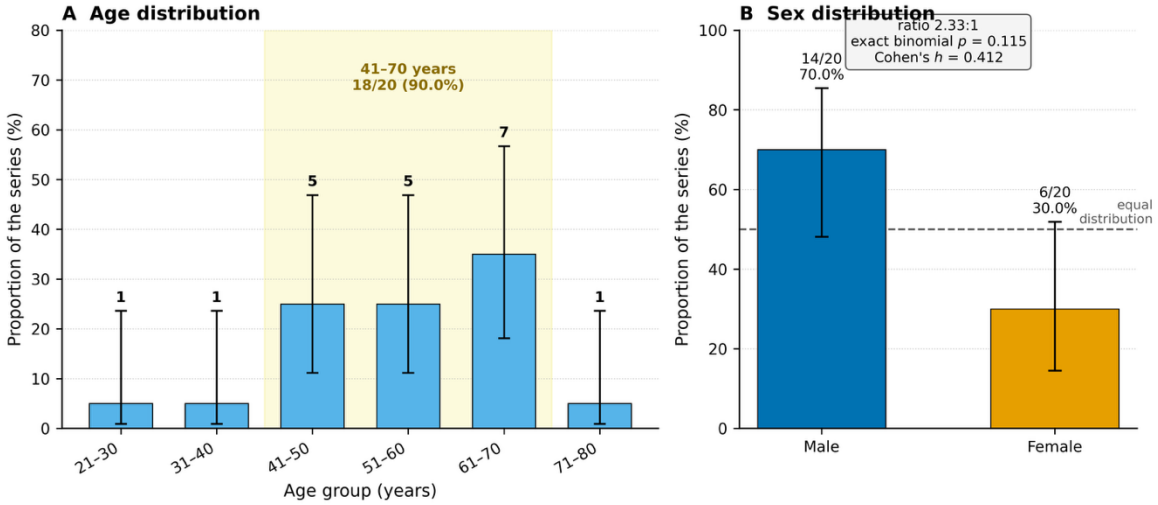

Figure 3. *Demographic distribution. (A) Age group distribution, with the 41–70 year band shaded. (B) Sex distribution against an equal-distribution reference, with the exact binomial test and Cohen's h.*

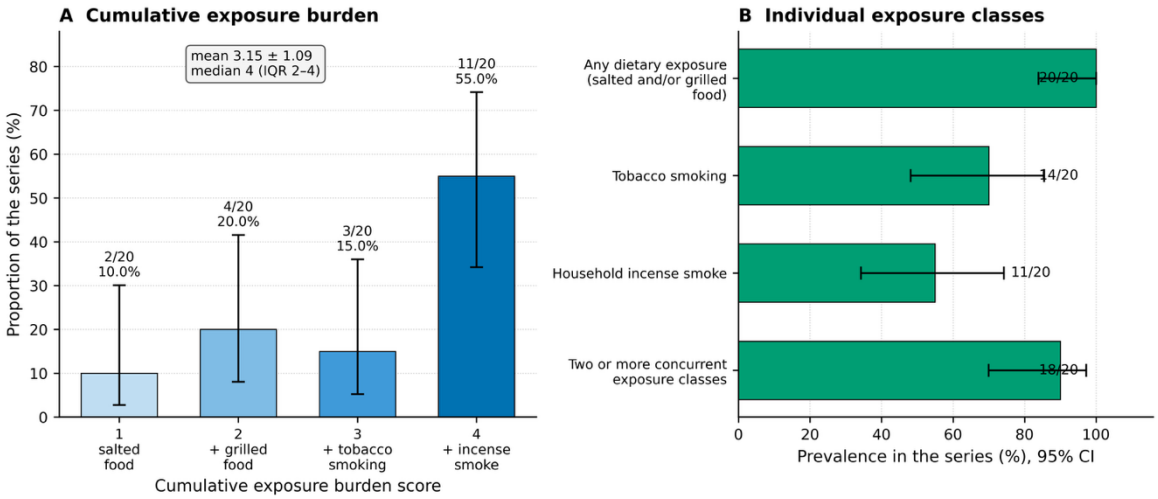

Figure 4. *Carcinogen exposure profile. (A) Cumulative exposure burden score. (B) Prevalence of each individual exposure class, with 95% Wilson score confidence intervals.*

Histopathological distribution

Histopathological diagnoses are presented in Table 2 and Figure 2. Pleomorphic adenoma was the commonest single diagnosis, accounting for 10 of 20 lesions (50.0%, 95% CI 29.9–70.1). High-grade, poorly differentiated mucoepidermoid carcinoma was the second commonest at 6 of 20 (30.0%, 95% CI 14.5–51.9). Papillary carcinoma, schwannoma with cystic degeneration, chronic sialadenitis and atypia of undetermined significance each accounted for one case (5.0%, 95% CI 0.9–23.6).

Aggregated by biological behaviour, benign lesions predominated at 12 of 20 (60.0%, 95% CI 38.7–78.1), comprising 10 pleomorphic adenomas, one schwannoma and one case of chronic sialadenitis. Malignant tumours accounted for 7 of 20 (35.0%, 95% CI 18.1–56.7) and the single indeterminate lesion for 5.0% (95% CI 0.9–23.6). No Warthin tumour, adenoid cystic

carcinoma, acinic cell carcinoma, secretory carcinoma, salivary duct carcinoma or carcinoma ex pleomorphic adenoma was identified.

Disaggregating by biological category clarifies two denominators used throughout. Of the 18 neoplastic lesions — that is, excluding the single non-neoplastic case of chronic sialadenitis and retaining the indeterminate lesion — 11 were benign (61.1%, 95% CI 38.6–79.7) and 7 malignant (38.9%, 95% CI 20.3–61.4). Among the 12 benign lesions, 10 were epithelial (pleomorphic adenoma) and 2 were non-epithelial or non-neoplastic (schwannoma with cystic degeneration, chronic sialadenitis). Among the 7 malignant lesions, 6 were of a single histological type and grade. Mesenchymal and inflammatory lesions presenting clinically as parotid tumours therefore accounted for 2 of 20 patients (10.0%, 95% CI 2.8–30.1), and lesions that could not be assigned to a definite behavioural category accounted for a further 1 of 20 (5.0%, 95% CI 0.9–23.6).

Table 2. *Histopathological diagnoses and aggregated biological behaviour (n = 20).*

Histopathological diagnosis	Behaviour	n	% [95% CI]
Pleomorphic adenoma	Benign, neoplastic	10	50.0 [29.9–70.1]
Mucoepidermoid carcinoma, high grade / poorly differentiated	Malignant	6	30.0 [14.5–51.9]
Papillary carcinoma	Malignant	1	5.0 [0.9–23.6]
Schwannoma with cystic degeneration	Benign, neoplastic	1	5.0 [0.9–23.6]
Chronic sialadenitis	Benign, non-neoplastic	1	5.0 [0.9–23.6]
Atypia of undetermined significance	Indeterminate	1	5.0 [0.9–23.6]
Aggregated by behaviour			
Benign		12	60.0 [38.7–78.1]
Malignant		7	35.0 [18.1–56.7]
Indeterminate		1	5.0 [0.9–23.6]

Percentages are of the full series (n = 20). Chronic sialadenitis is non-neoplastic and is classified as benign by behaviour but excluded from neoplasm denominators elsewhere. Atypia of undetermined significance corresponds to category III of the Milan System for Reporting Salivary Gland Cytopathology. The lesion reported as papillary carcinoma could not be assigned to a primary salivary entity in the current classification; see Methods 2.4 and the sensitivity analysis in Table 3.

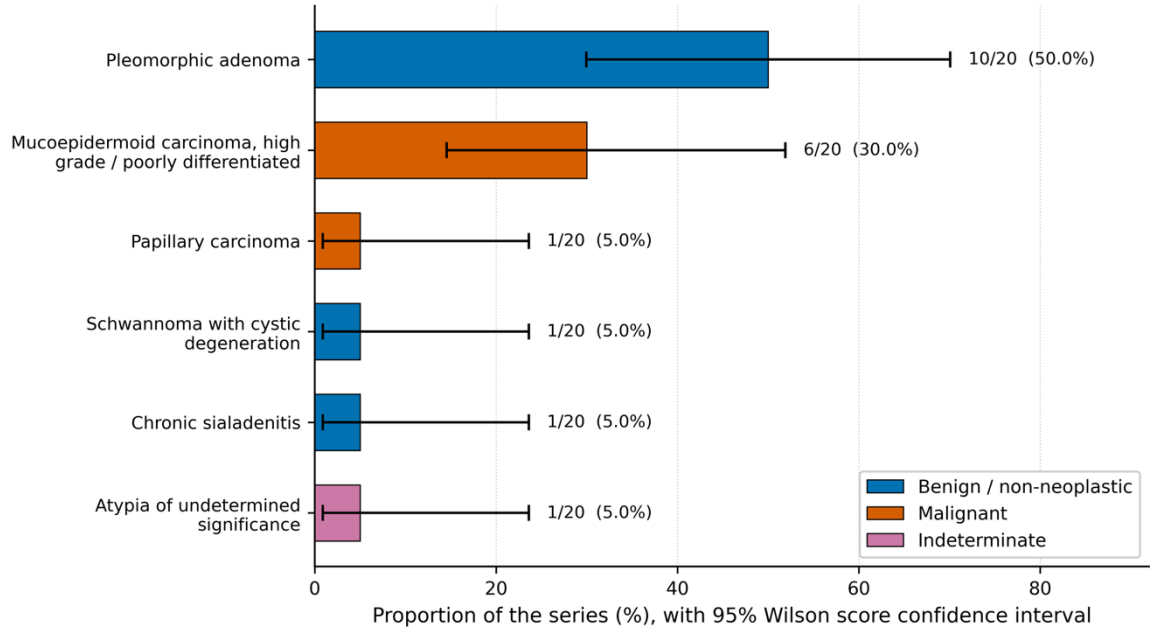

Figure 2. *Distribution of histopathological diagnoses with 95% Wilson score confidence intervals (n = 20). Interval widths of 20 to 40 percentage points reflect the sample size and are shown for every estimate.*

Comparison with published reference proportions

One-sample exact binomial comparisons against published reference proportions are presented in Table 3 and Figure 5. Two proportions diverged significantly from the literature. High-grade mucoepidermoid carcinoma accounted for 6 of 7 malignancies (85.7%, 95% CI 48.7–97.4) against a reference proportion of approximately 30% for mucoepidermoid carcinoma among salivary malignancies (p=0.004, Cohen's h=+1.21, a large effect). No Warthin tumour was identified among the 18 neoplastic lesions (0.0%, 95% CI 0.0–17.6) against a reference proportion of approximately 30% (p=0.003, h=−1.16).

Two further proportions were concordant with the literature. The overall malignant proportion of 7 of 19 determinate diagnoses (36.8%, 95% CI 19.1–59.0) was higher than the conventional 20% but did not reach significance (p=0.082, h=+0.38). Pleomorphic adenoma accounted for 10/18 neoplasms (55.6%, 95% CI 33.7–75.4), fully consistent with the established 40 to 60% range (p=0.815, h=+0.11). Both significant results clear a Bonferroni threshold of 0.0125 for the four prespecified comparisons, and both remain significant across the reported ranges of their reference proportions. In the prespecified sensitivity analysis excluding the unclassifiable papillary carcinoma case, mucoepidermoid carcinoma accounted for 6/6 malignancies (100.0%, 95% CI 61.0–100.0; p=0.001, h=+1.98) and the malignant proportion fell to 6/18 determinate diagnoses (33.3%, 95% CI 16.3–56.3; p=0.232), so the principal finding is strengthened rather than weakened by that exclusion.

Table 3. Observed proportions compared with reference proportions from the published literature, one-sample exact binomial tests.

Comparison	Observed n/N	Observed % [95% CI]	Reference % [reported range]	p	Cohen's h
Malignant tumours	7/19	36.8 [19.1–59.0]	20 [15–25]	0.082	+0.38
Pleomorphic adenoma among neoplasms	10/18	55.6 [33.7–75.4]	50 [40–60]	0.815	+0.11
Mucoepidermoid carcinoma among malignancies	6/7	85.7 [48.7–97.4]	30 [25–35]	0.004	+1.21
Warthin tumour among neoplasms	0/18	0.0 [0.0–17.6]	30 [20–30]	0.003	-1.16
Sensitivity analysis — unclassifiable papillary carcinoma case excluded					
Mucoepidermoid carcinoma among malignancies	6/6	100.0 [61.0–100.0]	30 [25–35]	0.001	+1.98
Malignant among determinate diagnoses	6/18	33.3 [16.3–56.3]	20 [15–25]	0.232	+0.30

Tests are one-sample exact binomial, two-sided. Reference proportions and their reported ranges are drawn from the cited literature. Each reference is itself an estimate rather than a known constant, so these tests are anticonservative; both significant results remain significant across the full reported reference range and clear a Bonferroni threshold of 0.0125 for the four prespecified comparisons. Cohen's h benchmarks (0.2 small, 0.5 medium, 0.8 large) were derived for two-sample comparisons and are used here only as an approximate guide to magnitude. Denominators vary by comparison and are stated in the table.

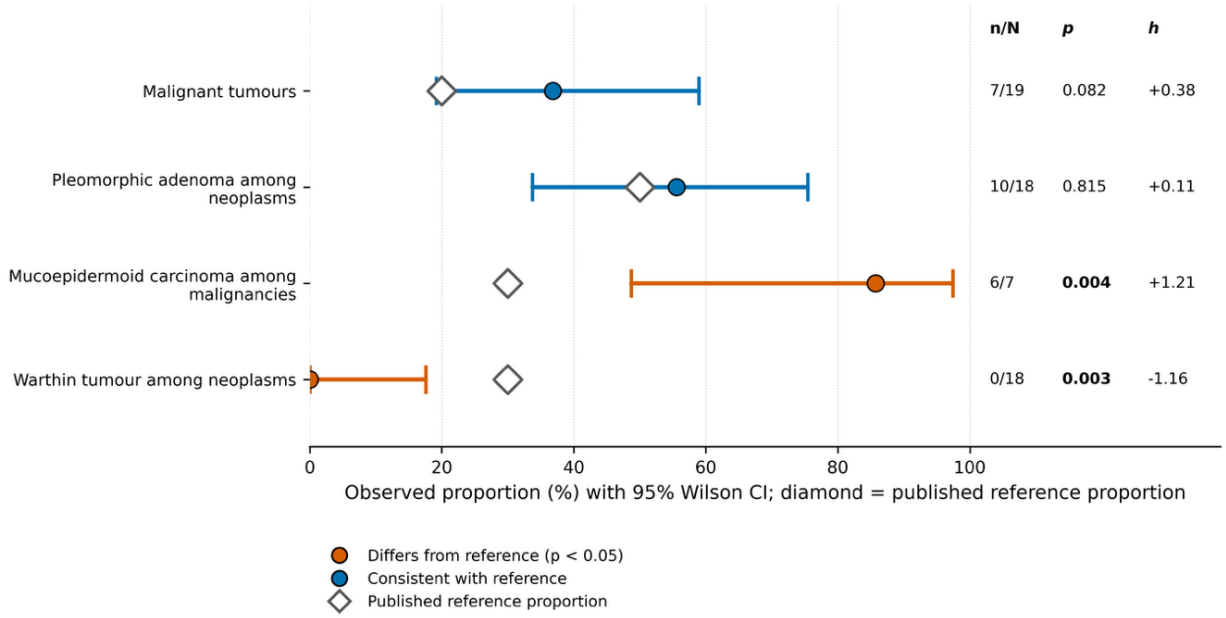

Figure 5. *Observed proportions with 95% Wilson score confidence intervals compared with reference proportions from the published literature (diamonds). One-sample exact binomial p-values and Cohen's h are shown. The reference diamonds are literature point estimates carrying their own uncertainty, which is not displayed; both significant results remain significant across the full reported range of their reference value.*

Sensitivity analysis over the admissible dataset space

Because patient-level cross-classification was unavailable, association measures were bounded by exhaustive enumeration rather than estimated; results are presented in Table 4 and Figure 6. Across the 16 contingency tables compatible with the observed margins, the odds ratio for malignancy associated with the maximal exposure burden ranged from 0.01 to 40.71, with Fisher exact p-values spanning 0.000 to 1.000 and 6 of 16 admissible tables (37.5%) reaching p<0.05. Equivalent ranges were obtained for tobacco smoking (odds ratio 0.01 to 15.00), male sex (0.01 to 15.00), age above 60 years (0.00 to 28.33) and unilateral presentation (0.00 to 20.45). Every attainable interval spanned the null value of 1.0.

The Cochran–Armitage trend statistic across the four exposure burden levels took values from z=−3.98 to z=+2.78 across the 186 admissible tables, so a significant decreasing trend and a significant increasing trend were both attainable; 56 of 186 tables (30.1%) reached p<0.05 in one direction or the other. At the multivariable level, Firth-penalised logistic regression fitted across 25,000 admissible datasets yielded adjusted odds ratios that were unbounded in both directions for all three predictors, with median values close to 1.0 (Table 5). At least one predictor reached p<0.05 in only 1.7% of admissible datasets, below the 5% expected by chance at α=0.05; this reflects the conservatism of the procedure, in which Firth shrinkage and small-sample standard errors together reduce the rate of nominal significance, rather than any anomaly in the data.

No association between any patient characteristic and malignancy is identifiable from these data. Because the enumeration is exhaustive, this is not a statement that no association was detected but a stronger one: no arrangement of these twenty patients consistent with the observed marginal distributions could support a claim of association.

The enumeration also bounds what could be claimed under the most favourable arrangement of the data. For the maximal exposure burden, the single most extreme admissible table yields an odds ratio of 40.71 for malignancy; the single most extreme table in the opposite direction yields 0.01. Neither is more probable than the other on the evidence available, and the distance between them is the precise measure of what these marginal data leave undetermined.

Table 4. *Sensitivity analysis: attainable range of every association measure across all contingency tables consistent with the observed marginal distributions.*

Predictor of malignancy	Admissible tables	Attainable OR range	Attainable Cramér's V	Attainable risk difference (%)	Fisher exact p range	Tables with p<0.05
Maximal exposure burden (score 4) vs score 1–3	16	0.01 – 40.7	0.01 – 0.90	-87.5 to +70.0	0.000 – 1.000	6/16 (37.5%)
Tobacco smoking vs no tobacco smoking	13	0.01 – 15.0	0.04 – 0.89	-92.3 to +53.8	0.000 – 1.000	5/13 (38.5%)
Male vs female sex	13	0.01 – 15.0	0.04 – 0.89	-92.3 to +53.8	0.000 – 1.000	5/13 (38.5%)
Age >60 years vs ≤60 years	16	0.00 – 28.3	0.01 – 1.00	-100.0 to +63.6	0.000 – 1.000	7/16 (43.8%)
Unilateral vs bilateral presentation	15	0.00 – 20.5	0.05 – 1.00	-100.0 to +58.3	0.000 – 1.000	7/15 (46.7%)
Cochran–Armitage trend across exposure burden 1→4	186	z: -3.98 to +2.78	—	—	0.000 – 0.963	56/186 (30.1%)

Every non-negative integer contingency table consistent with the observed marginal distributions was enumerated exhaustively; values are exact attainable extremes, not estimates. OR, odds ratio, with the Haldane-Anscombe correction of 0.5 applied where a zero cell arises. Fisher tests are two-sided. Cramer's V for a 2x2 table is equivalent to the phi coefficient. The indeterminate case is excluded from all benign-versus-malignant comparisons. The percentage of admissible tables reaching p<0.05 describes the enumerated space under uniform weighting and is not a posterior probability that an association exists.

Table 5. *Sensitivity analysis: attainable range of adjusted odds ratios from Firth-penalised logistic regression fitted across patient-level datasets consistent with the observed marginal distributions.*

Predictor	Attainable adjusted OR range	Median adjusted OR [2.5th–97.5th percentile]	Admissible datasets with p<0.05
Male sex	0 (unbounded below) – ∞ (unbounded above)	1.01 [0.11–12.60]	0.5%
Age >60 years	0 (unbounded below) – ∞ (unbounded above)	1.04 [0.12–7.85]	0.7%
Exposure burden (per unit)	0.00 – 1376.9	1.00 [0.37–2.96]	0.5%

Firth-penalised logistic regression fitted across 25,000 admissible patient-level datasets generated by independent label permutation, which preserves every marginal distribution exactly but also imposes mutual independence. Attainable bounds were obtained separately by hill-climbing and are the assumption-free quantity; unbounded ranges reflect complete separation attainable within the admissible space. At least one predictor reached p<0.05 in only 1.7% of admissible datasets, below the 5% expected by chance, reflecting the conservatism introduced by Firth shrinkage and small-sample standard errors.

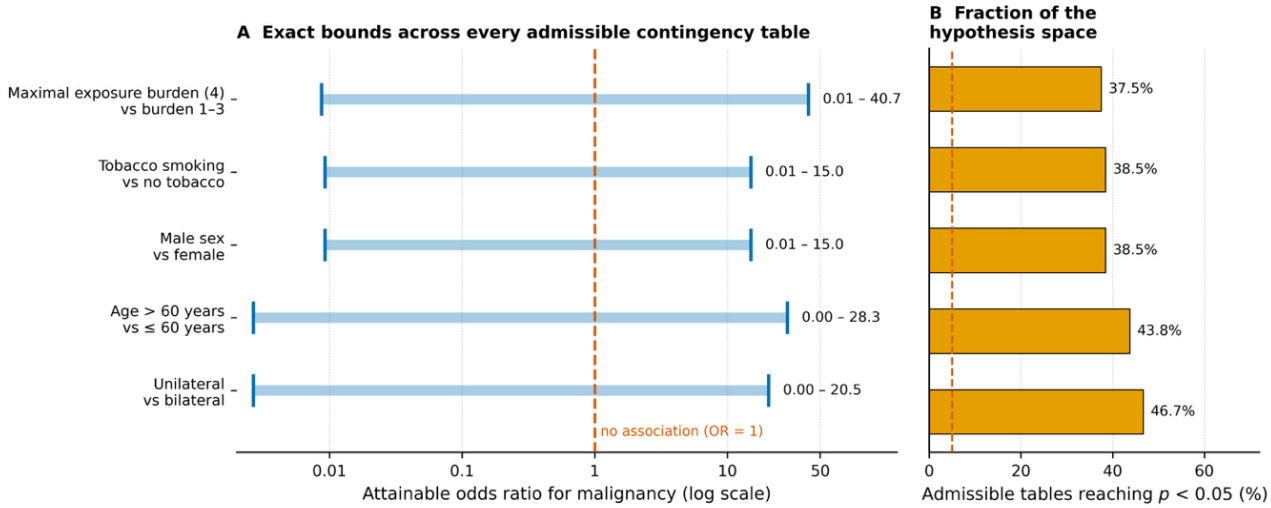

Figure 6. *Sensitivity analysis over the space of datasets consistent with the observed marginal distributions. (A) Attainable odds ratio range for malignancy across every admissible contingency table; all five intervals span the null. (B) Percentage of admissible tables in which the association reaches p < 0.05; the dashed line marks 5%, the rate expected by chance alone at α = 0.05. This percentage describes the enumerated space under uniform weighting and is not a posterior probability that an association exists.*

4. Discussion

This five-year series from the Otorhinolaryngology–Head and Neck Surgery Outpatient Clinic of Prof. dr. I.G.N.G. Ngoerah General Hospital, Denpasar, provides the first histopathological characterisation of parotid tumours reported from Bali. Benign lesions predominated at 60.0%, with pleomorphic adenoma commonest at 50.0%, in a predominantly male cohort concentrated between 41 and 70 years. Two features diverged sharply from published distributions: high-grade mucoepidermoid carcinoma comprised almost the entire malignant burden, and no Warthin tumour was identified. Every patient reported dietary carcinogen exposure and 90.0% carried two or more concurrent exposure classes, although the marginal structure of the data precludes linking exposure to diagnosis.

Benign predominance places this series within the international pattern. A five-year Romanian population study likewise found most parotid tumours benign,[1] an eight-year institutional series spanning the pandemic reported a comparable distribution,[20] and a ten-year review of 255 parotidectomies confirmed pleomorphic adenoma as the dominant neoplasm.[21] The pleomorphic adenoma proportion of 55.6% among neoplasms is indistinguishable from the

established 40 to 60% range (p=0.815), matching a Sudanese series in a comparable resource setting.[22] The malignant proportion of 36.8% is roughly double the conventional 20% but did not reach significance (p=0.082); an excess of this magnitude is the expected signature of tertiary referral, in which benign lesions are more often managed peripherally while suspicious masses are referred onward, and a Nigerian tertiary series reported a comparable pattern.[3] No Indonesian salivary gland series was retrievable for direct comparison, which is itself the gap this study addresses.

The concentration of malignancy in high-grade mucoepidermoid carcinoma is the more substantive finding: 85.7% of malignancies here against an expected 30% (p=0.004, h=+1.21). A genomic series of 454 mucoepidermoid carcinomas found the parotid the most frequently affected site, identified MAML2 rearrangement in 42%, and found CDKN2A, MET and TP53 mutations enriched in aggressive phenotypes;[23] a 128-case series detected MAML2 fusion in 84% overall, strongly associated with low grade and independently predictive of survival (p=0.048).[9] No molecular testing was performed in the present series, so the following is inference from morphology alone: the exclusively high-grade phenotype observed here would be expected to correspond to the fusion-poor, mutation-rich end of that spectrum, which carries the least favourable prognosis — a reading supported by epidemiological and prognostic analyses,[24] by evidence that site of origin modifies outcome,[25] by immunophenotypic markers of recurrence risk,[26] and by earlier series correlating grade with age, sex and site.[27] The malignant spectrum is also unusually narrow: acinic cell carcinoma, reported in 77 parotid cases across Italian centres[28] and in 75 oral and maxillofacial cases internationally,[29] was absent, as were epithelial-myoepithelial carcinoma[30] and the fusion-defined myoepithelial tumours now shown to be epigenetically distinct from PLAG1-rearranged lesions.[31] No adenoid cystic carcinoma was identified, a subtype whose occult nodal metastasis rate shapes neck management.[32] A broader five-year analysis of neoplastic and non-neoplastic salivary disorders gives the wider denominator against which such absences should be read.[33]

The complete absence of Warthin tumour is the most unexpected result and is hard to attribute to chance: zero of 18 neoplasms against an expected 30% yields p=0.003 with a large negative effect (h=−1.16). Warthin tumour is ordinarily the second commonest benign parotid neoplasm, and its principal risk factor is tobacco, documented in 85.3% (95% CI 76.9–93.7) of cases in one cohort against 51.4% of comparators;[17] tobacco smoking was recorded in 14/20 patients here, so the expected substrate was amply present. Its incidence has risen in populations with historically high male smoking prevalence, which makes total absence in this cohort more anomalous rather than less. Three explanations merit consideration, and they are distinguishable by evidence this study does not hold. Ascertainment is the likeliest: Warthin tumour is slow-growing, often asymptomatic and increasingly managed by observation or tissue-preserving surgery, so a clinic-based series restricted to biopsied or resected patients may under-capture it,[34] and a fourteen-year review of 150 parotidectomies illustrates how strongly the surgical denominator shapes this tumour's apparent frequency.[35] Distinguishing this explanation requires the institutional denominator of parotid specimens examined over the period and a record of lesions diagnosed cytologically and managed without biopsy, neither of which was retrievable here. Second, its pathogenesis involves mitochondrial dysfunction, chronic inflammation and senescence rather than a simple carcinogen dose–response,[10] so high smoking prevalence does not guarantee its appearance. Third, a genuine population difference cannot be excluded, and this is the hypothesis most worth testing; it would require a population-based series capturing all parotid masses rather than only those biopsied. Bilateral presentation — classically associated with Warthin tumour — occurred in 7/20 patients without a single corresponding diagnosis. Because bilateral cases were sampled on the dominant side only, seven contralateral lesions remain uncharacterised, and that sampling decision is itself a candidate explanation for the dissociation. Preoperative magnetic resonance imaging, now supported by validated discriminative models, would be the appropriate tool for resolving it prospectively.[36]

Mechanistically, the benign and malignant lesions here reflect two distinct molecular routes. Pleomorphic adenoma arises from PLAG1 or HMGA2 rearrangement, which drives ductal and myoepithelial proliferation and the characteristic chondromyxoid stroma but is insufficient for invasion or metastasis.[7] Progression to carcinoma ex pleomorphic adenoma requires further events: a meta-analysis of 18 studies found androgen receptor consistently expressed in the malignant form yet minimal or absent in benign pleomorphic adenoma.[37] Pleomorphic adenoma is better understood as a continuum extending to borderline and atypical forms than as a single entity,[38] and further molecular heterogeneity continues to emerge.[39] That most patients present and undergo excision while the tumour is still benign limits the opportunity for transformation, consistent with a 5-year recurrence rate of 1% in 745 surgically managed cases.[40] The proposed pathway is summarised in Figure 7, with the exposure linkage shown as hypothesised rather than demonstrated.

Four clinical implications follow. First, because malignancy here was almost entirely high-grade, the threshold for definitive tissue diagnosis should be low. Fine-needle aspiration is a reasonable first test (sensitivity 85.2%, specificity 96.2%),[11] but frozen section is materially superior for surgical planning, proving actionable in 98% against 80% and predicting the appropriate extent of surgery significantly more often (p<0.001).[12] Second, reporting should adopt the Milan System, which would have placed this series' single indeterminate case into a defined pathway rather than leaving it unresolved; the risk of malignancy for atypia of undetermined significance is 53.85% in one prospective series[41] and 50 to 60% across validation studies,[42] its reproducibility is multi-institutionally confirmed,[43] pooled analyses quantify each category's risk,[44] and its adoption has measurably changed practice.[45] Third, mesenchymal and inflammatory mimics must be anticipated, as both occurred here: intraparotid schwannoma has been misclassified cytologically through its clear-cell Antoni B areas,[46] and among 544 patients with chronic sialadenitis the parotid was involved in 78.6% of affected glands.[47] Coding to the current World Health Organization classification is necessary for comparability.[14] Fourth, surgical and adjuvant decisions should follow current randomised and pooled evidence: the periauricular incision reduced transient facial palsy (RR 0.60, 95% CI 0.39–0.93) and Frey syndrome (RR 0.27, 95% CI 0.13–0.55) across eleven trials,[48] extracapsular dissection and partial superficial parotidectomy have been compared directly for benign disease,[49] nodal management should follow grade-specific metastasis data,[50] and pooling 26,612 patients showed no survival advantage for postoperative radiochemotherapy over radiotherapy alone (HR 1.065, 95% CI 0.998–1.137).[51]

From a public health perspective the exposure profile is notable in its own right, even though it cannot be linked to diagnosis. Daily household incense burning is routine in Balinese Hindu practice and is a genuine chemical exposure: 67 organic compounds have been quantified in incense emissions, including 17 polycyclic aromatic hydrocarbons, with particulate emission factors exceeding charcoal, wood and cigarette combustion,[16] and personal monitoring identifies incense and smoking as the dominant contributors to indoor fine particulate levels.[52] The epidemiological signal is established for nasopharyngeal carcinoma, where daily incense use carried an odds ratio of 1.59 (95% CI 1.31–1.95).[15] Ionising radiation remains recognised but weakly evidenced, a meta-analysis of 415,887 participants rating the certainty for salivary gland cancer as very low.[53] That every patient reported dietary carcinogen exposure and 18/20 carried

multiple concurrent exposures is a notable population characteristic. Any recommendation for primary prevention follows from that external evidence base rather than from the present findings, which include no comparison group and no demonstrable exposure–outcome association.

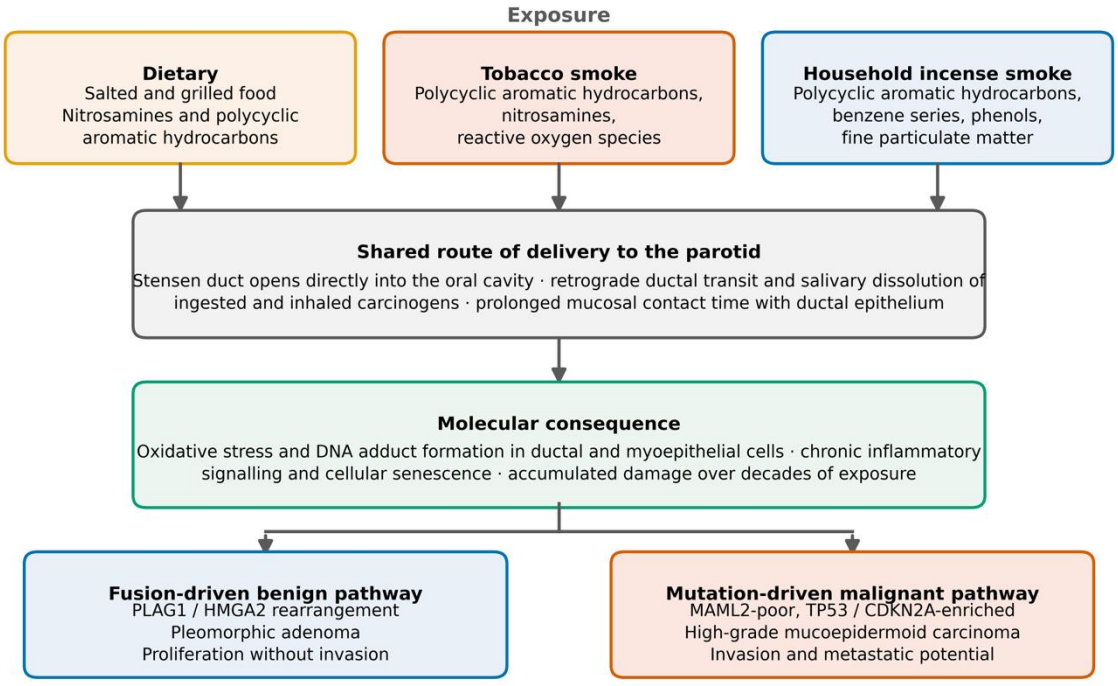

Figure 7. *Proposed pathway linking dietary and inhalational carcinogen exposure to parotid tumour development, showing the divergence between the fusion-driven benign and mutation-driven malignant routes. The schematic is drawn entirely from the published literature and carries no data from the present series, which cannot establish any exposure-to-tumour linkage.*

Three lesions in this series were not parotid carcinomas or adenomas at all, and together they account for 15.0% of the cohort. Their handling illustrates a diagnostic reality that frequency tables tend to obscure. A schwannoma with cystic degeneration presented as a parotid mass indistinguishable clinically from an epithelial neoplasm; intraparotid schwannoma is a recognised cytological trap, having been reported as a neuroendocrine tumour and as Milan category IVB on the strength of clear-cell Antoni B areas.[46] A case of chronic sialadenitis likewise presented as a tumour, which is unsurprising given that among 544 patients with chronic sialadenitis the parotid was the affected gland in 78.6% of instances.[47] The third, reported as atypia of undetermined significance, corresponds to Milan category III and carries a risk of malignancy of 53.85% in one prospective series[41] and 50 to 60% across validation studies.[42] That case was excluded from benign-versus-malignant comparisons here, but clinically it is the one patient in this cohort for whom the diagnostic question remained open at the end of the episode, and Milan-based reporting would have placed it into a defined pathway of re-aspiration or excision rather than leaving it unresolved.[54] Immunohistochemical panels, now well codified for salivary lesions, are the appropriate adjunct in exactly these cases.[55] A practical implication follows for any centre reading this series as a local benchmark: roughly one parotid mass in seven will not prove to be a salivary epithelial neoplasm, and the diagnostic pathway must accommodate that.

Placing these findings in their Indonesian and regional context is necessary and only partly possible. Indonesian head and neck cancer research is concentrated in Java and Sumatra and is dominated by oral and nasopharyngeal disease; a twenty-year registry projection of oral squamous cell carcinoma illustrates both the analytical capability available nationally and the sites that have attracted attention.[56] Multicentre Indonesian oncology cohorts demonstrate that coordinated data collection across fourteen centres is achievable,[57] and Prof. dr. I.G.N.G. Ngoerah General Hospital participates in such networks,[19] which makes the absence of salivary gland data a matter of attention rather than capacity. We identified no Indonesian salivary gland series suitable for direct numerical comparison, so the benchmarks used here are necessarily international. That is a limitation of the evidence base rather than of this study, and it is the gap the present work begins to close. The regional case for attention is quantified: Southeast Asian registry data identify elevated salivary gland cancer incidence in Indonesia specifically, alongside a regional head and neck mortality rate nearly double the global figure.[2] A fifty-year institutional cohort of salivary gland carcinoma demonstrates what longitudinal follow-up can establish about subtype-specific prognosis,[58] and analyses of locoregional metastatic behaviour across parotid malignancies of varying grade show how grade-stratified nodal data inform surgical planning.[59] Neither type of analysis is currently possible from Indonesian data, and both become possible only once descriptive baselines of the kind reported here exist across several centres.

Four specific studies follow from these findings, and naming their designs is more useful than a general call for further research. First, a multicentre Indonesian registry of salivary gland tumours, pooling consecutive cases from the referral hospitals of several provinces, would establish whether the mucoepidermoid preponderance reported here is a Balinese phenomenon, an Indonesian one, or an artefact of single-centre referral; the precision calculation above indicates that approximately 97 cases would be required to estimate a proportion to within ten percentage points, which is achievable across four or five centres over five years. Second, a population-based series capturing all parotid masses presenting to a defined catchment, rather than only those biopsied, is the only design that can resolve whether the absence of Warthin tumour reflects ascertainment or a genuine population difference; this requires

linkage between outpatient, imaging and pathology records rather than pathology archives alone. Third, an analytic case–control study with patient-level exposure recording is needed before any statement about carcinogen exposure and tumour type can be made. Its comparison group should be patients presenting to the same clinic with non-neoplastic head and neck complaints, and its exposure instrument must capture what the present data lack: frequency and duration of salted and grilled food consumption, pack-year tobacco exposure, and hours of daily household incense exposure. Fourth, molecular characterisation of the mucoepidermoid carcinomas in this and comparable Indonesian series would test the inference drawn here from morphology alone. MAML2 fusion status is the single most informative assay,[9] HER2 positivity varies by histological subtype in ways that carry therapeutic implications,[60] and the continuing discovery of novel fusions in salivary neoplasms indicates that the taxonomy is not yet settled.[61] Where deep lobe involvement is present, contemporary evidence on selective deep lobe parotidectomy should inform the surgical approach.[62]

This study has several strengths. Total sampling across a complete five-year window at the provincial tertiary referral centre eliminates investigator selection within the eligible pool, and every diagnosis rests on histopathological examination, the reference standard for salivary gland disease. All proportions carry 95% Wilson score confidence intervals, and the two principal findings are tested formally against published reference proportions with effect sizes rather than asserted narratively. Exposure has been recoded into an analysable ordinal burden score. Finally, the limits of what these data can support were quantified rather than assumed, by bounding every association measure across the complete space of datasets consistent with the observed margins, and the principal finding was subjected to a prespecified sensitivity analysis for the one unclassifiable diagnosis.

The limitations are substantial. Twenty patients over five years yields confidence intervals spanning roughly 40 percentage points around a 50% estimate; ±10 percentage point precision would require approximately 97 patients. Patient-level cross-classification of diagnosis against sex, age, laterality and exposure was not retrievable, so no association with malignancy could be estimated; the enumeration analysis shows this to be structural rather than a matter of analytic choice, since attainable odds ratios span the null in every case. Exposure was recorded from clinical notes without a validated instrument or any measure of dose, duration or intensity, and is subject to recall and documentation bias; without a comparison group these prevalences cannot be read as risk. Age was recorded only in ten-year bands, precluding a measured mean. The denominator of all parotid masses seen in the clinic was not retrievable, so the eligibility fraction and magnitude of selection cannot be quantified, and as a single-centre tertiary series the malignant proportion is likely inflated. Slides were not re-reviewed and interobserver agreement was not assessed, which matters particularly for mucoepidermoid carcinoma grading, the judgement underlying the principal finding; nor was the classification edition recorded, and the study period spans the 2022 fifth-edition transition. Two of the five study years fall within the period of curtailed outpatient and elective surgical activity associated with the COVID-19 pandemic, which would be expected to defer indolent and asymptomatic lesions preferentially while suspicious masses continued to be referred; this is a competing explanation for both the elevated malignant proportion and the absence of Warthin tumour, and it cannot be excluded. Finally, no follow-up, staging, treatment or outcome data were available, so nothing can be said about prognosis.

5. Conclusion

Parotid tumours at this tertiary referral centre in Bali were predominantly benign (60.0%, 95% CI 38.7–78.1), with pleomorphic adenoma the commonest diagnosis (50.0%), occurring mainly in men aged 41 to 70 years. Two features distinguish this series from published distributions: high-grade mucoepidermoid carcinoma comprised 85.7% of malignancies against an expected 30% (p=0.004, h=+1.21), and no Warthin tumour was identified against an expected 30% (p=0.003, h=−1.16) despite tobacco exposure in 70.0% of patients. Because malignancy in this series was almost entirely high-grade, the consequence of diagnostic delay is greater than the malignancy rate alone would imply, and clinicians should adopt Milan System reporting with frozen section for surgical planning. The universal dietary and frequent inhalational exposure documented here is a notable population characteristic, but an exhaustive bounds analysis established that it cannot be linked to tumour type from these data. An analytic case–control study with patient-level exposure recording, and a population-based series capturing all parotid masses rather than only those biopsied, are the necessary next steps — particularly to test whether the absence of Warthin tumour reflects ascertainment or a genuine population difference.

Ethics approval and consent to participate: The study protocol was reviewed by the Research Ethics Committee of the Faculty of Medicine, Universitas Udayana, Denpasar, Indonesia, which granted an ethical exemption (No. 0659/UN14.2.2.VII.14/LT/2026; protocol number 2026.02.1.0286). Individual informed consent was not required because the study analysed archived medical records and histopathology reports. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication: Not applicable. No individually identifiable patient data, images or clinical details appear in this manuscript.

Availability of data and materials: The aggregated data supporting the findings of this study are presented within the article. The underlying medical records are held by Prof. dr. I.G.N.G. Ngoerah General Hospital and are not publicly available because of patient confidentiality obligations; the anonymised analysis dataset is available from the corresponding author on reasonable request and with the permission of the institution.

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

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