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Risk stratification of fine-needle aspiration cytology of parotid neoplasms based on the Milan system—Experience from a tertiary center in Asia

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Abstract

Background: The recently described Milan system provides a unified way of categorizing salivary gland fine-needle aspiration (FNA) cytology. We aim to use this system to stratify risk of malignancy in parotid FNAs.

Methods: In this retrospective case series, 376 FNAs were preoperatively performed for 573 parotidectomies over 14 years.

Results: Risk of malignancy on FNA is as follows: nondiagnostic 14.5%, non-neoplastic 26.7%, atypia of undetermined significance 29.3%, benign neoplasm 2.7%, neoplasm of uncertain malignant potential 19.1%, suspicious for malignancy 87.5%, and malignant 100%. The specific diagnoses of pleomorphic adenoma and Warthin tumor on FNA have high positive predictive value of 97.5% and 96.6%, respectively. Multivariate regression associates smaller size of lesion with a nondiagnostic or indeterminate result. Seniority of operator is associated with a lower likelihood of a nondiagnostic result.

Conclusions: This large Asian series validates the Milan system as a valuable tool in stratifying malignancy risk of parotid FNAs.

KEYWORDS

cytology, fine-needle aspiration, parotid gland neoplasms, salivary gland neoplasms

1 | INTRODUCTION

Salivary gland neoplasms make up 6% to 8% of head and neck neoplasms.[1] Eighty-five percent of these originate in the parotid gland, and the majority of these tumors are benign.[2,3]

Performing a preoperative fine-needle aspiration (FNA) allows the surgeon to avoid unnecessary resection of inflammatory lesions and hematological malignancies. It allows better risk-benefit assessment in patients who have benign tumors and are poor surgical candidates. It enables better preoperative counseling and surgical planning for malignant lesions.[4,5] This includes planning the extent of resection, the likelihood of neck dissection, and management of the facial nerve. Other sampling methods are less ideal. An incisional biopsy risks tumor spillage, facial nerve injury, and fistula formation,[6] whereas a core biopsy risks tumor seeding along the needle tract.[7]

There have been a multitude of studies examining the accuracy of preoperative FNA on parotid neoplasms, including large meta-analyses pooling data from these studies.[8,9] However, these studies are troubled by the lack of a uniform system for reporting of cytology findings. This makes for difficulties in the application of data and in interpreting sensitivity and specificity figures. The creation of a guideline on the utility of FNA was hindered by variability

in individual study results and the need to improve on quality of reporting.[9]

A standardized way of categorizing salivary gland FNAs has been suggested independently before.[10,11] Recently, a group of international pathologists have collaborated to propose a uniform system of reporting known as the Milan system for reporting salivary gland cytopathology.[12,13] This parallels the well-established Bethesda system[14] for reporting of thyroid FNAs in creating categorical tiers that take into account the uncertainties pathologists face in calling an FNA sample as malignant or benign.

The primary aim of this study is to generate normative data on malignancy risk in parotid FNAs from our large Asian series. In doing so, we hope to validate the value of the Milan system as a tool in stratifying malignancy risk. Our secondary aims are to analyze the factors affecting FNA result, explore the value of a repeat FNA, and report demographics describing the incidence and range of parotid neoplasms at our tertiary center.

2 | MATERIALS AND METHODS

Ethical approval was sought from the Domain Specific Review Board of the Office of Human Research Protection Programme of the National Healthcare Group, Singapore.

Retrospective review of electronic case notes of all parotid surgeries (any surgery performed in our department with "parotid" included in its description) performed between January 2004 and December 2017. Only partial, superficial, deep, or total parotidectomies were included, performed for lesions of parotid origin. Inflammatory lesions that preoperatively could not be discerned apart from neoplasms were also included.

Parotidectomies performed for lesions that were deemed preoperatively to be of nonparotid origin were excluded. Patients who had an incision and drainage or an incisional biopsy of the parotid gland were excluded. Patients were also excluded if critical data regarding operative findings and histology were not available electronically.

The need for preoperative FNA was decided by the surgeon based on clinical grounds or imaging. FNA was performed as previously described,[11] either by the surgeon by physically palpating the lesion or by a radiologist with US guidance. A 25-gauge needle was used to obtain samples that were immediately processed by a cytology technician. If a sample was of insufficient quality or quantity, this was documented. The surgeon then had a choice as to whether the sample was discarded or sent for reporting. If the sample was discarded, it was included in our study as a "non-diagnostic" sample based on examination by the cytology technician.

Routine cytology reporting was performed by a pathologist. A report consisted of a cytological description and a diagnosis. Classification into categories of the Milan system was performed by a head and neck pathologist with expertise in cytopathology, based on the cytology report, and included reexamination of cytology slides. Blinding to the final histology report was enforced. The categories of the Milan system are (I) nondiagnostic, (II) non-neoplastic, (III) atypia of undetermined significance (AUS), (IVA) benign neoplasm, (IVB) salivary neoplasm of uncertain malignant potential (SUMP), (V) suspicious for malignancy (SM), and (VI) malignant.

Other relevant demographic and clinical data were gathered from electronic patient records. The Student *t* test was used to compare continuous parametric variables, whereas the Pearson chi-squared test was used to compare nominal parametric variables. Risk factors were identified through multinomial logistical regression. Goodness of fit was calculated using the Pearson chi-square method. Statistical significance was taken to be at $P < .05$. Statistical analysis was performed using SPSS 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0.; IBM Corp, Armonk, New York).

TABLE 1 Demographical data

	Malignant	Nonmalignant	*P* value
Sample	72	399	
Age at operation, mean years (SD)	55.3 (±16.2)	52.8 (±14.9)	.19[a]
ASA grade, %			.28[b]
1	10.5	16.9	
2	70.2	70.0	
3	19.3	13.1	
Sex, % men	48.6	59.4	.09[b]
Ethnicity, %			.68[b]
Chinese	81.9	83.5	
Malay	8.3	7.3	
Indian	5.6	5.0	
Others	4.2	4.3	
At first presentation,			
Duration of symptoms, mo (SD)	25.9 (±54.1)	23.2 (±42.3)	.68[a]
Previous parotid mass, %	5.6	3.3	.29[b]
Smoking history, %	13.9	27.1	**.02**[b]
Presence of pain, %	16.7	5.5	**.003**[b]
Facial weakness, %	16.7	1.5	**.000**[b]
Preoperative imaging performed, %	83.3	66.7	**.005**[b]
FNA not performed, %	22.2	19.8	.64[b]

Note: Bold indicates $p < 0.05$.

Abbreviations: ASA, American Society of Anaesthesiologists; FNA, fine-needle aspiration.

[a]Student *t* test.

[b]Chi-squared test.

3 | RESULTS

3.1 | Selection of cases

Five hundred seventy-three parotidectomies were performed. Seven were deduplicated as there was ipsilateral completion surgery for disease clearance or revision surgery for disease recurrence. Twenty-nine were excluded as they were deemed preoperatively to be malignancies of surrounding sites, and parotidectomy was performed to obtain clear margins. This included 10 external auditory canal lesions, 3 skin lesions, 3 intracranial lesions, 2 pinna lesions, 2 nasopharyngeal lesions, 1 submandibular lesion, 1 nasal dorsum lesion, 1 thyroid lesion with cervical metastases, 1 lesion within the facial canal of the temporal bone, 1 oropharyngeal lesion, and 1 jaw lesion. Sixty-six were excluded as critical data were not available electronically, all of whom had surgery performed before 2007.

TABLE 2 Histological data

Histology	Number	%
Malignant	72	15.3
Mucoepidermoid carcinoma	19	4.0
Lymphoma	9	1.9
Carcinoma ex pleomorphic adenoma	9	1.9
Acinic cell carcinoma	7	1.5
Lymphoepithelial carcinoma	6	1.3
Adenocarcinoma (not otherwise specified)	4	0.8
Adenoid cystic carcinoma	4	0.8
Squamous cell carcinoma	3	0.6
Basal cell adenocarcinoma	2	0.4
Mammary analogue secretory carcinoma	2	0.4
Poorly differentiated carcinoma	2	0.4
Salivary duct carcinoma	2	0.4
Polymorphous adenocarcinoma	1	0.2
Myoepithelial carcinoma	1	0.2
Oncocytic carcinoma	1	0.2
Nonmalignant	399	84.7
Epithelial neoplasm	351	74.5
Pleomorphic adenoma	192	40.8
Warthin tumor	133	28.2
Basal cell adenoma	14	3.0
Oncocytoma	9	1.9
Cystadenoma	3	0.6
Nonepithelial neoplasm	11	2.3
Vascular/lymphatic	5	1.1
Lipoma	4	0.8
Schwannoma	2	0.4
Non-neoplastic	37	7.9
Lymphoepithelial cyst	19	4.0
Chronic inflammation	8	1.7
Nodular oncocytic hyperplasia	7	1.5
Kimura's disease	2	0.4
Kikuchi's disease	1	0.2

3.2 | Demographic and histologic data

There was no statistically significant difference in age at operation, American Society of Anaesthesiologists (ASA) grade, sex, and ethnicity between patients who had malignant or nonmalignant parotid lesions, as seen in Table 1. There was also no statistically significant difference in the duration of symptoms before first presentation. Both were as likely to have a previous ipsilateral parotid mass that was resected. Patients with malignant lesions were less likely to have a smoking history. Patients with malignant lesions were more likely to experience facial pain. They were also more likely to experience facial weakness. Patients with malignant lesions were more likely to have undergone preoperative imaging either based on clinical suspicion of malignancy or based on FNA suspicion. Both were as likely to have undergone surgery without a preoperative FNA.

Histological data are shown in Table 2 as described by the World Health Organization classification of tumors.[15] Of the parotid lesions excised, 15.3% were malignant and 84.7% were nonmalignant. The most common malignant lesions were mucoepidermoid carcinoma, lymphoma, carcinoma ex pleomorphic adenoma, acinic cell carcinoma, and

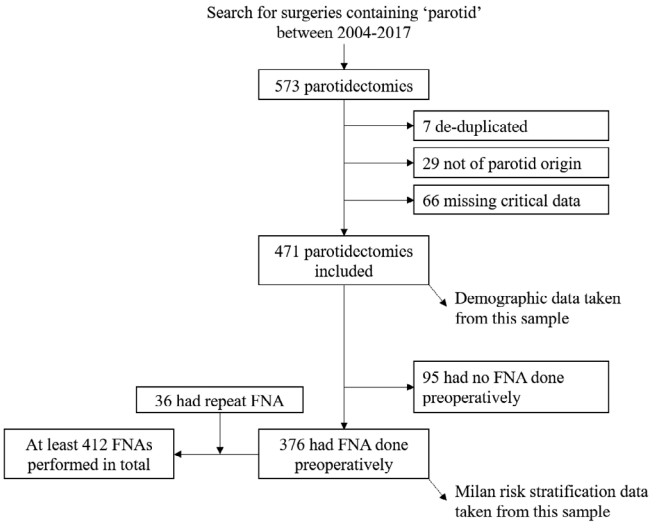

FIGURE 1 Summary of cases included and excluded. FNA, fine-needle aspiration

lymphoepithelial carcinoma. The majority of nonmalignant lesions were epithelial neoplasms, with pleomorphic adenoma and Warthin tumor being the most common. Eleven lesions (2.3%) were neoplasms of nonepithelial origin and 37 lesions (7.9%) were non-neoplastic lesions.

3.3 | Risk of malignancy on FNA

Of the 471 parotidectomies described in Figure 1, 95 did not have FNA performed preoperatively. Reasons for omission included low clinical suspicion of malignancy, availability of preoperative imaging suggestive of benignity or intraoperative plans to perform frozen section and, if necessary, further perform a total parotidectomy for disease clearance. This meant that 376 parotidectomies had preoperative FNA performed at least once. Thirty-six had preoperative FNAs performed more than once. Reasons for a repeat FNA included 27 who were either nondiagnostic or felt to be unrepresentative of the lesion, 8 in patients who opted to observe a lesion or who defaulted from follow-up, and later represented with a larger mass, and 1 who was reported as atypia but was repeated to obtain a specific diagnosis. Only the initial FNA performed was used for analysis.

Figure 2 shows the risk of malignancy based on preoperative FNA stratified according to categories of the Milan

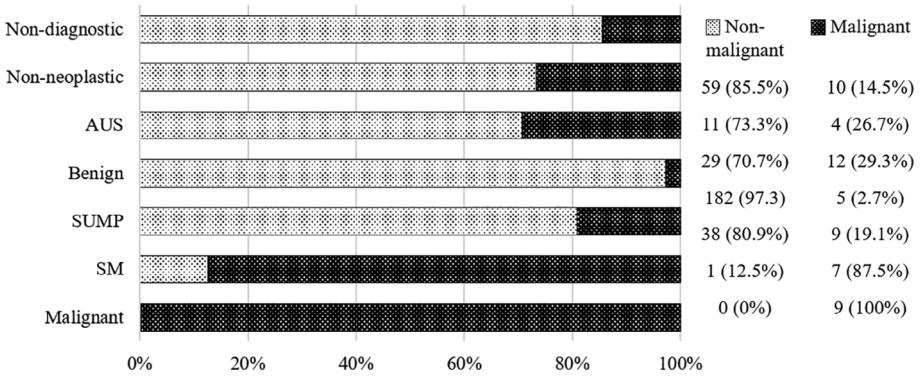

FIGURE 2 Risk of malignancy for each category of the Milan system. AUS, atypia of undetermined significance; SM, suspicious for malignancy; SUMP, salivary neoplasm of uncertain malignant potential

TABLE 3 Cases that were benign, nondiagnostic, or non-neoplastic on FNA and malignant on histology

FNA category	FNA diagnosis	Size (cm)	Histological diagnosis
Neoplastic—benign	Myoepithelial cell-rich tumor suggestive of a pleomorphic adenoma or myoepithelioma	5.5	Carcinoma ex pleomorphic adenoma
	Pleomorphic adenoma	3.5	Adenoid cystic carcinoma
	Pleomorphic adenoma	2.5	Adenoid cystic carcinoma
	Pleomorphic adenoma	3.2	Adenocarcinoma ex pleomorphic adenoma
	Warthin tumor	1.0	Acinic cell carcinoma
Non-neoplastic	Granulomatous inflammation	3.0	Lymphoepithelial carcinoma
	Inflamed cyst	1.0	Low-grade mucoepidermoid carcinoma
	Inflammatory yield	4.0	Low-grade mucoepidermoid carcinoma
	Lymphoid yield	1.7	Angioimmunoblastic T-cell lymphoma
Nondiagnostic	Blood	2.0	Carcinoma ex pleomorphic adenoma
	Blood	1.7	Small B-cell lymphoma
	Blood	1.0	Low-grade mucoepidermoid carcinoma
	Blood	2.0	Basal cell adenocarcinoma
	Cyst contents	0.8	Low-grade mucoepidermoid carcinoma
	Epithelial cells	1.8	Marginal zone lymphoma
	Insufficient yield	2.2	Intermediate-grade mucoepidermoid carcinoma
	Insufficient yield	2.0	Low grade mucoepidermoid carcinoma
	Insufficient yield	3.2	Myoepithelial carcinoma
	Salivary gland tissues	1.7	Poorly differentiated carcinoma

Abbreviation: FNA, fine-needle aspiration.

TABLE 4 Accuracy of specific diagnoses on FNA

FNA diagnosis	Accurate	Inaccurate	Details
Pleomorphic adenoma	115 (97.5%)	3 (2.5%)	One adenocarcinoma ex pleomorphic adenoma Two adenoid cystic carcinoma
Warthin tumor	56 (96.6%)	2 (3.4%)	One acinic cell carcinoma One nodular oncocytic hyperplasia

Abbreviation: FNA, fine-needle aspiration.

system. FNAs with a nondiagnostic or non-neoplastic result had a significant risk of malignancy (14.5% and 26.7%, respectively). Of the non-neoplastic lesions on FNA, 33.3% were confirmed to be inflammatory in nature on final histology. FNAs with AUS had a 29.3% risk of malignancy. Benign FNAs had a low risk of malignancy of 2.7%, SUMP had a 19.1% risk of malignancy, SM had an 87.5% risk of malignancy, and malignant FNAs had a 100% risk of malignancy.

Table 3 shows cases in benign, non-neoplastic, or nondiagnostic categories on FNA, with malignant diagnoses on histology. Nondiagnostic FNAs yielded insufficient material in either quantity or quality, blood, cyst contents, or salivary gland tissue. There is a preponderance for low-grade mucoepidermoid carcinomas, lymphomas, and carcinoma ex pleomorphic adenomas being missed on FNA.

Table 4 shows the positive predictive values (PPV) for specific diagnoses on FNA. FNAs reported as pleomorphic adenoma have a high PPV, with 97.5% also being pleomorphic adenomas on final histology. Adenocarcinoma ex pleomorphic adenoma and adenoid cystic carcinoma were mistaken as pleomorphic adenoma on FNA. FNAs reported as Warthin tumor have a PPV of 96.6%, with acinic cell carcinoma and oncocytic hyperplasia being mistaken for Warthin on FNA.

3.4 | Factors influencing FNA result

Table 5 shows the FNA categories according to mean largest diameter, imaging performed before FNA in the form of CT and/or MRI, and seniority of operator performing the FNA. Categories were grouped together for logistical regression analysis to determine if any of the factors influenced FNA result. The definitive categories of benign and malignant were grouped together, and the categories that gave an indeterminate diagnosis (AUS, SUMP, and SM) were grouped together. The nondiagnostic and non-neoplastic categories were analyzed as separate groups.

Logistical regression revealed that smaller size of the lesion was a predictive factor for obtaining either an indeterminate or nondiagnostic FNA compared to a definitive FNA on both univariate and multivariate analysis. Performing imaging before FNA did not influence FNA result. FNA performed by an attending (equivalent to consultant) was less likely to result in a nondiagnostic FNA compared to FNA performed by a junior resident (equivalent to medical officer or senior house officer) on multivariate but not univariate analysis. However, both were as likely to obtain an indeterminate FNA or non-neoplastic FNA. There was also no difference in results obtained for FNAs done by a junior resident or senior resident (equivalent to registrar). There was also no difference in results obtained for FNAs done with US guidance.

3.5 | Repeat FNA

Twenty-five FNAs that were nondiagnostic on initial attempt were repeated preoperatively with or without US guidance, as seen in Table 6. This resulted in 28% that were nondiagnostic on repeat attempt, 20% that were AUS, 24% that were SUMP, and 28% that were benign. The proportion that was nondiagnostic did not differ statistically on initial or repeat FNA (18.4% compared to 28%, $P = .23$). The majority of benign repeat FNAs were done under US guidance, whereas the majority of the rest were not. Only one lesion turned out to be malignant on final histology, with a histological diagnosis of lymphoma.

4 | DISCUSSION

Looking at the demographic data, patients with both malignant and nonmalignant parotid lesions had similar ASA grade, sex, and ethnicity distributions. They also presented to our clinic after a similar duration, suggesting that malignant lesions may also follow a seemingly indolent course in otherwise fit and well patients. A previous case series reported a similar duration of approximately 2 years before presentation, although no comparisons were made between benign and malignant lesions.[16]

Both were as likely to have had a previous ipsilateral parotid mass that was resected. All were either benign or of unknown benignity in patients who subsequently developed benign lesions, whereas 50% were malignant in patients who subsequently developed malignant lesions. This is in keeping with known recurrence of benign lesions, as well as the possibility of malignant transformation.[17]

Patients with benign lesions were more likely to have a smoking history, accounted for by the proportion of smokers who developed Warthin tumors.[18] In our study, smoking conferred an odds ratio of 8.1 in developing a Warthin tumor, even after accounting for sex and ethnicity. Patients with malignant lesions were more likely to experience facial

TABLE 5 FNA categories by size and operator

FNA category	Mean largest diameter (cm)	*P* values	Imaging done before FNA (%)	*P* values	Seniority of FNA operator						
					Junior resident (%)	Senior resident (%)	*P* values	Attending (%)	*P* values	US guided (%)	*P* values
Definitive	**3.8**		**12.2**		**42.5**	**20.9**		**32.7**		**3.9**	
Benign	3.1		11.2		41.0	21.5		33.3		4.2	
Malignant	4.5		33.3		66.7	11.1		22.2		0.0	
Indeterminate	2.5	**.002**[a]	12.5	.98[a]	**43.2**	**24.3**	.77[a]	**28.4**	.57[a]	**4.1**	.98[a]
AUS	2.6	**.003**[b]	12.2	.50[b]	44.1	20.6	.91[b]	26.5	.31[b]	8.8	.67[b]
SUMP	2.7		14.9		43.2	27.0		29.7		0.0	
SM	2.1		0.0		33.3	33.3		33.3		0.0	
Nondiagnostic	**2.6**	**.007**[a]	**21.7**	.05[a]	**48.2**	**23.2**	.97[a]	**16.1**	.06[a]	**12.5**	.08[a]
		.006[b]		.20[b]			.82[b]		**.0**[b]		.34[b]
Non-neoplastic	**2.8**	.44[a]	13.3	.90[a]	**53.3**	**20.0**	.70[a]	**20.0**	.31[a]	**6.7**	.79[a]
		.35[b]		.62[b]			.19[b]		.14[b]		.83[b]

Note: The definitive and junior resident categories were taken as reference categories for regression analysis. Bold indicates $p < 0.05$.

Abbreviations: AUS, atypia of undetermined significance; SM, suspicious for malignancy; SUMP, salivary neoplasm of uncertain malignant potential; US, ultrasound.

[a]Univariate analysis.

[b]Multivariate analysis.

TABLE 6 Result of repeat FNA that was nondiagnostic the first time

Repeat FNA result	Number	US guided	Malignant on final histology
Nondiagnostic	7 (28%)	2	0
AUS	5 (20%)	2	1
SUMP	6 (24%)	0	0
Benign	7 (28%)	5	0

Abbreviations: AUS, atypia of undetermined significance; SUMP, salivary neoplasm of uncertain malignant potential; US, ultrasound.

pain and weakness, and care should be taken in investigating a patient with unexplained facial symptoms. It is known that facial pain, paraesthesia, and weakness are associated with an increased risk of malignancy[19] and that facial weakness correlated with tumor stage.[20]

Of the parotid lesions excised, 15.3% were malignant and 84.7% were nonmalignant. Mucoepidermoid carcinoma was the most common malignant neoplasm. Pleomorphic adenoma and Warthin tumor were the most common benign neoplasms. Inflammatory lesions were also seen, with lymphoepithelial cysts being common. These findings are similar to figures reported in larger case series, considering the heterogeneity of salivary neoplasms, and their rarity.[16,21-23]

We also included parotid cysts and other inflammatory lesions that could not be excluded as neoplasms preoperatively. We excluded lesions that were clearly not of parotid origin, for instance, external ear canal squamous cell carcinomas or other malignancies arising from the surrounding skin. Our aim was to provide data of clinical relevance to the surgeon making a preoperative assessment of a lump deemed to be of parotid origin.

Although performed retrospectively, FNA data are likely to be representative of our population as the majority of parotid masses presenting to our department were counseled for excision. The long duration over which data were collected suggests that even if lesions were initially opted to be observed, any high-grade malignancies would have manifested over time. Benign lesions that have grown in size over time would also have been excised. Nondiagnostic FNAs that were not sent off to the pathologist for reporting were also documented in the patient's case notes and were included for analysis.

The non-neoplastic category stands out as an exception. Because data are derived only from patients who underwent parotid surgery, lesions that were non-neoplastic that did not undergo excision are not included. This introduces a selection bias and results in the risk of malignancy for non-neoplastic lesions being falsely inflated and hence should be interpreted with caution.

Our study has helped to provide normative data to our institution, which will equip clinicians to better counsel patients. Barring the non-neoplastic category, our risk of malignancy figures are broadly comparable to those implied by the Milan group,[13] shown in Table 7. Our figures for SM and malignant FNAs confer a higher risk of malignancy but are within the ranges cited by the Milan group and are in keeping with the high risks of malignancy implied by these categories. Our data are also comparable to recently published retrospective studies reporting risk of malignancy figures based on the Milan system.[24-26] To our understanding, this is the largest data set from an Asian center that has reported extensive data according to the Milan system.

TABLE 7 Comparison of risk of malignancy figures with the Milan group

Category	Risk of malignancy derived from our study (%)	Risk of malignancy as quoted by the Milan group (%) (range)
I. Nondiagnostic	14.5	25 (0-67)
II. Non-neoplastic	26.7	10 (0-20)
III. AUS	29.3	20 (10-35)
IVA. Neoplasm: Benign	2.7	<5 (0-13)
IVB. Neoplasm: SUMP	19.1	35 (0-100)
V. SM	87.5	60 (0-100)
VI. Malignant	100	90 (57-100)

Sixty-six cases (11.5%) were excluded as electronic data were not available. Surgery for all of these lesions was performed between 2004 and 2007, the transition period from paper to electronic records. Reporting bias may have been introduced as malignant lesions on longer term follow-up would more likely have also made the transition to electronic records. Similarly, 95 cases (20.2%) did not have a preoperative FNA performed. This proportion did not differ between malignant and nonmalignant lesions (22.2% compared to 19.8%, $P = .64$). Often, this was because the surgeon felt surgery was indicated and a preoperative FNA would not change management. This went in accompaniment with an intraoperative frozen section and plans for further resection to obtain clear margins if high-grade malignancy was seen. Biases introduced may have resulted in the risk of malignancy being overestimated, giving a more conservative estimate.

Our figures for nondiagnostic, AUS and SUMP also varied from the figures given by the Milan group. Their risk of malignancy estimates were derived from a series of studies that included three meta-analyses, the largest and most recent of which takes previously published data and reclassifies using the Milan system.[27] Out of 4514 pooled FNAs, only 100 were nondiagnostic, 64 were SUMP, and 8 were AUS, with only 1 study out of 29 using an "atypical" category. The seemingly low level of uncertainty seen when

reporting FNAs is more likely to stem from different reporting systems used by each study and a difficulty in reconciling them with the Milan system. These figures contrast with our data, which suggest that pathologists face a higher degree of uncertainty when reporting FNAs.

Overall, our study validates the Milan system as a valuable tool in stratifying malignancy risk based on a large body of data from a tertiary otorhinolaryngology center in Asia. It also provides demographic and histological data on the range of parotid lesions in our population. Our study identifies smaller size of the lesion as a factor predicting a higher likelihood of a nondiagnostic or an indeterminate FNA result and seniority of operator as a factor predicting lower likelihood of a nondiagnostic result.

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