

Clinical utility of frozen section for submandibular gland tumours in the era of Milan classification

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Dear Editor,

Salivary gland tumours are rare, with less than 10% occurring in the submandibular gland and most arising from the parotid gland.¹ Fine needle aspiration and cytology (FNAC) is commonly performed as part of initial workup for a submandibular gland mass. However, some patients will have indeterminate FNAC, i.e. non-diagnostic, atypia of unknown significance (AUS) and salivary gland neoplasm of uncertain malignant potential (SUMP) with a risk of malignancy (ROM) ranging from 15–35%, as per the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC),² which has been validated for submandibular gland tumours in the authors' previous study.³ Intraoperative frozen section (FS) serves as a second opportunity to diagnose malignancy and to evaluate for nodal spread if suspicious lymph nodes are seen intraoperatively. As per the latest National Comprehensive Cancer Network (NCCN) guidelines for salivary gland cancers,⁴ elective neck dissection can be considered for high-grade and/or T3/T4 tumours, and therapeutic neck dissection is recommended for clinically node positive cases. Hence, FS can guide the surgeon in deciding whether to proceed with neck dissection during index operation.

However, FS has its limitations including freeze artifacts, time constraints, and lack of ancillary studies during intraoperative consultation for conclusive diagnosis.⁵ Submandibular gland tumours are also morphologically diverse, which can make histopathologic diagnosis challenging.⁶ Compared to parotid tumours, submandibular gland tumours are rarer, more often malignant, and have a different histological subtype distribution.¹ Most published studies have focused on parotid tumours, since it is the most common salivary gland tumour. Few studies have evaluated how FS of submandibular gland tumours impacts intraoperative management or its diagnostic accuracy.

We retrospectively reviewed the electronic medical records of 49 patients who underwent submandibular

gland excision with pre-operative FNAC and intraoperative FS from May 2008 to December 2023 in Tan Tock Seng Hospital, Singapore, with the aim of studying (1) the diagnostic accuracy of FS in detecting malignancy and (2) its impact on intraoperative decision making, i.e. whether to proceed with neck dissection. Among the 92 patients, 49 underwent submandibular gland excision with pre-operative FNAC had intraoperative FS. Decision for FS was made by the physician based on their clinical suspicion of malignancy, influenced by various factors including history, imaging findings and pre-operative FNAC. Among those who did not undergo FS (43/92), a large proportion (86.0%) had benign disease.

The authors found that FS performs well in detecting malignancy in submandibular gland tumours, with high sensitivity and specificity (Table 1), which is corroborated by other studies with similar findings.^{7,8} FS was also found to be particularly valuable in patients with indeterminate FNAC pre-operatively. Among the 32 patients with indeterminate results on FNAC, i.e. non-diagnostic, AUS, SUMP, FS was able to definitively rule out malignancy in 18 (56.3%) patients and diagnose malignancy in 4 (12.5%) patients. If the tumour is likely to be T3 and above based on pre-operative imaging, FS can help by confirming malignancy and enabling clinicians to proceed with neck dissection. In this study's cohort, in 1 malignant case (7.1%) with indeterminate FNAC, the confirmation of malignancy on FS, combined with pre-operative imaging that indicated that the tumour stage would be at least T3, supported immediate neck dissection and helped avoid revision surgery.

Lymph nodes were sent for FS in 8 patients, 5 benign and 3 malignant, when noted to be clinically suspicious. We found that by confirming absence of nodal disease, FS helped to avoid unnecessary therapeutic neck dissection in these malignant cases. Four out of 14 malignant tumours were lymphomas (28.6%), of which FS showed either lymphoid rich

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Table 1. Sensitivity and specificity of frozen section (FS) in detecting malignancy when indeterminate FS is excluded or included.

Excluding indeterminate FS					
FS	Histology		Sensitivity, %	Specificity, %	
	Benign	Malignant			
	Malignant	0 (FP)			5 (TP)
	Benign	30 (TN)			1 (FN)
Including indeterminate FS					
FS	Histology		Sensitivity, %	Specificity, %	
	Benign	Malignant			
	Malignant	5 (FP)			13 (TP)
	Benign	30 (TN)			1 (FN)

FP: false positive; FN: false negative; FS: frozen section; TP: true positive; TN: true negative

lesion or atypical lymphoid proliferation. While the diagnosis of lymphoma is difficult to make on FS as immunostaining is required and histopathology is considered the gold standard for diagnosis of lymph node pathologies,⁹ the identification of lymphoid cells on FS helped the surgeon to decide intraoperatively not to proceed with elective neck dissection as it is not indicated for either lymphoma or benign lymphoid changes.

In cases where FNAC was classified as MSRSGC category IVa, i.e. benign neoplasm, 12/13 (92.3%) were benign on FS, 1 (7.7%) was indeterminate, and all were benign on final histology. Based on the MSRSGC, the ROM for category IVa is <3%. Given the low ROM, the added value of FS in these patients is limited, since intraoperative FS is unlikely to change management.

Due to difficulties in determining grade of malignancy, FS may have limited utility in influencing a clinician's decision to proceed with neck dissection during index operation. In this study, FS was not able to diagnose the grade of malignancy in all cases. With 39 subtypes of salivary gland pathologies described in the fifth edition of the World Health Organization Classification, salivary gland tumours have a wide range of morphological features and can pose as a diagnostic challenge to the pathologist at FS.⁶ Furthermore, immunohistochemistry staining or diagnostic molecular pathology tests, such as next-generation sequencing, may be required in challenging cases with poorly differentiated histomorphology.¹⁰ Given the technical and time constraints of FS, it is often not possible to conclude the grade of malignancy, and clinicians may have to await final histology to determine if elective

neck dissection is necessary, particularly for tumours that are T1/T2.

This study has a few limitations, namely, small sample size and retrospective study design precluding the standardisation of clinical practice. A larger scale, prospective study will be useful in drawing more conclusive evidence regarding the utility of FS in submandibular gland lesions.

In conclusion, FS demonstrates high diagnostic performance for detecting malignancy in submandibular gland tumours, particularly in patients with indeterminate preoperative FNAC. However, in terms of influencing intraoperative decision making, the utility of FS in T1/T2 tumours is limited by its inability to reliably distinguish grade of malignancy intraoperatively, and decisions regarding neck dissection should therefore await final histopathology. The authors propose a targeted approach in which FS should be considered for cases with indeterminate preoperative FNAC and high clinical or radiological suspicion of advanced, i.e. T3/T4 or metastatic disease, where confirmation of malignancy on FS can facilitate decision for neck dissection during the index operation.

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Ethics statement

This was a retrospective review of medical records where no identifiable data was collected. The study was approved by National Healthcare Group Domain Specific Review Board, Singapore (2024-3222).

Declaration

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