Accuracy of fine-needle aspiration and frozen section for the detection of squamous metastasis in cystic masses of the lateral neck

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Abstract

Cystic masses of the lateral neck are mostly benign. However, the incidence of metastatic squamous cell carcinoma (SCC) in cervical cystic masses initially diagnosed as benign is quite high in patients older than 40 years. The aim of this study was to compare the diagnostic accuracy of preoperative cytology and intraoperative frozen section (FS) in detecting malignancy in cystic masses of the neck. We reviewed 61 patients who underwent preoperative ultrasound-guided fine-needle aspiration cytology (FNAC) and neck biopsy of a cystic neck mass, and analysed the concordance between FNAC and intraoperative FS with respect to definitive histology. HPV status was also tested. Of 49 eligible cases, the accuracy of preoperative FNAC was 70.5% (weighted kappa 0.53), meaning moderate agreement between cytology and final diagnosis. Intraoperative FS consultations detected 16 cases of SCC metastasis while the remaining 33 cases were negative for SCC, showing perfect agreement with histology. Since FS results were useful in evaluating cystic neck masses, despite a moderate accuracy of cytology, we suggest intraoperative FS analysis for all cystic neck masses. This technique can allow us to switch to therapeutic neck dissection, multiple upper aerodigestive tract biopsies, tongue base mucosectomy, and bilateral tonsillectomy in the same surgical setting.

Keywords: Frozen section; Squamous cell carcinoma; Neck dissection; Lymph node metastasis; Cystic neck mass; Human papillomavirus

Introduction

Cystic masses of the lateral neck in young adults are mostly benign. However, the incidence of squamous cell carcinoma (SCC) metastasis in cervical masses ranges from 11% to 30% in patients older than 40 years.[1,2]

A confounding factor is human papillomavirus (HPV)-driven oropharyngeal SCC. This type of tumour, which arises from the deepest lymphatic tissue of Waldeyer's ring,[3,4] often remains undetectable, but tends to spread rapidly via the lymphatics, the first clinical sign being a lymph node metastasis with cystic degeneration that mimics a benign lateral neck cyst.[5]

According to the National Comprehensive Cancer Network (NCCN) guidelines,[6] ultrasound examination of the lateral neck, including fine-needle aspiration cytology (FNAC), is recommended. Nevertheless, differentiation between a benign cyst and a SCC metastasis with cystic appearance by preoperative examination alone might be difficult, even for a qualified pathologist.[7]

Today, although FNAC is a standard procedure in the diagnosis of neck masses,[8] the results may be reported as misleading, so management of a cystic mass with not-exhaustive/uncertain FNAC remains an open question. Current guidelines suggest repeating FNAC, or performing core needle biopsy (CNB) or rarely, open excisional biopsy of the mass, and waiting for definitive histology.[6] Lesions suspicious for the presence of lymph node metastasis must therefore be confirmed by histopathology, especially in adults.[9]

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Frozen section (FS) analysis performed during open biopsy in patients with neck masses is an underused practice in this field. To our knowledge few authors have evaluated discordance between FS and final diagnoses in cervical cysts, and reports range from 1.4% - 12.9%.[3,10,11]

The impact of cervical lymph node biopsy before therapeutic neck dissection has been controversial because some authors have reported increased local recurrence and worse healing due to previous neck violation. Others, however, have described complications after cervical lymph node biopsy followed by definitive neck dissection.[12]

Concerning the suspicion of malignancy in cystic lesions, the question remains whether an open biopsy resecting a whole lymph node with intraoperative FS consultation is superior to preoperative examination in terms of sensitivity and specificity, and whether this procedure is oncologically safe.[8] In the case of an intraoperative finding of SCC metastasis, the surgeon can switch to definitive treatment, which means mapping biopsies with endoscopy of the upper aerodigestive tract (UADT), tongue base mucosectomy, bilateral tonsillectomy, and comprehensive neck dissection in the same surgical setting, instead of waiting for definitive histology of the lymph node biopsy before planning a second cervical surgery in an already violated surgical field.[12] This approach requires extensive explanation to the patient and adequate informed consent.

On a background of such literature, this study aimed to report the accuracy of preoperative FNAC and intraoperative FS in the detection of metastasis from SCC in lateral neck cysts. Specifically, in a retrospective chart review, we investigated the rate of cystic lymph node metastasis in patients initially presenting with a lateral cystic mass, and the sensitivity, specificity, positive and negative predictive values, and accuracy of both FNAC for preoperative diagnosis and FS analysis for intraoperative diagnosis.

Material and methods

In this retrospective cohort study we reviewed data on 61 patients who had a cystic lateral neck lump with no evidence of primary tumour (T0) between January 2014 and March 2021 in a single tertiary centre. Exclusion criteria were infectious aetiologies, evidence of a primary tumour at clinical examination with UADT endoscopy, past head and neck oncological surgery, neoadjuvant radiotherapy, and solid aspect of the neck mass. Preoperatively, all patients had clinical examination, UADT endoscopy, and ultrasound-guided FNAC. We reserved imaging examination (CT/MR) for some selected cases that required more detailed evaluation. If malignancy was not detected preoperatively, patients underwent cervical open biopsy with intraoperative FS consultation. When FS evaluation documented SCC, UADT endoscopy for mapping biopsies, tongue base mucosectomy, bilateral tonsillectomy, and comprehensive neck dissection were performed during the same surgical session.[13] Patients were therefore routinely informed before surgery about the possibility of a neck dissection, receiving an exhaustive explanation of the programme and a double informed consent providing for both surgical options: cervical biopsy with intraoperative FS with or without therapeutic treatment on the UADT and lymph nodes. Standard techniques for FNAC and FS are reported in Supplemental Material.

We recorded data regarding patients, clinical features of the mass, FNAC results, HPV status, FS and formal histological results in total anonymity, in full compliance with ethical values and Italian privacy law (Law Decree n.196/2003). The study was approved by the University Ethics Committee (No. 96/2019).

Reliability of the FNAC and FS assessments was determined by calculating sensitivity, specificity, positive and negative predictive values (PPV), and accuracy with corresponding 95% confidence intervals (CI) according to binomial distribution. Agreement was estimated by means of Cohen's weighted kappa. Statistical analysis was performed using R Statistical Software version 4.1, 2021 (R Core Team, R Foundation for Statistical Computing).

Results

This study included 61 patients with cystic neck masses who were submitted to open neck biopsy with intraoperative FS. We excluded seven who did not provide consent for data processing and five with incomplete information. The remaining 49 included 27 men (55.1%) and 22 women (44.9%) (mean (SD) age 53 (15) years, range 38 – 78).

All patients underwent FNAC before surgery with the diagnosis being 8 SCC metastases (16.3%), 22 benign cysts (44.9%), 4 cases suspicious of malignant lymphoma (8.2%), and 15 undefined/inconclusive examinations (30.6%). Table 1 shows the performance of FNAC versus definitive histology. Overall accuracy was 70.5% (weighted kappa 0.53) meaning a moderate agreement between cytology and final diagnosis. FS consultations detected 16 cases of SCC metastasis while the remaining 33 cases were negative for metastatic squamous cells.

Table 2 shows the performance of extemporaneous biopsy for metastasis from SCC versus histology. These results were in perfect agreement with histology showing an overall accuracy of 100%. Within the undefined FNAC group, the extemporaneous evaluations detected five cases of SCC metastasis that were all confirmed by definitive histology. The remaining 10 that were negative for squamous metastasis comprised five benign cysts and five malignant lymphomas. Table 3 shows the histological diagnoses.

HPV status was determined in 40 cases: 17 were tested both on FNAC and FFPE samples, and the results were in agreement. Three samples (7.5%) had inadequate material for analysis and histology revealed malignant lymphoma, 28 were HPV-negative cases, and nine were positive for HPV. Sixteen were confirmed as SCC metastasis by definitive histology. In this HPV-positive subgroup, FNAC diagnoses were: benign cysts (n = 2), cases suspicious of SCC metastasis (n = 2), non-diagnostic cytology (n = 3), and atypical cells only (n = 2).

Table 1
Performance of fine needle aspiration cytology (FNAC) and extemporaneous biopsy versus histology.

	Histology			Total
	Benign	SCC metastasis	Other malignant lesions	
FNAC:				
Benign	14	5	3	22
SCC metastasis	1	6	1	8
Other malignant lesions	0	0	4	4
Indeterminate[a]	5	5	5	15
Sensitivity (95% CI)	93.3% (68.1 to 99.8)	54.5% (23.4 to 83.3)	50.0% (15.7 to 84.3)	
Positive predictive value (95% CI)	63.6% (40.7 to 82.8)	75.0% (34.9 to 96.8)	100% (39.8 to 100)	
Overall accuracy (95% CI)	70.5% (52.5 to 84.9)			
Agreement	Weighted kappa: 0.53 (0.28 to 0.78)			
Extemporaneous biopsy:				
Negative	20	0	13	33
Positive	0	16	0	16
Sensitivity (95% CI)	100% (83.2 to 100)	100% (79.4 to 100)	0% (0.0 to 24.7)	
Positive predictive value (95% CI)	60.6% (42.1 to 77.1)	100% (79.4 to 100)	0% (0.0 to 20.6)	
Overall accuracy (95% CI)	73.5% (58.9 to 85.1)			

CI: Confidence interval.
[a] Indeterminate FNACs were not included in the calculation of performance indices.

Table 2
Performance of extemporaneous biopsy for metastasis from squamous cell carcinoma versus histology.

	Histology		Total
	Negative	Positive	
Extemporaneous biopsy:			
Negative	33	0	33
Positive	0	16	16
Sensitivity (95% CI)	100% (79.4 to 100)		
Specificity (95% CI)	100% (89.4 to 100)		
Positive predictive value (95% CI)	100% (79.4 to 100)		
Negative predictive value (95% CI)	100% (89.4 to 100)		
Overall accuracy (95% CI)	100% (92.7 to 100)		

CI: Confidence interval.

Table 3
Histological results.

Histology	No. (%) (n = 49)
Benign cystic lesions:	20 (40.8)
Branchial cleft cyst	14
IgG4-related disease	1
Epidermoid cyst	2
Inflammatory lesions (lymphadenitis)	2
Castleman disease	1
SCC metastasis	16 (32.7)
Other malignant lesions:	13 (26.5)
Large cell-B lymphoma	9
Hodgkin lymphoma	3
Metastatic papillary thyroid cancer	1

Concerning treatment, when extemporaneous consultation found SCC metastasis, open biopsy switched to UADT endoscopy with multiple blinded biopsies, tongue base mucosectomy, bilateral tonsillectomy, and neck dissection in the same setting. Among these 16 cases, final histology found 10 oropharyngeal SCC (7 tonsils, 3 tongue base) and six cancers of unknown primary (CUP).

Discussion

This study aimed to assess the accuracy of preoperative FNAC diagnosis and intraoperative FS evaluation versus definitive histology in detecting metastasis from SCC in cystic lesions of the lateral neck. Although the sample was quite small, extemporaneous biopsy showed perfect agreement in distinguishing SCC metastasis from other lesions, while FNAC had a quite low agreement with final histology. This result seems to confirm a low sensitivity of cytology in cystic masses, even if routinely performed under ultrasound guidance and by both a radiologist and a cytopathologist.

FNAC under ultrasound guidance allows one to evaluate the site of origin, characteristics, and anatomical relations of the mass, and to avoid necrotic areas, which further increases accuracy.[14–16] However, accuracy decreases substantially when cystic rather than solid masses are studied, with a rate of false-negative/indeterminate results ranging from 11% - 30%[1,3,7,12]

To obtain a histopathological diagnosis in the case of undefined cytology, the guidelines suggest repeating FNAC, performing CNB, or rarely, open biopsy of the mass.[6] In our

experience, we observed that intraoperative FS consultation reached maximum specificity and positive predictive value with no false positive cases, showing promising results even when preoperative FNAC did not provide a clear diagnosis.

Unlike definitive histology, extemporaneous biopsy can distinguish the presence of metastatic squamous cells from other benign or malignant lesions because, in this field of neck surgery, only SCC metastasis has the indication to be treated with neck dissection.[12] If FS examination reveals SCC metastasis, we suggest proceeding with neck dissection, bilateral tonsillectomy, tongue base mucosectomy, and multiple biopsies of the UADT at the same time; if FS is negative for SCC metastasis, the specimen is sent for definitive histology and the response is awaited before further additional treatments are planned. By doing so, the benefits would be to avoid further general anaesthesia and reduce the treatment time, which could affect prognosis in patients with hidden metastatic neck disease.

Contextually, the patient's perspective is important. We know that there is a vast gulf in terms of morbidity from a lateral neck mass excision compared with a neck dissection with mucosectomy and tonsillectomy. Providing an exhaustive preoperative interview with the patient is important not only for informed consent, but also for the psychological aspect, because patients effectively find out that they have had a malignancy only when they wake up after surgery.

On the other hand, some authors are sceptical about this approach because the intraoperative and final diagnosis might be discordant because of diagnostic misinterpretation or technical issues.[10] However, some authors have documented an increased rate of local recurrence, worse healing, and decreased survival for neck violation in cases of therapeutic neck dissection after open biopsy due to a change in the anatomy of the cervical fascia. There was thus an increasing need to assess the accuracy of FS to detect SCC metastasis within cystic masses of the lateral neck.

FSs are widely employed in otolaryngology, but in oral cancer surgery their use is mostly reserved for the evaluation of resection margins.[17,18] Although some authors[19–21] have demonstrated their utility in assessing solid cervical masses, we know of few reports that have addressed FS analysis in cystic lesions. Begbie et al[3] were the first to compare FNAC and FS analysis in cervical cysts, finding 100% sensitivity for FS, but they enrolled only eight patients. Recently, Franzen et al[11] published their experience in which patients underwent surgery with UADT endoscopy and intraoperative FS evaluation of the cystic mass, without preoperative FNAC. They found their approach reliable, and suggested an algorithm that includes possible neck dissection in the same setting when FS detects SCC, bypassing preoperative FNAC.

Recently, Tabet at al[22] compared FNAC, CNB, and FS in the diagnosis of cystic masses. The diagnostic algorithm they propose starts with FNAC; in the case of an indeterminate FNAC, they suggest proceeding with CNB because its sensitivity in metastasis detection is higher. If CNB is non-diagnostic, they suggest FS to confirm the absence of malignancy. However, the indications for CNB in cystic lesions are controversial because of the high risk of inadequate sampling and complications.[23] Moreover, the authors do not further specify which surgical approach should be adopted when FS evaluation reveals metastasis, and use of this algorithm may require increased diagnostic time.

In our study HPV status was determined in most cases, also showing slightly high sensitivity when the evaluation was performed on FNAC samples. Nevertheless, HPV-positive cysts were strongly suspicious of metastatic SCC arising in the oropharynx while the majority of branchial cysts were HPV-negative, confirming previous reports.[24]

Even though the sample size was small, the malignancy rate in cystic neck masses (32%) recorded in our cohort was consistent with the literature (9.2%-31%),[1,13] so the wide range of sensitivity values (33% -75%) for FNAC in cystic lesions is not negligible. As a result, we encourage the management of all cystic masses by preoperative FNAC followed by open biopsy with intraoperative pathologist consultation. In our opinion, preoperative FNAC is still fundamental because it becomes a turning point in the diagnostic process, making it possible to search for HPV, so much so that some authors propose that tongue base mucosectomy may not be indicated for cases of HPV-negative unknown primary carcinoma based on a low likelihood of finding the primary.[13]

In conclusion, intraoperative pathologist consultation may allow a switch to definitive surgical treatment of the neck without the need to wait for definitive histology before planning additional treatment. FNAC lets us identify patients who require more significant surgery, allowing them to be adequately prepared. Minimising uncertainty in the treatment pathways can be of significant benefit to patients, for this reason they should be reassured and adequately informed in the preoperative phase.

Conclusions

FS analysis has proved to be particularly useful for the evaluation of cystic neck masses in which cytology has shown lower accuracy. We suggest preoperative FNAC and intraoperative FS analysis for all cystic neck masses, for the chance of a malignant finding. In the case of an intraoperative diagnosis of SCC metastasis, it is possible to proceed to UADT endoscopy with blinded biopsy, bilateral tonsillectomy, tongue base mucosectomy, and neck dissection in the same session.

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Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patients' permission

The study was approved by the University Ethics Committee (No. 96/2019). No patient information has been included.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bjoms.2022.07.009.

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