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SFORL Guidelines

Cytopathological analysis of salivary gland cancer: REFCOR recommendations by the formal consensus method

M. Courtade-Saïdi [a], E. Uro-Coste [a], S. Vergez [b,c,*], B. Verillaud [d], N. Pham Dang [e], E. Chabrillac [c], N. Fakhry [f], C. Bigorgne [g], V. Costes-Martineau [h]

[a] *Département d'anatomie et de cytologie pathologiques, faculté de santé, institut universitaire du cancer Toulouse – Oncopole, université Toulouse III Paul-Sabatier, Toulouse, France*
[b] *Département de chirurgie ORL et cervicofaciale, université Toulouse III Paul-Sabatier, CHU de Toulouse-Larrey, Toulouse, France*
[c] *Département de chirurgie, institut universitaire du cancer Toulouse – Oncopole, Toulouse, France*
[d] *Inserm U1141, département d'ORL et de chirurgie cervicofaciale, hôpital Lariboisière, université Paris-Cité, AP–HP, Paris, France*
[e] *Inserm, Neuro-Dol, service de chirurgie maxillofaciale, université Clermont Auvergne, CHU de Clermont-Ferrand, 63000 Clermont-Ferrand, France*
[f] *Département d'ORL et chirurgie cervicofaciale, hôpital La Conception, Aix-Marseille université, AP–HM, Marseille, France*
[g] *Centre de pathologie et d'imagerie, Paris, France*
[h] *Département de biopathologie, CHU de Montpellier, Montpellier, France*

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ABSTRACT

Objective: To determine the indications for fine-needle cytology and the modalities of frozen section pathological analysis in the management of salivary gland cancer.
Material and methods: The French Network of Rare Head and Neck Tumors (REFCOR) formed a steering group who drafted a narrative review of the literature published on Medline and proposed recommendations. The level of adherence to the recommendations was then assessed by a rating group according to the formal consensus method.
Results: Fine-needle cytology is recommended as part of the diagnostic work-up for a major salivary gland tumor suspicious for malignancy. Fine-needle cytology should be performed after MRI to avoid artifacts. Frozen section analysis is recommended to confirm the malignant nature of the tumor, to adapt the extent of resection and to indicate neck dissection. Whenever possible, the entire tumor and adjacent salivary or periglandular tissue should be sent for frozen section analysis.
Conclusion: Fine-needle cytology and frozen section analysis play an essential role in the management of salivary gland cancers.

1. Introduction

There is a wide variety of salivary gland tumors and recommended treatment likewise varies. Pre-treatment work-up includes imaging and cytopathology as complementary examinations [1]. The work-up is crucial to management, guiding treatment [2–4]. Controversies continue, notably regarding the role of fine-needle cytology and frozen section analysis [5,6].

The present recommendations aim to determine indications for fine-needle cytology and the modalities of frozen section pathologic analysis in the management of salivary gland carcinoma.

2. Material and methods

These recommendations of the French Network of Rare Head and Neck Tumors (REFCOR) were written up by a steering group, adhering to a methodology previously published by the REFCOR [7]. The aim was to determine indications for fine-needle cytology and the modalities of frozen section pathologic analysis in the management of salivary gland carcinoma.

The narrative review was based on analysis of publications in the American Medline database for the period January 1, 2018 to November 1, 2021, using the search-term "salivary gland cancer", by one of the present authors (EC) and completed by non-systematic review by each author, adapted to the study objectives, without limitations of date, and updated before publication (Appendix 1). Articles were selected according to innovativeness and level of evidence: methodology, sample size, bias. The 121 selected articles (Appendix 1) comprised 7 guidelines,

* Corresponding author. Département d'ORL et chirurgie cervico-faciale, CHU de Toulouse-Larrey, 24, chemin de Pouvourville, 31059 Toulouse cedex 9, France.
E-mail address: vergez.s@chu-toulouse.fr (S. Vergez).

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9 meta-analyses, 18 literature reviews, 2 multicenter prospective studies, 2 single-center prospective studies, 20 multicenter retrospective studies, 56 single-center retrospective studies, 7 case reports.

The narrative drawn up after the review of the literature on salivary gland cancer was accompanied by recommendations graded by the level of evidence of the underlying literature.

The formalized expert consensus methodology (https://www.has-sante.fr/jcms/c_272505/fr/recommandations-par-consensus-formalise-rcf) involves assessing level of adhesion, agreement and disagreement between experts for each recommendation. The proposed recommendation is submitted to a rating group of 9 or 10 experts appointed by the steering group. It is read and graded twice, from 1 (totally inappropriate) to 9 (totally appropriate), to quantify adhesion. On the HAS French Health Authority methodology, grade distribution and median are used to classify the proposal as "appropriate", "uncertain" or "inappropriate". Agreement is classified as "strong", "relative" or "undecided". Proposals with strong agreement as of the first round are not submitted to the second round; the others are revised by the steering group before the second round of grading. Finally, the entire narrative was revised by volunteers at national level after e-mailing to the contact lists of the REFCOR, French Society of ORL and French Society of Head and Neck Oncology.

3. Results

This section presents the recommendations formulated at the end of the formalized consensus process. The narrative accompanying each recommendation is presented in the Discussion section below.

3.1. Cytology analysis

Recommendations by formalized consensus

It is recommended to include fine-needle cytology whenever possible in the diagnostic work-up for salivary gland tumor suspected of malignancy (grade B), not typical of pleomorphic adenoma or cystadenolymphoma on MRI (expert agreement) [appropriate proposal, relative agreement].

It is recommended to perform fine-needle cytology after MRI to avoid interpretation artifacts (expert agreement) [appropriate proposal, strong agreement].

3.2. Pathology analysis

Recommendations by formalized consensus

Frozen section analysis is recommended to confirm malignancy, adapt resection extent and associate neck dissection when indicated (grade C) [appropriate proposal, strong agreement].

So far as possible, the entire tumor plus adjacent salivary or periglandular tissue should be sent for analysis (expert agreement). In case of tumoral inclusion of the facial nerve, frozen section analysis with tumor biopsy may be considered to confirm malignancy before sacrificing the nerve (expert agreement) [appropriate proposal, relative agreement].

The conclusion of the pathology report should include tumor grade whatever the pathologic type (expert agreement) [appropriate proposal, strong agreement].

4. Discussion

All proposals were considered appropriate, with maximal ("strong") agreement, except the indications frozen section analysis and for fine-needle cytology in tumors not typical of cystadenolymphoma or pleomorphic adenoma, considered appropriate but with only relative agreement.

4.1. Indications for fine-needle cytology

Fine-needle cytology is a key examination for preoperative diagnosis and treatment strategy in case of salivary gland mass. It is simple to perform, with very few complications (hematoma 0.1%, infection or inflammation 0.16%, pain 0.1%) and there is almost no risk of facial nerve lesion [8] (level of evidence 4).

The diagnostic performance of fine-needle cytology in salivary gland tumor was the focus of many studies and of several meta-analyses [9–11]. Sensitivity varies according to use of ultrasound guidance and operator and cytopathologist experience [10] (level of evidence 4).

Before 2018, there was no consensual terminology for cytopathology reports in the salivary glands, hindering comparative analysis between series [8,12]. In 2018, the Milan system was published, based on the work of an international expert panel, notably developing a uniform cytology language in order to improve understanding between pathologists and clinicians [13,14].

4.1.1. Sampling methodology

Fine-needle biopsy should be performed by a trained clinician, radiologist or cytopathologist, after MRI, as in the 3 months prior to MRI it could induce inflammatory or hemorrhagic remodeling, hindering MRI analysis (expert agreement) [1]. Fine 22–27 G needles are used, preferably without aspiration, although aspiration may be necessary to evacuate cystic lesions. In situ examination by the cytologist (or trained radiologist) can check sampling quality, with repetition if necessary to obtain an analyzable amount [15], although this is rarely feasible in practice [12].

The sample is then either spread on slides and air-dried or collected in liquid medium (composition varying between suppliers). In the latter case, the needle can be rinsed in the fixation liquid. In practice, the pathologist decides which procedure he or she prefers.

4.1.2. Is ultrasound guidance recommended for all fine-needle cytology procedures?

One practical question in fine-needle cytology is whether sampling should be under ultrasound guidance or directly guided by palpation.

A meta-analysis found that ultrasound guidance improved sensitivity (0.85; 95% CI, 0.76–0.91) and specificity (0.98; 95% CI, 0.95–0.99) compared to procedures without ultrasound guidance (respectively, 0.78; 95% CI, 0.74–0.82 and 0.97; 95% CI, 0.96–0.98) [8].

In head and neck lesions in general (salivary glands, neck lymph nodes, thyroid), the rate of non-diagnostic samples is significantly greater under palpation than ultrasound guidance (respectively 17.1% vs. 6.2%), particularly in sub-centimeter lesions (respectively 38.6% vs. 2.9%). Discordance between cytology and definitive pathology is likewise less with ultrasound guidance (5.4%) than with palpation (12.8%) [16]. On the other hand, the pitfalls inducing cytologic diagnostic error were unaltered by ultrasound guidance in the study by Consamus [17] (level of evidence 4); this mainly concerned lesions difficult to interpret on cytology. Kuan recommended ultrasound guidance in deep and poorly accessible lesions [18].

Moreover, ultrasound characteristics may themselves help in diagnosis. The diagnostic performance of cytology when isolated or associated to ultrasound was comparable for benign tumors (83% and 84%, respectively) but significantly better with associated ultrasound for malignant tumors (86% vs. 93%) [19]. However, Yariv did not replicate this in a smaller study [20].

The advantages of ultrasound guidance consist in being able to target the mass with continuous visualization of the needle within it and of tissue zones in a mixed heterogeneous mass, leading to better sampling.

Importantly, the first recommendation in the official UK guidelines in salivary gland tumor is for fine-needle cytology under ultrasound guidance in all salivary gland tumors [21].

4.1.3. *Is cytology recommended systematically for preoperative work-up in case of salivary gland mass?*

4.1.3.1. Cost-effectiveness. Several authors stressed that the procedure is simple and inexpensive and provides important information for patient management [22,23] (level of evidence 4), postponing or avoiding surgery in elderly or frail patients with a benign tumor or inflammatory lesion on cytological analysis.

4.1.3.2. Studies prior to the Milan system. Prior to the Milan system, the meta-analyses by Schmidt and Liu studied the diagnostic performance of fine-needle cytology in differentiating between benign and malignant tumors, with sensitivity of respectively 80% and 78% (95% CI, 74–82%) and specificity of 97% and 98% (95%CI, 97–98%) [8,12]. Diagnostic relevance was estimated at 99% (95% CI, 98–100%) by Liu [8]. Performance was higher in the meta-analysis by Rajenda [24]: sensitivity 87–100% and specificity 90–100%.

4.1.3.3. Studies using the Milan system. Like the Bethesda system in thyroid cytopathology, the Milan system made it possible to assess malignancy risk according to diagnostic category, with accompanying treatment recommendations. Using the Milan terminology, the meta-analysis by Farahani found comparable performance in determining the tumoral nature of the lesion and for diagnosis of malignancy in a lesion identified as neoplastic, with sensitivity of respectively 97% and 82% and specificity of 95% and 98% [9]. The authors stressed the usefulness on in situ sample cellularity assessment (ROSE technique) and the significantly enhanced performance of cytology when performed and interpreted by an operator experienced in salivary pathology. The meta-analysis by Wei, assessing the diagnostic performance of cytology in determining malignancy (taking together the categories "Salivary gland neoplasm of uncertain malignant potential [SUMP]" and "malignant") found 88% sensitivity and 74% specificity [25]. Performance is better, at respectively 95% and 95%, in distinguishing between a benign or malignant neoplastic process and absence of neoplasm. Performances are comparable for tumors in the submandibular gland [26] (level of evidence 4) and for pediatric tumors [27] (level of evidence 4).

UK [21] and American guidelines [28] for salivary gland tumors place ultrasound-guided fine-needle cytology and MRI in first line.

Microbiopsy is not recommended in first line, due to theoretic risk of facial nerve lesion, dissemination, hematoma and salivary fistula [29] (level of evidence 4). Performance is considerably better than cytology for diagnosing malignancy, but complications are more frequent [5] (level of evidence 4). The risk is negligible with fine-needle cytology which is therefore the 1st line pre-treatment cellular diagnostic examination. Microbiopsy should rather be in 2nd line in case of failure of cytology or if surgical treatment is not feasible (expert agreement). In a retrospective study of 212 patients with preoperative MRI and ultrasound-guided biopsy, Laccourreye et al. found that the latter did not significantly enhance diagnostic performance. However, it seems more effective after radiotherapy and when MRI is doubtful or suggestive of malignancy (level of evidence 4) [30].

Table 1
Sensitivity of frozen-section analysis in malignant tumors.

Reference (level of evidence 4)	Sensitivity
Wang et al., 2012 [33]	79.7% (148 cases)
Badoual et al., 2006 [34]	43–100% (124 cases)
Tew et al., 1997 [35]	70% (34 cases)
Chan et al., 1992 [36]	70% (number of cases not stated)
Ogawa et al., 2018 [37]	77.7% (18 cases)
Atula et al., 2017 [38]	100% (7 cases)
Zbären et al., 2004 [39]	95.5% (45 cases)
Zbären et al., 2008 [40]	93% (68 cases)
Olsen et al., 2013 [41]	98.5% (268 cases)
Fakhry et al., 2014 [43]	80% (30 cases)

4.1.4. *Contribution of complementary techniques*

Complementary techniques can be implemented on cytology samples. They provide diagnostic precision, notably to definitively confirm malignancy. Immunocytochemistry, for example, enhances characterization of ductal and secretory carcinoma. FISH (fluorescence in situ hybridization) enables definitive diagnosis when positive for cystic adenoid carcinoma, mucoepidermoid carcinoma or secretory carcinoma [31,32] (level of evidence 4).

4.1.5. *Why recommend fine-needle cytology in salivary gland tumor?*

- Excellent cost-effectiveness.
- Particularly effective when ultrasound-guided.
- Good diagnostic performance; the Milan system assesses malignancy risk.
- Differentiates between non-neoplastic or benign tumor and carcinoma or lymphoma, thus possibly changing the treatment strategy.
- Coupled to MRI, it guides surgical strategy and patient information.

4.2. *Role of frozen-section analysis*

Only single-center retrospective studies with low level of evidence are available on the diagnostic performance of frozen-section analysis in salivary gland tumor. A 2011 meta-analysis found 90% sensitivity (95% CI, 81–94%) and 99% specificity (95% CI, 98–99%), taking benign and malignant tumors together [12]. In malignant tumors, sensitivity was 70–100% and specificity generally > 95% [33–42] (Table 1).

MRI coupled to preoperative fine-needle cytology and clinical findings shows very good performance [28] (level of evidence 4). Frozen-section analysis, however, is recommended to confirm malignancy, given the high surgical stakes, confirming malignancy and guiding surgery. Definitive pathologic examination of the specimen is needed to determine treatment, as the quality of frozen sections is lower than paraffin-fixed sections, which moreover allow immunohistochemical and molecular examination.

Errors in frozen-section analysis are minimized if the specimen is whole rather than fragmented. One of the most reliable signs of malignancy is poor tumor delineation and invasion of peritumoral issue, which can only be assessed if the interface between tumoral and healthy tissue can be examined by the pathologist [44] (level of evidence 4). Tumor enucleation and specimen fragmentation prevent analysis of this aspect and must be avoided, as diagnosis of benign versus malignant status would not in fact be definitive, and resection quality cannot be assessed if the margins are not visible.

The pathologist needs to be sufficiently trained to avoid certain false positives or negatives. Case reports and expert opinions

highlight several. Extensive keratinizing metaplasia and necrosis with infarction in pleomorphic adenoma often associated with cystic process or trauma (e.g., fine-needle cytology) can lead to false diagnosis of malignancy or metastasis such as squamous cell carcinoma, mucoepidermoid carcinoma or other malignant salivary gland tumors [45–49] (level of evidence 4). Also, it is difficult to diagnose carcinoma developing from pleomorphic adenoma if the one is enclosed in the other: non-invasive forms of carcinoma developing from pleomorphic adenoma; in this case, diagnosis is difficult even on definitive examination [50] (level of evidence 4). And finally a very myxoid loose aspect in certain pleomorphic adenomas, especially in the orbital lacrimal glands, can induce misdiagnosis as orbital rhabdomyosarcoma on frozen-section analysis [51] (level of evidence 4).

4.3. Pathology report

The pathology report should adhere to the guidelines of the International Collaboration on Cancer Reporting (ICCR). The type of surgery and of samples should be included. The conclusion must include the pathologic type and grade, perineural and vascular invasion or not, extension and margin status [52] (expert agreement).

5. Conclusion

Cytopathology analysis complements diagnostic imaging and is an essential part of diagnostic management in salivary gland tumor, guiding treatment. The present recommendations highlight the essential role of fine-needle cytology and frozen-section analysis in managing salivary gland tumor.

An appendix (Appendix 1), accessible as supplementary material in the online version of this article at the website specified at the end of the article, details the references of the articles read for the study.

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Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.anorl.2023.11.002.

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