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SFORL Guidelines

Surgery of sublingual and minor salivary gland cancer: REFCOR recommendations by the formal consensus method

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ABSTRACT

Objective: To determine the indications and modalities for resection in the management of primary sublingual and minor salivary gland cancer, and the specific features of each primary location.
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: Histological evidence (submucosal biopsy) is recommended before surgical treatment of minor salivary gland carcinoma. Surgical treatment is recommended, with optimal oncologic margins, adapted to anatomical factors, histologic type and grade and functional consequences, with reconstruction if necessary.
Conclusion: Treatment of primary minor salivary and sublingual gland cancer is surgical, with wide resection margins. The modalities of resection and reconstruction are highly dependent on tumor location, extension and histologic type.

1. Introduction

Minor salivary gland tumors are mainly located in the oral cavity: in decreasing order of frequency, hard palate, gums, then lips and tongue [1] (level of evidence: 4). The most frequent histologic types are mucoepidermoid carcinoma, adenoid cystic carcinoma and, more rarely, acinic cell carcinoma and low-grade polymorphic adenocarcinoma [2–6] (level of evidence: 4). First-line treatment of malignant minor salivary gland tumor is surgical [7] (level of evidence: 4), by complete resection with clear margins [8,9] (level of evidence: 3). Several retrospective studies reported surgery to be an independent factor for better survival [10–13] (level of evidence: 4). However, studies comparing surgical versus non-surgical treatment involved selection bias, often including non-resectable tumors in the non-surgical group [10] (level of evidence: 4).

The aim of the present recommendations was to determine the indications and modalities of resection in the management of primary minor salivary gland and sublingual cancer and the specificities of each primary location.

2. Material and methods

The present recommendations of the French Network of Rare Head and Neck Tumors (REFCOR) were drawn up by a steering group adhering to a previously published methodology [14]. The aim was to determine the indications and modalities of resection in the management of primary minor salivary gland and sublingual cancer and the specificities of each primary location.

The narrative review was based on an analysis of articles in the American Medline database, with a search over the period January

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1st, 2018 to November 1st, 2021, using the keyword "salivary gland cancer" by one of the authors (E.C.), completed by a non-systematic review by each author, adapted to objectives, without date limits and updated before publication (Appendix 1). Articles were selected for innovation and level of evidence: i.e., methodology, sample size and potential bias. The 54 selected articles (Appendix 1, in Supplementary data) comprised 6 guidelines, 3 meta-analyses, 15 literature reviews, 22 single-center retrospective studies, and 7 multicenter retrospective studies.

The narrative drawn up in the light of this review of the literature on salivary gland cancer is accompanied by recommendations, graded according to the level of evidence of the 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 emailing to the contact lists of the REFCOR, French ENT Society and French Society of Head and Neck Oncology.

3. Results

This section presents the recommendations drawn up by formalized expert consensus. The narrative relating to each recommendation in presented in the Discussion section below.

Recommendations by formalized consensus

Histologic proof (submucosal biopsy) is recommended ahead of surgical treatment of minor salivary gland carcinoma (grade C) [appropriate proposal, strong agreement].

Surgical treatment of minor salivary gland carcinoma is recommended, with optimal resection margins adapted to anatomic factors, histologic type and grade and functional consequences, with reconstruction if necessary (grade C) [appropriate proposal, strong agreement].

4. Discussion

Agreement was maximal ("strong") for both recommendations.

4.1. Primary tumor surgery: sublingual gland

Surgery had significantly favorable prognostic impact in the 210 patients reported by Lee et al. [15] (level of evidence: 4). The first-line treatment of choice is surgery with monobloc resection and oncologic safety margins (grade C), which may require margins within the oral floor muscles, submandibular excretory system or lingual nerve and/or mandible [1,16] (level of evidence: 4). Segmental mandibulectomy is recommended in case of preoperative bone lysis (grade C). The impact of margin quality on survival has yet to be demonstrated, with few published series [17,18]. Indications for adjuvant treatment are the same as in the submandibular gland [9,19] (level of evidence: 4).

4.2. Primary tumor surgery: minor salivary glands

Before any surgery for minor salivary gland cancer, submucosal biopsy for pathologic diagnosis is recommended (grade C) [20]. Diagnostic enucleation is advised against (grade C).

Resectable tumor in an operable patient is an indication for resection, but extent depends on factors such as location, histologic type and grade [1] (level of evidence: 4). Margins in oral minor salivary gland adenoid cystic adenoma are positive in 30–50% of cases, depending on the report [4,21]. Along with the neurotropism of this histologic type, this requires wide resection with maximal margins and extensive nerve resection in case of invasion (grade C). Frozen section analysis may be useful to ensure resection quality (grade C).

4.2.1. Oral cavity minor salivary gland tumor

4.2.1.1. Palatine region. Malignant minor salivary gland tumor is more frequent in the palatine region [22–24] (level of evidence: 4). The 3 most frequent histologic types are mucoepidermoid carcinoma, adenoid cystic carcinoma and adenocarcinoma [2,22–24] (level of evidence: 4). The meta-analysis by Martinez-Rodriguez et al. reported that the main location of oral cavity minor salivary gland adenoid cystic carcinoma was the hard palate (110/193 patients) [21] (level of evidence: 4).

The therapeutic decision should take account of bone and/or nerve invasion on imaging and tumor histology and grade [1,22] (level of evidence: 4).

Resection of low-grade tumor without bone lysis on imaging includes the periosteum for margins and can spare the bone [1]. Conversely, bone resection is recommended in case of bony palate invasion or extension close to the bone in high-grade tumor [1].

4.2.1.2. Internal cheek. The most frequent pathologic types are mucoepidermoid carcinoma, acinic cell adenocarcinoma, and then polymorphic adenocarcinoma [1,25] (level of evidence: 4). One specificity of treatment of internal cheek minor salivary gland tumor is ensuring safety margins within the cheek muscles, which may require full-thickness resection and/or segmental resection of the parotid Stensen duct, especially for low-grade advanced-stage tumor and high-grade tumor [1].

4.2.1.3. Retromolar trigone region. This region comprises the retromolar trigone, intermaxillary commissure and internal mandibular base region. The most frequent subtype is mucoepidermoid carcinoma.

One specificity of treatment of retromolar trigone minor salivary gland tumor is the possible need for a mandibular bone block or for mandibulectomy in case of mandibular invasion on MRI [1]. Resection of a low-grade tumor without bone lysis on imaging includes a cortical bone block for margins [1]. Conversely, bone resection is recommended in case of bony invasion or extension close to the bone in high-grade tumor [1].

4.2.2. Oropharyngeal minor salivary gland tumor

The most frequent histologic types are adenoid cystic carcinoma, mucoepidermoid carcinoma and adenocarcinoma [22] (level of evidence: 4). The subregions most frequently involved are the tongue base followed by the soft palate and tonsils [22] (level of evidence: 4).

Surgery uses a transoral or transmandibular approach or pharyngotomy, depending on tumor location and extension. The advent of robot-assisted surgery now optimizes operative comfort and can sometimes avoid transcervical approaches for early tumors [26,27].

Due to submucosal progression, almost half the cases in the series reported by Iyer et al. and Goel et al. had positive margins

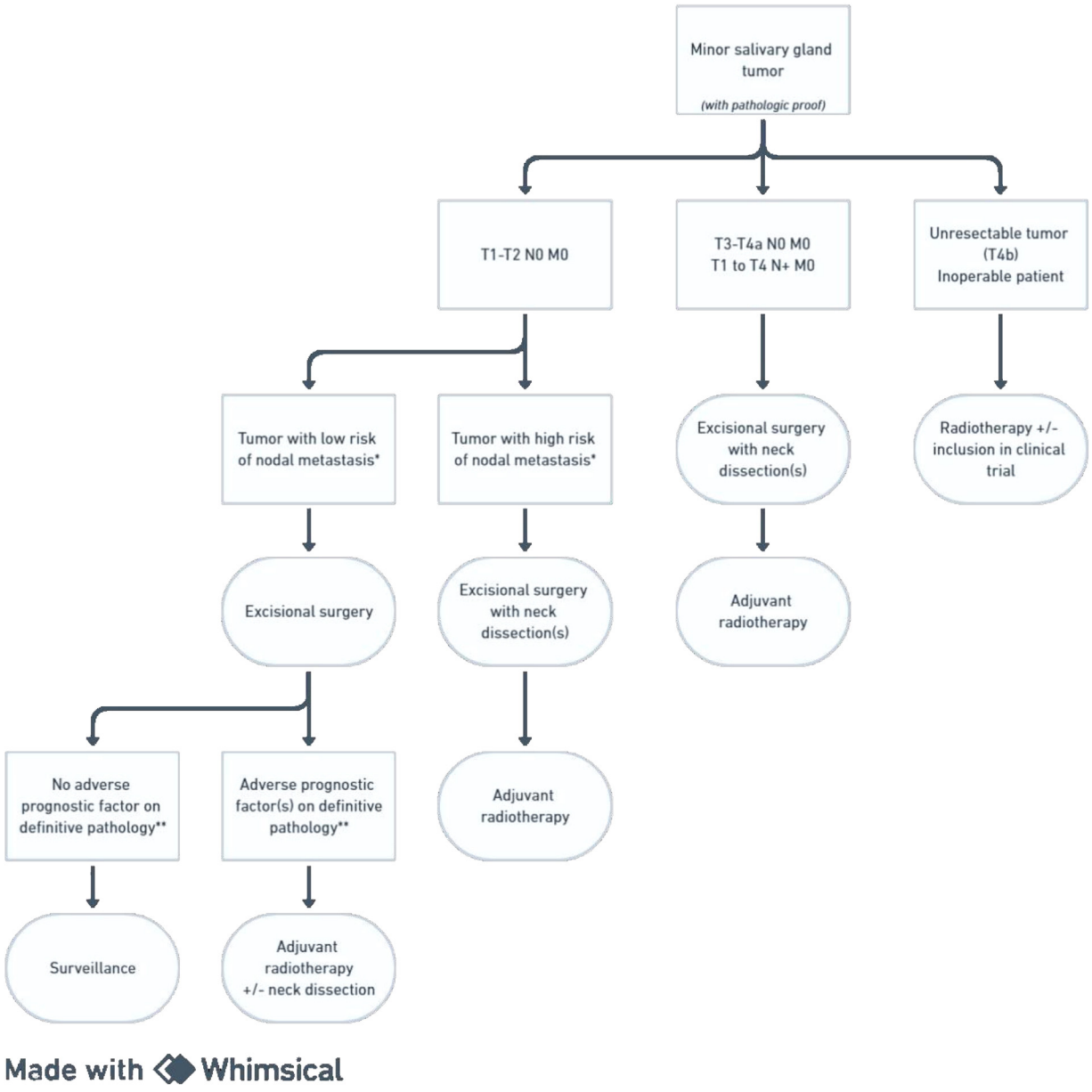

Fig. 1. Decision-tree for non-metastatic minor salivary gland tumor. *Low risk of nodal metastasis = low-grade T1 or T2 (except secretory carcinoma) and T1 or T2 adenoid cystic carcinoma not invading the oral mucosa; high risk of nodal metastasis = any tumor not meeting these low-risk criteria. **Negative histoprognostic factors = R1/R2 margins without feasible revision surgery and/or perineural invasion (except adenoid cystic carcinoma and low-grade polymorphic adenocarcinoma, where perineural invasion does not have the same negative histoprognostic value), and/or vascular emboli, and/or lymphatic emboli, and/or poorly differentiated tumor.

[26,27] (level of evidence: 4). Wide safety margins should therefore be included in tongue-base resection and adenoid cystic carcinoma (grade C).

4.2.3. Laryngeal minor salivary gland tumor (grade C)

Laryngeal minor salivary gland tumor is very rare, at < 1% of malignant laryngeal tumors. The reported cases concerned all three levels of the larynx.

Treatment may be surgical, by partial or more often total laryngectomy, due to submucosal progression [22] (level of evidence: 4).

5. Conclusion

Treatment of primary minor salivary and sublingual gland cancer is surgical, with wide margins. Resection and reconstruction modalities greatly depend on tumor location, extension and histologic type. Margins should be especially wide in adenoid cystic adenoma and high-grade tumor. Preoperative histologic diagnosis is thus indispensable, with submucosal biopsy, to guide resection and reconstruction strategy (Fig. 1).

An appendix (Appendix 1), available in the Supplementary data of the online version at the website specified at the end of this article, details the references of the selected articles.

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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 doi:10.1016/j.anorl.2023.11.011.

References

[1] Carlson ER, Schlieve T. Salivary gland malignancies. Oral Maxillofac Surg Clin North Am 2019;31:125–44, http://dx.doi.org/10.1016/j.coms.2018.08.007.
[2] Kakarala K, Bhattacharyya N. Survival in oral cavity minor salivary gland carcinoma. Otolaryngol Head Neck Surg 2010;143:122–6, http://dx.doi.org/10.1016/j.otohns.2010.02.033.
[3] Loh KS, Barker E, Bruch G, O'Sullivan B, Brown DH, Goldstein DP, et al. Prognostic factors in malignancy of the minor salivary glands. Head Neck 2009;31:58–63, http://dx.doi.org/10.1002/hed.20924.
[4] Park SI, Park W, Choi S, Jang Y, Kim H, Kim S-H, et al. Clinical outcome of minor salivary gland cancers in the oral cavity: a comparative analysis with squamous cell carcinomas of the oral cavity. Front Oncol 2020;10:881, http://dx.doi.org/10.3389/fonc.2020.00881.
[5] Poletto AG, Mello FW, Melo G, Rivero ERC. Prevalence of mucoepidermoid carcinoma among intraoral minor salivary gland tumors: a systematic review and meta-analysis. J Oral Pathol Med 2020;49:720–6, http://dx.doi.org/10.1111/jop.13073.
[6] Lin Y, Wang Y, Zhang H, August M, Xiang X, Zhang F. Sublingual gland tumors worldwide: a descriptive retrospective study of 839 cases. J Oral Maxillofac Surg 2020;78:1546–56, http://dx.doi.org/10.1016/j.joms.2020.04.023.
[7] Wang X, Luo Y, Li M, Yan H, Sun M, Fan T. Management of salivary gland carcinomas – a review. Oncotarget 2017;8:3946–56, http://dx.doi.org/10.18632/oncotarget.13952.
[8] Mantravadi AV, Moore MG, Rassekh CH. AHNS series: do you know your guidelines? Diagnosis and management of salivary gland tumors. Head Neck 2019;41:269–80, http://dx.doi.org/10.1002/hed.25499.
[9] Barry B, Verillaud B, Jegoux F, Pham Dang N, Chabrillac E, Vergez S, et al. Chirurgie des cancers des glandes salivaires principales : recommandations REFCOR par consensus formalisé. Eur Ann Otorhinolaryngol Head Neck Dis 2024 [In Press].
[10] Liu T-R, Yang A-K, Guo X, Li Q-L, Song M, He J-H, et al. Adenoid cystic carcinoma of the nasopharynx: 27-year experience. Laryngoscope 2008;118:1981–8, http://dx.doi.org/10.1097/MLG.0b013e3181801d23.
[11] Cianchetti M, Sandow PS, Scarborough LD, Morris CG, Kirwan J, Werning JW, et al. Radiation therapy for minor salivary gland carcinoma. Laryngoscope 2009;119:1334–8, http://dx.doi.org/10.1002/lary.20501.
[12] Mendenhall WM, Morris CG, Amdur RJ, Werning JW, Villaret DB. Radiotherapy alone or combined with surgery for salivary gland carcinoma. Cancer 2005;103:2544–50, http://dx.doi.org/10.1002/cncr.21083.
[13] Mendenhall WM, Morris CG, Amdur RJ, Werning JW, Hinerman RW, Villaret DB. Radiotherapy alone or combined with surgery for adenoid cystic carcinoma of the head and neck. Head Neck 2004;26:154–62, http://dx.doi.org/10.1002/hed.10380.
[14] Vergez S, Chabrillac E, Fakhry N. Cancers salivaires : recommandations par consensus formalisé, sous l'égide du réseau d'expertise français sur les cancers ORL rares (REFCOR). Eur Ann Otorhinolaryngol Head Neck Dis 2024 [In Press].
[15] Lee RJ, Tong EL, Patel R, Satyadev N, Christensen RE. Malignant sublingual gland tumors: demographics, prognostic factors, and treatment outcomes. Oral Surg Oral Med Oral Pathol Oral Radiol 2016;121:180–7, http://dx.doi.org/10.1016/j.oooo.2015.09.019.
[16] Rinaldo A, Shaha AR, Pellitteri PK, Bradley PJ, Ferlito A. Management of malignant sublingual salivary gland tumors. Oral Oncol 2004;40:2–5, http://dx.doi.org/10.1016/s1368-8375(03)00104-0.
[17] Andreasen S, Bjørndal K, Agander TK, Wessel I, Homøe P. Tumors of the sublingual gland: a national clinicopathologic study of 29 cases. Eur Arch Oto-Rhino-Laryngol 2016;273:3847–56, http://dx.doi.org/10.1007/s00405-016-4000-y.
[18] Liu Y, Li H, Qin L, Huang X, Su M, Han Z. Prognostic factors in malignant sublingual salivary gland tumors. J Oral Maxillofac Surg 2017;75:1542–8, http://dx.doi.org/10.1016/j.joms.2016.12.010.
[19] Thariat J, Ferrand F-R, Fakhry N, Even C, Vergez S, Chabrillac E, et al. Radiothérapie des cancers salivaires : recommandations REFCOR par consensus formalisé. Eur Ann Otorhinolaryngol Head Neck Dis 2024, http://dx.doi.org/10.1016/j.anorl.2023.11.006 [In Press].
[20] Courtade-Saïdi M, Uro-Coste E, Vergez S, Verillaud B, Pham Dang N, Chabrillac E, et al. Analyses cytopathologiques des cancers salivaires : recommandations REFCOR par consensus formalisé. Eur Ann Otorhinolaryngol Head Neck Dis 2024 [In Press].
[21] Martínez-Rodríguez N, Leco-Berrocal I, Rubio-Alonso L, Arias-Irimia O. Epidemiology and treatment of adenoid cystic carcinoma of the minor salivary glands: a meta-analytic study. Med Oral Patol Oral Cir Bucal 2011;16:e884–9, http://dx.doi.org/10.4317/medoral.17200.
[22] Bradley PJ, Ferris RL. Surgery for malignant sublingual and minor salivary gland neoplasms. Adv Otorhinolaryngol 2016;78:113–9, http://dx.doi.org/10.1159/000442131.
[23] Wang X-D, Meng L-J, Hou T-T, Zheng C, Huang S-H. Frequency and distribution pattern of minor salivary gland tumors in a northeastern Chinese population: a retrospective study of 485 patients. J Oral Maxillofac Surg 2015;73:81–91, http://dx.doi.org/10.1016/j.joms.2014.08.019.
[24] Wang D, Li Y, He H, Liu L, Wu L, He Z. Intraoral minor salivary gland tumors in a Chinese population: a retrospective study on 737 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;104:94–100, http://dx.doi.org/10.1016/j.tripleo.2006.07.012.
[25] Pires FR, Pringle GA, de Almeida OP, Chen S-Y. Intra-oral minor salivary gland tumors: a clinicopathological study of 546 cases. Oral Oncol 2007;43:463–70, http://dx.doi.org/10.1016/j.oraloncology.2006.04.008.
[26] Goel AN, Badran KW, Braun APG, Garrett AM, Long JL. Minor salivary gland carcinoma of the oropharynx: a population-based analysis of 1426 patients. Otolaryngol Head Neck Surg 2018;158:287–94, http://dx.doi.org/10.1177/0194599817735309.
[27] Iyer NG, Kim L, Nixon IJ, Palmer F, Kraus D, Shaha AR, et al. Factors predicting outcome in malignant minor salivary gland tumors of the oropharynx. Arch Otolaryngol Head Neck Surg 2010;136:1240–7, http://dx.doi.org/10.1001/archoto.2010.213.