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SFORL Guidelines

Radiotherapy for salivary gland cancer: REFCOR recommendations by the formal consensus method

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ABSTRACT

Objective: To determine the indications for radiotherapy in salivary gland cancer and to specify the modalities and target radiation volumes.
Material and methods: The French Network of Rare Head and Neck Tumors (REFCOR) formed a steering group which 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: Postoperatively, radiotherapy to the primary tumor site ± to the lymph nodes is indicated if one or more of the following adverse histoprognostic factors are present (risk > 10% of locoregional recurrence): T3–T4 category, lymph node invasion, extraglandular invasion, close or positive surgical margins, high tumor grade, perineural invasion, vascular emboli, and/or bone invasion. Intensity-modulated radiation therapy (IMRT) is the gold standard. For unresectable cancers or inoperable patients, carbon ion hadrontherapy may be considered.
Conclusion: Radiotherapy in salivary gland cancer is indicated in postoperative situations in case of adverse histoprognostic factors and for inoperable tumors.

1. Introduction

Treatment of malignant salivary gland tumor is primarily surgical, based whenever possible on complete resection with clear margins. Radiotherapy is indicated for non-resectable tumor or postoperatively in case of adverse histoprognostic factors [1–4].

The aim of the present recommendations is to determine indications for radiotherapy in salivary gland tumor and to specify modalities and target radiation volumes.

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, following a previously published methodology [5]. The aim was to determine indications for radiotherapy in salivary gland tumor and to specify modalities and target radiation volumes.

The narrative review was based on an analysis of articles in the American Medline database, with a search over the period January 1st, 2018 to November 1st, 2021, using the keyword "salivary gland cancer" by one of the authors (EC), 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 77 selected articles on medical oncology (Appendix 1, in Supplementary data) comprised

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24 single-center retrospective studies, 19 multicenter retrospective studies, 2 randomized controlled trials, 4 single-center prospective studies, 10 guidelines, 17 literature reviews and 1 survey.

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 e-mailing 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.

3.1. Indications

Recommendations by formalized consensus

In malignant salivary gland tumor, radiotherapy to the primary tumor site ± to the lymph nodes is indicated for inoperable tumors or postoperative situations with adverse histoprognostic factors: T3–T4 category, lymph-node invasion, extraglandular invasion, close or positive margins, high tumor grade, perineural invasion, vascular emboli, and/or bone invasion; these factors incur a high risk (> 10%) of locoregional recurrence (grade B) [appropriate proposal, strong agreement].

In non-resectable or inoperable malignant salivary gland tumor, carbon ion hadrontherapy may be considered (expert agreement) [appropriate proposal, strong agreement].

Intensity-modulated radiotherapy (IMRT) is a gold-standard treatment for malignant salivary gland tumors (grade C) [appropriate proposal, strong agreement].

3.2. Target volumes

Recommendations by formalized consensus

The initial locoregional imaging work-up to determine target volumes comprises at least a CT scan and an MRI scan (expert agreement) [appropriate proposal, strong agreement].

Except in low-grade T1–T2 tumor and adenoid cystic carcinoma, when the primary tumor has been resected without concomitant neck dissection, with a cN0 neck on staging, the risk of lymph-node invasion or nodal relapse is high (> 10%). A complementary neck treatment is therefore recommended (grade C) by ipsilateral neck dissection or prophylactic ipsilateral neck irradiation (expert agreement) [appropriate proposal, relative agreement]:

- parotid gland: levels II-IV;
- submandibular gland and oral cavity: levels I–III ± IV.

Lymph-node levels are not irradiated after pN0 neck dissection if enough lymph nodes have been retrieved and there are no other adverse histoprognostic factors (expert agreement) [appropriate proposal, strong agreement].

Doses are 50 Gy equivalent[1] Cut and Paste the Footnote Outside The Floats[1]The idea of "equivalence" is introduced because radiotherapy may be performed by simultaneous integrated boost (SIB). For example, in SIB the radiation is not delivered to a large area at 50 Gy with up to 66 Gy to a smaller high-risk area within the large area; rather, the whole area is irradiated at different fractionated doses, with the same number of fractions throughout. for prophylactic irradiation (as in a N0 neck), 60 Gy equivalent in areas of intermediate risk (e.g., doubt on completeness of excision), 66 Gy equivalent in R1 resection, and 70 Gy equivalent in R2 resection (expert agreement) [appropriate proposal, strong agreement].

4. Discussion

All the proposals were deemed appropriate with maximal ("strong") expert agreement, except the equivalence between prophylactic neck dissection and prophylactic neck irradiation in case of discovery of high risk of occult nodal involvement on definitive pathology, which was deemed appropriate but with only relative agreement.

4.1. Indications for radiotherapy

Radiotherapy is indicated postoperatively in case of negative histopathologic factors: T3–T4 category, lymph-node invasion, extraglandular invasion, close or positive margins, high tumor grade, perineural invasion, vascular emboli and/or bone invasion, indicating high risk (> 10%) of locoregional recurrence, whether primary or nodal [6–11] (level of evidence: 4) (grade B). Intermediate grade or minor salivary gland tumor are further indications for postoperative radiotherapy for some authors [12]. It is not indicated in completely resected low-grade stage I or II tumor (grade B) in the absence of other adverse histoprognostic factors (grade B). Postoperative IMRT is indicated in high-grade stage II, III and IV and low-grade stage III and IV tumor (grade B). Proton therapy is another option here (grade C).

The role of concurrent chemoradiotherapy is controversial in salivary gland tumor, for lack of randomized studies [13–15] (level of evidence: 4). The Surveillance Epidemiology and End Results program study (SEER) suggested toxicity and negative impact on survival even after statistical adjustment for possible bias against chemotherapy [16,17] (level of evidence: 4). Thus, concurrent chemoradiotherapy is not recommended outside of clinical trials (grade A). Two international randomized studies (RTOG 1008, and SANTAL by GORTEC-REFCOR) are underway.

Radiotherapy is also applied in non-resectable and radioresistant tumors, but curative potential is lower with classic modalities and carbon ion hadrontherapy may be used [18–23] (level of evidence: 4) (expert agreement). This type of radiotherapy uses hadrons, which are particles of the atomic nucleus. It is not indicated after complete or microscopically incomplete resection (R1) (grade A). However, there have been no comparative trials to test superiority over photon therapy in salivary gland cancer, and

indications (primary treatment or re-irradiation) remain to be determined.

In radiosensitive tumor, classically curable with 30–45 Gy radiation, such as some lymphomas, isolated photon or proton therapy can be considered [24] (level of evidence: 4) (expert agreement). A recent National Cancer Database study of more than 4000 patients with non-metastatic major salivary gland malignant tumors reported benefit not only for locoregional control but also for survival (56 vs. 51% at 5 years) [10] (level of evidence: 4).

4.2. Radiation modalities

The gold-standard radiation technique for these tumors is IMRT (grade C). Intensity modulation refers to modulation of photon flow, notably using multi-blade collimators (dynamic covers on the beam to protect healthy tissue) and dose-rate adaptation. IMRT has replaced 3D conformal radiation (also by photons) and radiotherapy by electrons for head and neck cancer. It shows lower risk of severe toxicity than 3D radiotherapy [25–27] (level of evidence: 4), especially in complex oncologic or anatomic situations [28,29] (level of evidence: 4). In some early-stage lateralized cases, conformal radiation with 3D photon dosimetry is still an option (expert agreement). Neutrons, which are neutral nuclear particle, used from 1995 to 2005, are no longer recommended, despite good biological efficacy, due to reports of severe toxicity related to suboptimal dose distribution [19,30] (level of evidence: 4) (expert agreement). Hadrontherapy currently mainly uses charged particles – either protons, in 3 French centers, or carbon ions, notably in Italy, Germany and Austria, and possibly in France as of 2024–2025 with the ARCHADE project in Caen – and helium ions (alpha particles) in Germany since 2019. Proton therapy is an alternative to proton-based IMRT in children, adolescents and young adults. The smaller irradiated volume compared to IMRT or stereotactic radiotherapy is important for the protection of adjacent organs at risk and to limit long-term sequelae and rare radiation-induced cancer (expert agreement). Proton therapy is a useful option for tumors close to critical organs, and to limit the amount of healthy tissue exposed to radiation, however low the dose. These situations sometimes require dosimetric comparison, as photon techniques may be equivalent and are more easily accessed – indeed, they are ubiquitous in France, unlike proton therapy [31] (level of evidence: 4). Carbon ion hadrontherapy is an alternative to photon IMRT in case of radioresistant histology, unresected tumor or after macroscopically incomplete R2 resection: i.e., requiring tumor doses that are incompatible with adjacent issue conservation (expert agreement). Carbon ions can be used when the difference is considerable with the need for dose escalation in the tumor, thanks to the greater biological efficacy of carbon ions than photons or protons. Non-resectable adenoid cystic carcinoma is a particular indication for hadrontherapy, and especially for carbon ions, due to radioresistance and to perineural and skull-base extension [29,32–37] (level of evidence: 4) (expert agreement). Certain technical difficulties may, however, limit application of hadrontherapy. Laryngeal involvement and metallic material within the radiation field are strong contraindications to use of carbon ions. These difficulties also hinder planning for proton therapy, to which they may also constitute contraindications.

4.3. Target volumes

4.3.1. Prerequisites for radiotherapy planning

The preoperative cross-sectional imaging work-up is essential for determining target volumes. CT assesses intraglandular and deep tumor extension: e.g., to the infratemporal fossa or parapharyngeal spaces, tympano-meatal complex and middle ear, temporo-mandibular joint, skull base, mandibular bone and masticator muscles. Bone involvement in general, including the mandibular cortex, is better seen on CT than MRI. CT is also useful for determining lymph-node status: ultrasound would be excellent, but is non-planar and thus cannot be used for radiotherapy planning. The spatial resolution of MRI can also determine soft-tissue extension, notably for tumors of the deep lobe of parotid, and extension to nerves, and notably to the facial nerve, or bone marrow on T1-weighted sequences, with disappearance of spontaneous T1 fat hypersignal. Gadolinium-enhanced T1 with fat suppression sheds light on perineural invasion and bone or meningeal extension. Cortical bone extension is better assessed on CT. A pre-treatment panoramic dental view is necessary for dental care ahead of radiotherapy (grade A) [38].

4.3.2. Parotid gland cancer [39]

The tumor target volume at high risk of recurrence generally receives > 60–66 Gy postoperatively or 70 Gy in unresected tumor, and comprises the parotid bed and invaded structures, with a 5 mm safety margin (expert agreement). In deep-lobe tumors, the high-risk target volume should also include the poststyloid and parapharyngeal spaces, with a 5 mm craniocaudal safety margin. In case of macroscopic perineural invasion indicating nerve invasion, generally confirmed intraoperatively, the facial nerve (VII) is usually resected and the high-risk volume should at least include a 5 mm safety margin along the nerve course (expert agreement). It may be decided to extend the target volume as far as the stylomastoid foramen and its intrapetrous portion if imaging reveals invasion. In a series of 140 patients with perineural invasion in the pathology specimen, including the nerve course up to the skull base in the target volume significantly reduced the probability of skull-base tumor recurrence [40] (level of evidence: 4). The low-risk (or "prophylactic" or "preventive") volume, receiving 50 to 56 Gy depending on the protocol, includes the high-risk volume with a 5 mm isotropic margin and the poststyloid and parapharyngeal spaces (if outside the high-risk volume) and a 5 mm craniocaudal safety margin (expert agreement). In case of multiple micro- or macroscopic perineural invasion of the facial nerve, the nerve course is generally included up to the petrous bone. In case of skull-base recurrence risk factors (perineural invasion, T3–T4 category, R1 resection, deep-lobe invasion), the other cranial nerves (V3, IX, X, XI, XII) may be included in the low-risk volume up to the skull base [40–42] (level of evidence: 4) (expert agreement). In locally advanced deep-lobe tumor, the infratemporal fossa should be included in the low-risk volume. Finally, in IMRT it is classical for the first 3 mm of the skin to be "underdosed", which should be compensated for in case of cutaneous invasion in all these situations.

The target volumes are the same whatever the radiation technique.

4.3.3. Submandibular and sublingual gland cancer [39]

The target volume at high risk of recurrence includes the submandibular bed and adjacent invaded structures, with a 5 mm safety margin. In case of risk factors for skull-base recurrence (perineural invasion, T3–T4 category, R1 resection), at least the lingual and hypoglossal nerves may be included in the low-risk volume up to the skull base [40] (level of evidence: 4) as well as the ipsilateral parapharyngeal and poststyloid spaces up to the foramen ovale and hypoglossal canal. The principles described above for the parotid gland are applicable here.

4.3.4. Minor salivary gland cancer [39]

The principles described above are applicable, adapted according to tumor location.

4.3.5. Lymph-node irradiation [39]

Recommendations for lymph-node irradiation are based on the rate of occult metastases discovered on neck dissection without clinical signs of nodal involvement (cN0), nodal invasion or recurrence, and on the tumor's tendency for nodal spread, which varies significantly between pathologic types and according to grade and stage [43]. Indications for radiotherapy should be adapted according to neck dissection: radiotherapy targets the same levels (I, II, III, IV, V, external jugular level, ipsi- or bi-laterally) as the dissection, although some levels may also be dissected for the needs of the surgical approach to the tumor.

In cN0 patients, radiotherapy is somewhat controversial due to the highly variable rate of occult nodal metastasis [44–47] (level of evidence: 4). Except for low-risk tumors (low-grade T1–T2 except for secretory carcinomas and T1–T2 adenoid cystic carcinomas not invading the oral mucosa), when the primary tumor has been resected without concomitant neck dissection, with a cN0 neck on staging, ipsilateral neck dissection or ipsilateral neck irradiation may be performed [44,48,49] (level of evidence: 4), given the risk of nodal invasion and the > 10% risk of nodal recurrence (expert agreement).

Postoperatively, in patients free of nodal invasion on pathology (pN0), the neck does not require irradiation if enough non-metastatic lymph nodes are retrieved (> 18 in head and neck squamous cell carcinoma [50]) with T1/T2 and low-grade tumors [50] (expert agreement). Other situations should be discussed on a case-by-case basis. When dissection of a pN0 neck retrieves an insufficient number of lymph nodes, prophylactic radiation may be used in the levels that should have been resected. Thus the low-risk nodal volume for parotid tumor includes the non-invaded ipsilateral levels II, III and IV (± Ib and V) in case of >4 cm pN0 and/or high-grade tumor and/or of incomplete resection or recurrent tumor (expert agreement).

In case of lymph-node invasion on pathology (pN+) with a single pN1 metastatic adenopathy without extracapsular spread and localized in the first drainage levels within a dissection that retrieved a sufficient number of lymph nodes, abstention from radiotherapy can be considered on a case-by-case basis (expert agreement), by analogy with head and neck squamous cell carcinoma [51,52]. It is, however, likely that the dose delivered to the primary tumor will have included the lymphadenopathy, due to anatomical proximity. Beyond the first levels and in case of skip metastasis, lymph-node irradiation does not seem justifiable (expert agreement).

For the other pN+ patients, the high-risk volume includes the invaded nodal levels. The low-risk volume may be larger than would have been involved in neck dissection under certain conditions:

- superficial parotid lobe invasion and possible external jugular level involvement. Prophylactic-dose radiotherapy incurs no specific risk for the facial nerve, morbidity is low and indications are relatively broad;
- lymphadenopathies with extranodal spread. In IMRT, the first 3 mm of the skin is classically "underdosed" for technical and physical reasons, which should be compensated for in case of cutaneous invasion in all these situations by adding a bolus or extra dose of electrons or a specific delivery covering these first 3 millimeters (expert agreement);
- some levels at risk were not dissected. In malignant parotid tumor, level Ib should be included in case of lymphadenopathy in level IIa and level V should be included in case of lymphadenopathy in levels IIb, III or IV. Inclusion of the external jugular level and levels IV and V should be considered in case of superficial parotid lobe involvement (expert agreement);
- unilateral irradiation is the rule for major salivary glands, but prophylactic contralateral Ia-Ib-II irradiation can be considered, especially in case of 2 of the following 3 factors: multiple pN+ metastatic lymph nodes, extracapsular spread, and/or pT3–pT4 category with lymphovascular invasion (expert agreement);
- in minor salivary gland tumor, bilateral neck irradiation is recommended if neck dissection retrieved several ipsilateral metastatic nodes, the above risk factors apply and/or tumor extends beyond the midline (expert agreement).

4.3.6. Organs at risk and side effects

Early side effects are ipsilateral: local, cutaneous and mucosal (frequent, acute, transient, with mucositis, dysgueusia and dysphagia), and auditory (otitis media with effusion). In the long term, residual xerostomia (initially involved salivary gland and minor salivary glands of the oral cavity) and, in rare cases, osteoradionecrosis and secondary cancers were reported [6]. Hearing loss (inner ear) and trismus (masseter) are also possible. These late side effects can be limited with IMRT [53] (level of evidence: 2): dose limits for the relevant organs should be taken into account in planning the radiotherapy. However, these effects are highly dependent on tumor location and are not always avoidable.

5. Conclusion

Radiotherapy for malignant salivary gland tumors is reserved to cases with adverse postoperative histoprognostic factors and inoperable tumors. IMRT to the primary tumor site ± to the lymph nodes is the gold-standard attitude. In non-resectable malignant salivary gland tumors or inoperable patients, carbon ion hadrontherapy may be considered in radioresistant cases.

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.2023.11.006.

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