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Clinical practice guidelines

Radiotherapy of salivary gland tumours

Radiothérapie des tumeurs des glandes salivaires

A. Larnaudie[a,b], P.-Y. Marcy[c], N. Delaby[d], V. Costes Martineau[e,f], I. Troussier[g], R.-J. Bensadoun[f,g], S. Vergez[f,h], S. Servagi Vernat[i], J. Thariat[a,j,f,k,*]

[a] *Département de radiothérapie, centre François-Baclesse, 3, avenue General-Harris, 14000 Caen, France*
[b] *Service de radiothérapie, CHU de Dupuytren, 2, avenue Martin-Luther-King, 87000 Limoges, France*
[c] *Radiodiagnostic et radiologie interventionnelle, polyclinique Elsan, 332, avenue Frédéric-Mistral, 83190 Ollioules, France*
[d] *Unité de physique médicale, centre Eugène-Marquis, 35000 Rennes cedex, France*
[e] *Service d'anatomie pathologique, CHU de Montpellier, 34000 Montpellier, France*
[f] *Réseau d'expertise français sur les cancers ORL rares (Refcor), 94800 Villejuif, France*
[g] *Service de radiothérapie, centre de haute énergie, 06000 Nice, France*
[h] *Service d'ORL et chirurgie cervicofaciale, CHU de Toulouse/oncopôle, 31000 Toulouse, France*
[i] *Institut privé de radiothérapie, clinique Claude-Bernard, 97, rue Claude-Bernard, 57070 Metz, France*
[j] *Normandie université, 14000 Caen, France*
[k] *Groupe d'oncologie radiothérapie des cancers de la tête et du cou (Gortec), 37000 Tours, France*

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ABSTRACT

Primary tumours of the salivary glands account for about 5 to 10% of tumours of the head and neck. These tumours represent a multitude of situations and histologies, where surgery is the mainstay of treatment and radiotherapy is frequently needed for malignant tumours (in case of stage T3–T4, nodal involvement, extraparotid invasion, positive or close resection margins, histological high-grade tumour, lymphovascular or perineural invasion, bone involvement postoperatively, or unresectable tumours). The diagnosis relies on anatomic and functional MRI and ultrasound-guided fine-needle aspiration for the diagnostic of benign or malignant tumors. In addition to patient characteristics, the determination of primary and nodal target volumes depends on tumor extensions and stage, histology and grade. Therefore, radiotherapy of salivary gland tumors requires a certain degree of personalization, which has been codified in the recommendations of the French multidisciplinary network of expertise for rare ENT cancers (Refcor) and may justify a specialised multidisciplinary discussion. Although radiotherapy is usually recommended for malignant tumours only, recurrent pleomorphic adenomas may sometimes require radiotherapy based on multidisciplinary discussion. An update of indications and recommendations for radiotherapy for salivary gland tumours in terms of techniques, doses, target volumes and dose constraints to organs at risk of the French society for radiotherapy and oncology (SFRO) was reported in this article.

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RÉSUMÉ

Les tumeurs primitives des glandes salivaires représentent environ 5 à 10 % des tumeurs de la tête et du cou. Elles représentent une multitude de situations et de types histologiques dont l'histoire clinique est différente, et le traitement repose sur la chirurgie et assez souvent la radiothérapie (en cas de stade T3–T4, d'atteinte ganglionnaire, d'envahissement extraparotidien, d'atteinte des tranches de section, de haut grade, d'envahissement lymphovasculaire, périnerveux, ou osseux, ou en cas de tumeur non résécable). La séquence diagnostique d'imagerie comporte une IRM avec des séquences morphologique et fonctionnelle, puis une cytoponction échoguidée, notamment pour le diagnostic de malignité. La détermination des volumes cibles primitifs et ganglionnaires dépend des extensions et du stade, de l'histologie et du grade des

* Corresponding author.
E-mail address: jthariat@gmail.com (J. Thariat).

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tumeurs malignes des glandes salivaires. Cette prise en charge comporte un certain degré de personnalisation qui a été codifié dans les recommandations du Réseau multidisciplinaire d'expertise français des cancers ORL rares (Refcor) et peut justifier un avis en réunion de concertation pluridisciplinaire spécialisé. Dans certains cas d'adénomes pléomorphes récidivants et bien qu'il s'agisse de tumeurs bénignes, une radiothérapie peut être discutée dans le cadre d'une réunion de concertation pluridisciplinaire. Une mise à jour des recommandations de la Société française de radiothérapie oncologique (SFRO) sur les indications et les modalités techniques de radiothérapie des tumeurs des glandes salivaires en termes de fractionnement, délinéation des volumes cibles et organes à risque est présentée dans ce chapitre.

1. Introduction

1.1. Epidemiology and risk factors

Primary salivary gland tumours account for about 5 to 10% of head and neck tumours. The major salivary glands, include the parotids and the submandibular and sublingual glands. The minor salivary glands are distributed in the mucosae of the upper aerodigestive tract in the palate, floor of the mouth, base of the tongue, retromolar trigones, the peritonsillar region, the walls of the pharynx, the larynx, the trachea, and facial sinuses.

1.1.1. Malignant tumours

Parotid glands account for 80% of primary malignant tumours in the salivary glands while 10% are located in the submandibular glands. There are over 20 histological types. Some types have only been recently classified such as secretory carcinomas (MASC). The risk factors for these various tumours are not widely known. Secondary malignant tumours (usually corresponding to nodal metastases from skin or mucosalsquamous cell carcinomas) are possible, especially in the parotid gland and most commonly involving squamous cell tumours and lymphatic metastases from facial skin carcinomas. Other histological types are also possible.

1.1.2. Benign tumours

Some benign tumours of the salivary glands are recurrent, typically pleomorphic adenoma and can also require radiotherapy.

1.2. Anatomical review, drainage and pathways of extension

1.2.1. Pathways of tumour extension

For parotid tumours, the thin fascia that separates the deep lobe of the parapharyngeal space is a pathway to tumour extension from the deep lobe toward the posterolateral para-pharyngeal space, the oropharynx (soft palate, tonsillar fossa) and nasopharynx [1]. Similarly, an area of weakness exists in the direction of the external auditory canal opposite the cartilages of the concha and tragus. The retrostyloid space which contains the internal carotid artery, cranial nerves IX, X, XI, XII, the internal jugular vein, and sympathetic nerve plexus, is a pathway of vertical disseminationtoward the base of the skull and the deep spaces of the neck. The pterygomaxillary space, the middle part of the masticator space, containing the mandibular nerve (V3), is an area of dissemination toward the base of the skull via cranial nerve V3. Neurotropic tumours preferentially invade the facial nerve (VII), the pathway of extension to the base of the skull [2]. The mandibular nerve and the nerves of the periparotid spaces can be other pathways of extension. The masseter prolongation of the parotid gland follows Stenson's duct and can act as an anterior pathway of extension.

Arterial vascularisation of the parotid gland is supplied by branches of the external carotid artery: the posterior auricular artery, the superficial temporal and internal maxillary arteries [3]. Its venous plexuses drain into the internal jugular vein. Vascularisation of the submandibular gland is via the facial artery, a branch of the external carotid artery and the facial vein which gives way to the thyro-linguofacial trunk with the thyroid vein and lingual vein, and ends with the internal jugular vein. The sublingual gland is vascularised by the sublingual artery and submental artery, which stem from the lingual artery and facial artery, respectively.

1.2.2. Pathways of nodal extension

Preferential lymphatic drainage sites of primary malignant tumours of the salivary glands vary according to the gland affected [4], the site (median or lateral) and aggressive nature of the cancer (estimated using a range of factors: histology, grade, T stage, lymphovascular and perineural invasion, etc.). In the parotid gland, the preferential areas invaded are levels IIa-b, and then Ib, III and IV, and then V. The parotid gland is the only major salivary gland with lymphatic structures within its normal tissue. The main lymphatic drainage of the parotid gland passes through area VIII, which comprises superficial and deep parotid nodes (preauricular, intraparotid and subparotid) that drain into the deep jugular nodal chain (IIa, III, IV). Drainage in the inferior parotid gland occurs via the superficial cervical nodal chain, which follows the external jugular vein, and is a more accessory pathway of dissemination. The parotid gland is also a preferential area of drainage for skin in the head and neck area and can sometimes be a site of aberrant drainage in ear nose or throat (ENT) cancers.

1.3. Prognostic classification

The Tumour Node Metastasis (TNM) classification of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) is the most widely used classification to guide treatment decisions. However, it should be used in conjunction with the World Health Organisation (WHO) histological classification which combines low grade, intermediate grade or high grade malignant tumours. Therefore, in comparison to a low-grade tumour, an intermediate-grade tumour tends to recur more frequently and produce nodal metastases in over 10% of cases. New and very rare entities have been described in relation to which the lymphophilia, response to irradiation and prognosis are currently uncertain. These cases should be discussed at a regional or national multidisciplinary panel of experts belonging to the French network of rare head and neck tumours (Refcor) [5,6].

2. Management

The specialised and personalised management of such cases should be based on the 2008 recommendations, which currently are being updated for 2021, in national, twice-monthly multidisciplinary panels of Refcor, which are part of the French system of regional expert centres. Tables 1 and 2 present a summary of the

Table 1
Summary of treatment indications for salivary gland tumours.

Histology	Indications
Carcinomas and benign tumours of the major and minor salivary glands	Surgery: if tumour stage T1 to T4a No postoperative radiotherapy if: benign tumour, resection R0; malignant tumour stage T1–T2 low grade, resection R0 without perineural invasion Postoperative radiotherapy: adenoid cystic adenoid carcinoma whatever the grade; in presence of prognostic factors: high grade; R1 resection; T3–T4; nodal involvement; lymphovascular or perineural invasion; to be discussed in case of an intermediate grade with no other prognostic factor; to be discussed in case of a recurrent benign tumour, more than 5 cm in size or carrying a high risk for the facial nerve or R1 resection Option if not resectable: radiotherapy, in particular, for stage T4b or other inoperable tumours; concomitant chemotherapy with radiotherapy in the setting of a clinical trial
Lymphomas	Chemotherapy: postchemotherapy radiotherapy is possible in case of response or relapsed or refractory disease Option: radiotherapy with or without chemotherapy in localised forms

main indications, as well as the classifications used in salivary gland tumours.

2.1. Diagnostic assessment

A clinical examination of the face and neck, as well as the upper aerodigestive tract is performed in case of a suspected salivary gland tumour. These tumours are often diagnosed after the discovery of a painless mass. The clinical examination should measure the lesion and evaluate its locoregional extension and signs of malignancy (facial paralysis, neck adenopathy, the fixed aspect of the tumour, trismus, skin permeation, etc.) associated with any locoregional extension.

For malignant tumours of the minor salivary glands (especially in the pharynx and larynx), this examination is supplemented by an endocavity examination, possibly under general anaesthesia. An ultrasound examination of the neck region can be useful, as well as a preliminary examination for assessment; however, this technique is highly operator-specific and cannot be used for radiotherapy planning. The diagnostic sequence is based on MRI (option : CT) and ultrasound-guided fine-needle aspiration (FNA, i.e. cytology). AFNA is a worthwhile option to guide the diagnosis; however, the results are highly operator-specific. FNA should be performed after MRI to avoid altering the result of diffusion sequences, perfusion curves and signal analysis in T1-weighted images (T1 hypersignal due to bleeding at the needle puncture site) and in T2-weighted sequences. MRI with functional sequences (T1-, T2-weighted image analysis, diffusion and calculation of apparent diffusion coefficient [ADC], analysis of the diffusion curve) is a discriminating test for diagnosing malignancy. Apart from tissue characterisation, it assesses local and neurotropic extension. MRI, due to its excellent spatial resolution and soft-tissue contrast, will highlight extension to soft tissues, especially in tumours affecting the deep lobe of the parotid gland, in particular, on the facial nerve (location of a tumour nodule in relation to the parotid venous plane, pushing back and/or invasion of the fat in the parapharyngeal space, in T1-weighted images) or in the bone marrow (disappearance of a spontaneous T1-weighted hypersignal of the fat in T1-weighted sequences, without fatty saturation). A T1 sequence after injection of gadolinium and suppression of the fat allows an analysis of perineural infiltration, and bony or meningeal extensions.

Surgery should always be preceded by serial imaging; including an MRI (tissue characterisation, local and neurotropic extension) and, in infiltrating locally advanced tumours, a CT-scan should be performed to identify any invasion of the cortical bone or widening of the foramina of the base of the skull. In this case, a CT-scan of the ENT region and neck should be performed with injection of iodinated contrast medium to assess intraglandular and deep tumour extension, in the subtemporal fossa or the parapharyngeal spaces of the tympanomeatal complex and in the middle ear, the temporo-mandibular joint, the base of the skull (the foramen ovale (V-3), foramen rotundum (V-2), the nerve of the vidian canal (vidian nerve), the pterygo-palatine fossa (sphenopalatine node), the orbital fissures), the mandibular bone (inferior alveolar nerve canal V-3) and the masticator muscles (medial, lateral pterygoid, masseter, temporal muscles). It can also be used to assesses nodal invasion.

A chest CT-scan is performed to assess haematogenic extension to the lung.

A PET-CT-scan is a useful tool for assessing any extension of high-grade tumours (high standard uptake value [SUV] in lymph nodes of normal size), but is also a preferred examination for evaluating extension to the retropharyngeal nodes.

This imaging workup is important before surgery and to clarify the target volumes for irradiation.

2.2. Surgery

For carcinomas and especially the most radioresistant cases such as sarcomas, surgery is the standard treatment of malignant tumours in the salivary glands (with the exception of T4b tumours). However, a non-surgical treatment is the most common option for lymphomas. For malignant parotid tumours, surgery consists of total parotidectomy, with preservation of the facial nerve in the absence of gross involvement. Indications for lymph node dissection depend on clinical nodal status, histological type, grade, stage and lateralisation of the tumour.

A diagnostic review by RefcorPath (expert pathologists) is indicated whenever the pathology diagnosis does not correspond to the clinical findings, if the progression of the lesion is not consistent with the pathology diagnosis, if the pathology report does not include all elements required for the management of the case or when the pathology diagnosis is included in the following list (systematic review): undifferentiated, poorly differentiated or “round cell” tumours (other than lymphomas) including neuroendocrine carcinomas and adenoid cystic carcinomas, adenocarcinomas with no other indication, sarcomas and soft tissue tumours with intermediate malignancy. In fact, the diagnosis plays a decisive role in terms of the locoregional stage and choice of radiotherapy target volumes [5,6].

2.3. Radiotherapy

Intensity-modulation radiotherapy (IMRT) alone is indicated for curative purposes for unresectable malignant tumours and for radiosensitive histologies, such as lymphomas.

For malignant parotid tumours, IMRT is indicated postoperatively in the presence of unfavourable histologic-prognostic factors: stages T3–T4, nodal invasion, extra-parotid invasion, positive or close resection margins, histological high-grade tumour, lymphovascular or perineural invasion, bone involvement, indicating a high risk (> 10%) of locoregional recurrence, either at the

Table 2
Classifications used for salivary gland tumours.

TNM classification of the Union for International Cancer Control (UICC) 2017	
Tumours of the major salivary glands (parotid, submandibular or sublingual glands)	
Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour 2 cm or smaller in greatest dimension without extraparenchymal extension[a]
T2	Tumour larger than 2 cm but not larger than 4 cm without extraparenchymal extension[a]
T3	Tumour larger than 4 cm or tumour having extraparenchymal extension[a]
T4a	Moderately advanced disease Tumour invades skin, mandible, ear canal, and/or facial nerve
T4b	Very advanced disease Tumour invades skull base and/or pterygoid plates and/or encases carotid artery
Regional lymph nodes–clinical (cN)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE (-)
N2a	Metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE (-)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE (-)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE (-)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE (-)
N3b	Metastasis in any node(s) with clinically overt ENE (+)
WHO classification of 2017	
Malignant tumours	Acinic cell carcinoma, secretory carcinoma, mucoepidermoid carcinoma, Adenoid cystic carcinoma, polymorphous adenocarcinoma, epithelial-myoepithelial carcinoma, clear cell carcinoma, basal cell adenocarcinoma, sebaceous adenocarcinoma, intraductal carcinoma, cystadenocarcinoma, Adenocarcinoma NOS, salivary duct carcinoma, myoepithelial carcinoma, carcinoma ex pleomorphic adenoma, carcinosarcoma, poorly differentiated carcinoma (neuroendocrine and non-neuroendocrine, undifferentiated carcinoma, large cell neuroendocrine carcinoma, small cell neuroendocrine carcinoma), lymphoepithelial carcinoma, squamous cell carcinoma, oncocytic carcinoma
Borderline tumours	Sialoblastoma
Benign tumours	Pleomorphic adenoma, myoepithelioma, basal cell adenoma, Whartin tumour, oncocytoma, lymphadenoma, cystadenoma, sialadenoma papilliferum, ductal papilloma, sebaceous adenoma, canalicular adenoma and other ductal adenoma
Other epithelial lesions	Sclerosing polycystic adenosis, nodular oncocytic hyperplasia, lymphoepithelial lesions, intercalated duct hyperplasia
Soft tissue benign lesion	haemangioma, lipoma/sialolipoma, nodular fasciitis
Haematolymphoid tumours	Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT)

[a] Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.

tumour primary site or in a drainage lymph node (only one of these criteria is sufficient) [7]. Postoperative radiotherapy is not indicated for stages I and II low-grade tumours, or for fully resected tumours with no other unfavourable histologic-prognostic factors. Radiotherapy should always be discussed for adenoid cystic carcinomas in the absence of unfavourable histologic-prognostic factors. In intermediate-grade cases, for other carcinomas, radiotherapy should be discussed at a specialised multidisciplinary panel taking other unfavourable elements into consideration.

The treatment of recurrent pleomorphic adenomas (the diagnosis is assisted by high frequency ultrasound and ultrasound-guided fine-needle biopsy in the area of surgical excision), which are benign tumours, is surgery. Postoperative radiotherapy can be discussed in recurrent tumours larger than 5 cm, or involving an important risk for the facial nerve or if the resection margins are incomplete, as well as in a context of an unresectable tumour [8–11]. Radiotherapy options should be evaluated more formally at a multidisciplinary panel given the benign nature of such lesions and the risk of a radiation-induced secondary cancer.

2.4. Concomitant chemotherapy

Due to the absence of randomised studies, the use of concomitant chemotherapy is controversial for salivary gland tumours with some studies suggesting a deleterious effect of chemotherapy [12]. Thus, concomitant chemotherapy should be recommended as part of a therapeutic trial (in France, the Santal phase III trial being conducted by Gortec [head and neck oncology and radiotherapy group] and Refcor).

3. Radiotherapy

3.1. Dose and fractionation

When radiotherapy alone is administered to non-operated malignant tumours in the salivary glands (except lymphomas), the dose to be delivered is equivalent to 70 Gy in the tumour and the nodes involved. In nodal areas not affected, a 50 Gy-equivalent prophylactic dose is recommended. For postoperative radiotherapy, doses are equivalent to 50 Gy* via a simultaneous integrated boost (SIB) for irradiation (identical to stage N0 neck tumour), equivalent to 60 Gy in areas at intermediate risk (e.g. doubtful R0 resection) and equivalent to 66 Gy in case of R1 resection, or equivalent to 70 Gy for R2 resection R2 [13,14].

In the specific case of recurrent, non-transformed pleomorphic adenomas, the dose is approximately 50 to 60 Gy, at 2 Gy per fraction, five days a week. The dose can be higher when macroscopic volume remains.

For lymphomas, the curative dose is lower, approximately 30 to 45 Gy, depending on the histology and response if initial chemotherapy.

Table 3
Summary of recommendations for salivary gland tumour radiotherapy.

Indications	Target volume/total dose/fractions	Recommended techniques	Possible or acceptable techniques
Irradiation alone of parotid gland or other salivary gland cancers	Volumes: CTV $_{P1}$: primary GTV T + 5 mm; CTV $_{P2}$: 5 mm beyond CTV $_{P1}$ and including the entire compartment + taking into account the pathways of dissemination and anatomical barriers and histologic-molecular characteristics (in case of a parotid deep lobe compartment and midline extensions); CTV $_{N\_high\ risk}$: if clinical adenopathies; CTV $_{N\_low\ risk}$: homolateral nodal areas N0 (II, III, IV; and Ib in case of para-pharyngeal involvement or involvement in II, external jugular area and V in case of involvement of the superficial lobe or the nodal areas in proximity). Contralateral areas if tumour crosses the midline or multiple adenopathies); CTV-PTV 3–5 mm margin Doses: traditional fractionation with integrated boost with 2 Gy/f: CTV $_{P2}$: 52.8–56 Gy, CTV $_{P1}$ 70 Gy ± CTV with intermediate risk with 63 Gy; CTV $_{N\_high\ risk}$ 52.8–56 Gy if N0 and 0 Gy if cN+	IMRT (fixed beam [5 to 7 beams]) or arc therapy with IGRT at least weekly Proton therapy if benefit is estimated in terms of toxicity (NCCN 2020) or local control Carbon ions in sole treatment in setting of clinical trials for adenoid cystic carcinomas	
Postoperative irradiation of parotid gland tumours	Volumes: CTV $_{P1}$: tumour bed, parotid compartment (or preoperative GTV + 5 mm); CTV $_{P2}$: 5 mm beyond CTV $_{P1}$ taking into account pathways of diffusion and anatomical barriers and histo-molecular characteristics; CTV $_{N\_high\ risk}$: if pN+ with extranodal extension; CTV $_{N\_low\ risk}$: homolateral nodal areas (II, III, IV if N0) (Ib if para-pharyngeal involvement or involvement of II, external jugular area and V in case of involvement of the superficial lobe or the nodal areas in proximity) the contralateral areas in case of a tumour which has crossed the midline or multiple adenopathies); irradiation which can be omitted if ≥ 15 pN0; CTV-PTV margin 3–5 mm\ Doses: traditional fractionation with integrated boost 2 Gy/fraction: CTV $_{P2}$: 50–54 Gy in R0 tumour bed; CTV $_{P1\ 60}$ to 66 Gy if R1 or high risk; CTV $_{N\_low\ risk}$ 50–54 Gy if pN0 and 60 Gy if pN+, 66 Gy if pN+ with extranodal extension	IMRT (fixed beam [5 to 7 beams]) or arc therapy with IGRT at least weekly Proton therapy if benefit is estimated in terms of toxicity (NCCN 2020) or local control	IGRT at least daily 2-D ± 3-D
Postoperative external irradiation of submaxillary or sublingual gland cancers (and by extension, sample principles for the minor salivary glands)	Volumes: CTV $_{T}$: tumour bed, glandular compartment; CTV $_{N\_high\ risk}$: if pN+ with extranodal extension; CTV $_{N\_low\ risk}$: homolateral nodes (I, II, III, if N0) (contralateral areas if tumour has crossed the midline); CTV-PTV margin 3–5 mm Doses: traditional fractionation with integrated boost with 2 Gy/fraction: CTV $_{P2}$: 50–54 Gy to the tumour bed; CTV $_{P1}$ 60 to 66 Gy if R1 or high risk, CTV $_{N\_}$ 50–54 Gy if pN0 (or omission if complete nodal dissection ≥ 15 pN0) and 60 Gy if pN+, 66 Gy with extranodal extension		

GTV: gross tumour volume; CTV: clinical target volume; PTV: planning target volume; IGRT: image-guided radiotherapy; T: tumour; NCCN: National Comprehensive Cancer Network; cN+: clinical nodal involvement; pN+: histopathological nodal involvement.

Table 3 summarises the recommendations. The dose prescription can be:

- radiotherapy alone (planning target volume [PTV]):
  - PTV $_{T\ and\ N+}$: 70 Gy, 2 Gy per fraction,
  - PTV $_{prophylactic\ N}$: 50 Gy (56 Gy by SIB-IMRT in 1.6 Gy-fractions), 2 Gy per fraction;
- postoperative radiotherapy:
  - PTV $_{T:}$ 50 Gy with wide complete resection (margin > 5 mm) or 60 Gy in case of doubt in terms of quality of the resection, per fraction,
  - PTV $_{T\ R1}$: 66 Gy, 2 Gy per fraction,
  - PTV $_{N\ CR+}$: 66 Gy, 2 Gy per fraction,
  - PTV $_{prophylactic\ N}$: 50 Gy (52.8 Gy by SIB-IMRT in 1.6 Gy-fractions), 2 Gy per fraction.

3.2. Preparation: oral/dental care

The oral/dental check-up and care is similar to the one required for upper aerodigestive tract cancer and includes a dental panoramic X-ray (see general article [37]). However, due to some of special features involved in the radiotherapy of salivary gland tumours this assessment requires adjustment. In the case of unilateral irradiation, the dose received in the contralateral salivary gland may be minimal (less than 5 Gy), which means that dental extractions can be limited in cooperation with the radiation oncologist and stomatologist/dentist.

3.3. Position and preparation for the planning CT-scan

Patients should be installed in a supine position, with their arms alongside their body and their head in a hyperextended position supported by a foam-covered wedge, adjusted to the curve of the neck. The shoulders of patients should be placed in lower position. A five-point personalised thermoformed immobilisation system should be produced. A simulation CT-scan of the neck with injection of contrast medium, if possible, in two phases (60 mL of contrast medium with 1 mL/s and then after 3 min 50 mL of contrast medium with 1.5 mL/s with start-up of the CT-scanner at the end of the second injection) then with slices of 3 mm in thickness or less, from the apex of the skull to the tracheal bifurcation. MRI and PET-scans should ideally be performed in the irradiation position and then repositioned (image coregistration) with the simulation CT-scan, particularly in the presence of a dental artefact in order to assist the delineation of tumour volumes.

3.4. Delineation of target volumes

Apart from cases involving a median tumour or tumour overlapping the midline, irradiation to the primary site and drainage of nodal areas is unilateral.

3.4.1. Radiotherapy alone

3.4.1.1. Primary tumour target volume. If radiotherapy alone, the high-risk clinical target volume CTV-P1 comprises the gross tumour volume ($GTV_{T)}$ (the entire affected gland unless justified otherwise) and a margin of 5 mm. Neurotropic invasion, if applicable, as seen on the MRI imaging should be included. The low-risk clinical target volume CTV-P2 comprises the CTV-P1, the entire glandular compartment and extends into the diffusion space up to the anatomical barriers and should include the entire area of microscopic infiltration [15]. These CTVs should take into account the pathways of dissemination specific to each type of gland [16]. In cases of perineural invasion of the proximal nerve branches (lingual nerve and chord of the tympanic membrane, V-2 nerve and foramen rotundum, nerve V-3 and foramen ovale, vidian nerve and vidian duct), irradiation should extend beyond the inclusion of the macroscopic invasion of the nerve observed on the imaging with CTV-P1 and extend to the base of the skull; if small intra-glandular nerve branches are invaded, such irradiation is not required. For adenoid cystic carcinomas, perineural invasion is implicit (intrinsically with histology), the pathway of potentially invaded nerves in the glandular compartment up to the base of the skull may be discussed.

3.4.1.2. Nodal target volume. For malignant tumours in the parotid gland, apart from adenoid cystic carcinomas, it is recommended irradiating the ipsilateral nodal areas II, III, IV of neck cN0 (after MRI or CT-scan with injection of contrast medium) for stages T3-4 tumours or intermediate to high-grade tumours. Irradiation of area Ib can be discussed if parapharyngeal involvement. Irradiation of area V and the external jugular site can be discussed if the superficial lobe of the parotid gland is affected. Prophylactic nodal irardiation may be considered if there is a > 10% risk of extension or relapse rate in a given area [17]).

For submandibular or sublingual stage cN0 and intermediate or high-grade tumours and in the absence of lymph node dissection, irradiation of areas I–IV is recommended. The area of the facial pedicle should also be included in case of a high risk of nodal disease or massive nodal involvement (more than two nodes, extranodal extension (ENE) or massive perineural invasion or emboli).

3.4.1.3. Specific points for submandibular gland tumours. Although the indications for irradiation are similar to those of the parotid gland, nodal involvement is more common and should encourage the clinician to administer prophylactic irradiation at least to areas Ib-II-III (up to 44% of cases) [16,18].

3.4.1.4. Specific points for minor salivary gland tumours. Minor salivary gland tumours can cross the midline, and in this case, irradiation of the neck lymph node areas is bilateral.

3.4.2. Postoperative radiotherapy

3.4.2.1. Primary target volume. High-risk volumes (CTV-P1) correspond to the gland compartment (surgical bed) and a margin of 5 mm, or 10 mm along the nerve in case of confirmed neurotrophic involvement or in the absence of an anatomical barrier, for example, in case of bone involvement. For malignant parotid tumours, the CTV-P1 corresponds to the parotid compartment and to medial extensions added to it in the case of deep lobe tumours. Volumes at low risk (CTV-P2) include at least CTV-P1 with an additional margin of 5 mm and diffusion spaces. In case of confirmed neurotropic involvement of the facial nerve, its inclusion up to the internal acoustic meatus should be discussed.

The nodal CTV consists of the nodal areas invaded (if pN+). The nodal areas may not require irradiation if the nodal dissection covered areas Ib-IV and when there are up to ≥ 15 normal nodes. In other cases, the prophylactic CTV_N corresponds to the ipsilateral neck nodal areas II, III and IV (with or without Ib in case of parapharyngeal involvement and of cranial nerve V and external jugular vein area in case of involvement of the superficial lobe) in patients with a tumour larger than 4 cm, classified as N0, high grade, with incomplete resection or recurrent tumours [19]. Area Ib should also be included if adenopathy in area IIa; area V should be included if adenopathy in areas IIb, III or IV. Contralateral areas are not included except if the tumour has crossed the midline or in case of multiple adenopathies [20–22]. Inclusion in the CTV of the external jugular area and areas IV and, in particular, V should be discussed if involvement of the superficial lobe due to the rate of invasion or relapse is greater than 10% [17]). For submandibular or sublingual involvement (plus lymphophilia and even more so if bilateral), areas Ib and then Ia (sublingual) and II and then III–IV–V should be included in the CTV [18].

Irradiation can be discussed if perineural invasion (an analysis of the T1-weighted MRI sequence after injection of gadolinium is imperative along with fat saturation in the plane of the nerve incriminated, an analysis of the foramina of the base of the skull with a bony window in a CT-scan) involving a higher risk of nodal invasion, if neck dissection is insufficient.

3.4.2.2. Planning target volume (PTV) exclusively and postoperatively. A 5-mm margin usually is added to the CTV to obtain the PTV. It is patient-specific and will depend on the type of immobilisation used, the radiotherapy equipment and whether or not image-guided radiotherapy (IGRT) is available.

For recurrent pleomorphic adenomas, the clinical target volume corresponds to the parotidectomy compartment (and often multifocal extensions of teh primary around the salivary gland bed). There is no indication for the treatment of nodal areas.

3.5. Organs at risk

Early side effects are local, involving the skin and mucosa (and may be frequent, acute or transient). Late-onset side effects include ipsilateral acoustic disorders, cutaneous sclerosis, trismus, xerostomy and osteoradionecrosis [17]. These late-onset side effects can be reduced by IMRT, but are related to tumour location and cannot always be avoided. The main organs at risk are to be delineated according to international recommendations [23], as described in Table 4; however, not all individual glandular structures are described.

4. Irradiation techniques

The standard irradiation technique for these tumours is intensity modulated radiotherapy (IMRT). IMRT has replaced 3D conformal irradiation by photon therapy, and sometimes electrons, in cancers of the aerodigestive tract and also cancers of the salivary glands. IMRT reduces the risk of severe toxicity, especially in complex oncological or anatomical situations. In some lateralised and early-stage cases, conformal irradiation with 3D planning via photon therapy still remains an option [24].

Proton therapy (a type of particle therapy) can be an alternative to photon-based IMRT in radiotherapy alone, especially in children, adolescents and young adults, where toxicity can be reduced with proton therapy compared to IMRT (National Comprehensive Cancer Network [NCCN], 2020). In such cases, the smaller volumes irradiated (especially at low doses) with proton therapy can limit the risk of sequelae or radiation-induced cancer. Proton therapy is a useful option for tumours located near critical organs when the dose differential (tumoricidal dose in the tumour-level of tolerability of normal tissue) is clinically significant . This is a possible option due to the physical superiority of protons compared to photons (no exit dose). These cases sometimes require dosimetric comparisons as

Table 4
Radiotherapy of salivary gland tumours: dose constraints in organs at risk.

Organs at risk	D2%	Mean dose	Other dose of interest
Oral cavity (including the accessory salivary glands)		< 35 Gy	Not specifically documented for the accessory glands of the moveable tongue, hard palate, palate and cheeks
Spinal cord/medullary canal	< 50 Gy		
Brain stem	< 54 Gy		
Parotid		< 26 Gy	At least 1 = V_{26} < 50%
Submandibular gland		< 39 Gy	
Temporomandibular joints	< 50 Gy		
Mandible	< 65 Gy	< 60 Gy	V70 < 1 cm^3
Larynx	< 63–66 Gy	40–45 Gy	$D50_{\%}$ < 30 Gy
Inner ear	< 60 Gy		
Cochlea	< 54 Gy	≤ 40–45 Gy ≤ 35 Gy if conservation of hearing is essential	
Brachial plexus	< 60 Gy		
Constrictor of the pharynx	< 60 Gy	37 Gy	

V*x*: volume receiving *x* Gy; D*x*%: dose in *x*% volume. The following values have been established for fractionations of 1.8 to 2 Gy per fraction. Delineation recommendations: see section 3.4.

some photon techniques (IMRT or stereotactic radiotherapy) may be equivalent and are readily accessible. Particle therapy with carbon ions is an option for unresectable tumours or macroscopic residual volumes [25]; however, this option is only available in France as part of a therapeutic trial for adenoid cystic carcinoma or sarcomas. Noteworthy, certain technical constraints can be a limiting factor for particle therapy: laryngeal involvement and existence of metallic materials in the fields of irradiation are currently major contraindications to carbon ions and relative contraindications for proton therapy planning.

5. Positioning control

Patient and isocentre positioning are checked by on-board imaging (orthogonal views by low energy on-board imaging (OBI) (kV/kV) or cone-beam tomography (CBCT)) during the first three days and then at least weekly or more regularly depending on the likelihood of the tumour volume changing during radiotherapy [26].

6. Objectives and dose constraints

Dose constraints are listed in Table 4, other data are clarified in a dedicated article in this issue on constraints [27]. Published reports may differ especially in relation to benefit-risk compromise which varies according to each clinical situation [23,28–35].

7. Follow-up

Clinical follow-up is performed by different practitioners who have treated the patient such as the ENT surgeon, the radiation oncologist and medical oncologist, in alternating order. More regular follow-up is required during the first two years with clinical examinations every two to three months, and then every six months from year 3 to year 5. After 5 years, follow-up at least once a year is recommended. Such follow-up can be adapted to risk of recurrence depending on tumour grade and histologic–prognostic factors (initial nodal involvement, perineural and extraparenchymal extension).

The primary objectives are early diagnosis of local and locoregional recurrence to provide curative treatment, where possible, and monitor for any late-onset side effects of radiotherapy. An annual CT-scan with thoracic sections is used to screen for pulmonary metastases. An MRI of the neck region can be discussed in the presence of signs of recurrence, but also at more regular intervals during the first three years [36].

8. Conclusion

Indications for salivary gland radiotherapy take into account the histologic and prognostic characteristics common to squamous cell carcinomas of the upper aerodigestive tract, but also the histological subtype and grade. Target volumes should be adapted to any specific extensions based on the salivary gland affected and duly documented by multimodal imaging sections performed prior to surgery. Cases can be discussed at regional or national multidisciplinary panels of experts.

Authors contributions

J. Thariat: conceptualization, data curation, formal analysis, methodology, project administration, software, supervision, validation, visualization, writing – original draft, manuscript review and editing; R.-J. Bensadoun: conceptualization, data curation, formal analysis, validation, visualization, writing – original draft, manuscript review and editing; I. Troussier: data curation, validation, writing – original draft, manuscript review and editing; A. Larnaudie: project administration, validation, resources (illustrations), visualization, writing – original draft, manuscript review and editing; V. Costes-Martineau:, validation, writing – original draft, manuscript review and editing; N. Delaby: validation, writing – original draft, manuscript review and editing; P.-Y. Marcy: validation, resources (illustrations), manuscript review and editing; S. Servagi Vernat: validation, visualization; S. Vergez: validation, visualization, writing – original draft, manuscript review and editing.

Disclosure of interest

V. Costes-Martineau: declared having no relationship/activity/interest; R.-J. Bensadoun, N. Delaby, A. Larnaudie, P.-Y. Marcy, S. Servagi Vernat, J. Thariat, I. Troussier: did not disclose relationships/activities/interests; S. Vergez: BMS, MedTronic (honoraria for presentations).

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Appendix A. Web links

SFRO: https://www.sfro.fr/.
Refcor: http://refcor.org/.
Gortec: https://www.gortec.net/index.php/fr/.
NCCN: https://www.nccn.org/professionals/physician_gls/default.aspx.
TNM/UICC classification: https://www.uicc.org/resources/tnm.
Digital RecoRad™ tool: www.sfro-recorad.fr.

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