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Clinical practice guidelines

Management and work-up procedures of patients with head and neck malignancies treated by radiation

Prise en charge et procédure de préparation des patients atteints d'un cancer de la tête et du cou traité par irradiation externe

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ABSTRACT

Radiotherapy alone or in association with systemic treatment plays a major role in the treatment of head and neck tumours, either as a primary treatment or as a postoperative modality. The management of these tumours is multidisciplinary, requiring particular care at every treatment step. We present the update of the recommendations of the French Society of Radiation Oncology on the radiotherapy of head and neck tumours from the imaging work-up needed for optimal selection of treatment volume, to optimization of the dose distribution and delivery.

Mots clés :
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RÉSUMÉ

La radiothérapie délivrée seule ou en association avec un traitement systémique joue un rôle majeur dans le traitement des tumeurs de la sphère cervico-maxillofaciale, que ce soit comme traitement de première intention ou comme traitement postopératoire. La prise en charge de ces tumeurs est multidisciplinaire requérant une attention toute particulière à chacune des étapes du traitement. Nous présentons la mise à jour des recommandations de la Société française de radiothérapie oncologique sur la radiothérapie des tumeurs de la sphère cervico-maxillofaciale depuis les informations diagnostiques requises pour une bonne sélection des volumes à traiter jusqu'aux spécificités liées à l'optimisation et la délivrance de la dose.

1. Introduction

Malignant head and neck tumours primarily include tumours of the oral cavity, oropharynx, hypopharynx, larynx, nasopharynx, salivary glands, and to a lesser extent, tumours of the external auditory canal, eyelids, eye socket, skin layers as well as malignancies of the nose and sinuses.

The management of these tumours involves multidisciplinary therapy including surgery, radiotherapy and systemic treatments. The choice between these options and their possible combinations will depend on the location of the tumour, the stage of the disease, the general condition of the patient, their preferences, and the desired therapeutic goal, i.e., to maximise control of the disease while maintaining the quality of the various physiological functions (e.g., speech and swallowing). Single disciplinary treatments are preferred to multimodal treatments that are likely to make patients feel sicker, whenever possible and when offering the same efficacy. While a T1 or T2-N0 (or even N1) stage tumour can be treated either

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by surgery or by exclusive radiation, the same tumour associated with multiple cervical nodes will require more careful treatment with radiation combined with concomitant chemotherapy. In all cases, a first-line surgical option will be followed by radiotherapy or even radiotherapy and concomitant chemotherapy. This approach, however, is not followed by all teams.

Radiotherapy for head and neck tumours is based on a common framework regardless of the sub-location of the tumour, to which specificities will be added. This framework is outlined in the sections below and its specificities will be addressed in the chapters relating to the different sub-locations.

This operating procedure applies to primary and postsurgical treatment indications. In line with international recommendations for squamous cell carcinomas, an interval of less than 30 days between diagnosis (date of biopsy) and treatment is preferable [1]. For postsurgical radiation, it is strongly recommended starting treatment between six and eight weeks after surgery [2].

2. Assessment prior to radiotherapy

2.1. Clinical examination and diagnostic imaging

Treatment of ENT tumours must include various local/regional clinical examinations and an imaging assessment to identify the local, regional and metastatic extension of the tumour to optimise the definition of target volumes [3,4].

The basic clinical examination of mucosal tumours should include an examination of the oral cavity performed by the radiation oncologist who will treat the patient using a flexible fibrescope, plus a neck examination. A written report of the endoscopy performed under general anaesthesia by the ENT specialist, backed up as a minimum by diagrams and ideally documented by photographs and/or videos must be available. Patients with tumours located in the nasopharynx and/or base of the skull or nearby area will require an otological examination with audiogram supplemented by, depending on the extension of the tumour, an ophthalmologic examination. Patients receiving high-dose cisplatin therapy ($100\ mg/m^2$) will require an audiogram, at the start of treatment at least.

The local/regional imaging assessment must include either a CT scan with injection of a contrast agent or magnetic resonance imaging (MRI) with a gadolinium injection. The radiologist decides which of these two techniques will be used; however, it appears that MRIs are preferred for tumours of the nasopharynx, base of the skull, paranasal sinuses, oral cavity and oropharynx, i.e. all locations above the hyoid bone. A bone-window CT may be required to supplement the assessment of possible bone infiltration. The use of (^{18}F)-fluorodeoxyglucose positron emission tomography coupled with computed tomography (PET-CT) to assess lymph node extension in the neck is subject to discussion in view of its low sensitivity and specificity of around 80 to 85%. However, a PET-CT is required for the assessment of metastatic lymphadenopathies when no obvious primary focus is available for biopsy. When performed by an expert, a neck ultrasound with aspiration for cytological examination is a highly specific examination.

When searching for metastatic lesions in high-risk cancer (e.g. multiple cervical nodes, high smoker) a chest CT or PET-CT is required.

A pathology diagnostic report is required for all patients treated for ENT tumours. For oropharyngeal tumours, an investigation of immunohistochemical overexpression of p16 protein is standard. For nasopharynx tumours, the search for Epstein-Barr virus (EBV) expression is also standard.

For patients referred for postsurgical radiotherapy, the detailed surgery report should be made available to the radiation oncologist. The pathology report should also include tumour size, local extension, depth of infiltration (for oral cavity tumours), resection margins (R0, R1 or R2), presence of perineural and lymphatic infiltration, total number of lymph nodes collected and analysed, number and location of metastatic lymph nodes, and presence of capsule rupture.

A recent blood test should be performed and include at least a complete blood count, kidney and liver function profile, a coagulation test and a thyroid-stimulating hormone (TSH) measurement before treatment.

Finally, a nutritional assessment is also indicated especially in the presence of significant weight loss in the weeks or months before diagnosis. The use of a preventative percutaneous endoscopic gastrostomy tube is recommended for such patients.

2.2. Dental check-up

Any patient scheduled for radiotherapy of the ENT region should have a dental check-up prior to treatment, which should include a clinical examination and a radiological examination of the mandible (orthopantomogram/dental panoramic scan). The assessment may be supplemented by the following care:

- scaling;
- treatment of any dental caries (endodontics);
- tooth extraction, if necessary, for decayed, loose and damaged teeth, teeth with furcation defects, or located in the irradiated volumes;
- preservation, if possible, of teeth for use in future prostheses.

If teeth need to be extracted, ideally, the time between the extractions and the start of radiotherapy (or concomitant chemoradiotherapy) should be at least ten days. For simple extractions of one or two teeth without bone resection, a minimum interval of five days is permitted, provided the mucosa has healed.

Adequate dental care including brushing after each meal and daily lifetime application of fluoride is recommended after completion of radiation therapy in all patients still in possession of their own teeth. Seeing the dentist for a check-up every three to six months is recommended.

Prosthetic functional rehabilitation will not be carried out until at least three months after completion of radiotherapy. The use of implants is not a strict contraindication and should be assessed according to the volume irradiated, the dose received and the adherence of the patient to a strict hygiene regime including stopping smoking. Implants should not be placed until 12 months after the end of radiotherapy and the radiation oncologist will need to be contacted.

3. Immobilisation and localisation imaging

Systems used to immobilise and provide comfort to patients guarantee the accuracy of positioning and its reproducibility during the many treatment sessions required by tumours in the ENT region [5]. The patient is most frequently installed in a dorsal decubitus position, with their arms along the body in a position as comfortable and reproducible as possible. Patients must be bare chested and not wear any jewellery or dental or hearing aids. A median sagittal laser is used to check the alignment of the patient before manufacturing the immobilisation mask.

Particular attention should be paid to the choice of the neck support, which ideally will be moulded to the anatomy of the patient (Moldcare®, Accuform®, Totim®, etc.) and will therefore be used throughout the treatment. It must provide perfect support the patient's neck to allow it to be repositioned as naturally as possible

[6,7]. If no individualised neck support is provided, the quality of the "standard" supports should be checked regularly, to avoid any wear-and-tear variations, and a difference between supports used for scans and accelerators.

A personalised mouthpiece is sometimes required when irradiating oral cavity tumours in order to keep the mouth open and create space between target volumes and organs at-risk [8]. The mouthpiece needs to be manufactured before the immobilisation mask.

The use of a bolus is sometimes also necessary in the case of a superficial target volume. A thermoformable bolus can be highly adapted to the patient. It should be manufactured before the immobilisation mask so that it can be integrated into it. Care should be taken to ensure that there is no air gap between the patient's skin and the bolus to guarantee a "build-up" effect.

A five-clip immobilisation mask is recommended for positioning and immobilising patients with ENT tumours. However, for paranasal sinus tumours without neck irradiation, a three-clip mask is acceptable. The shoulders of the patient should be lowered, and their chin slightly raised to avoid wrinkles in the neck skin before applying the thermoplastic to the patient. When applying the mask to the patient, care must be taken to ensure it remains aligned and the thermoplastic is moulded perfectly to their morphology, especially in the area of the forehead, nose, chin and shoulders. In tracheotomy patients, the mask must have an opening limited to the size of the cannula. The drying time recommended by manufacturer must be respected. It is recommended removing and then repositioning the mask prior to the localisation imaging to ensure it is perfectly adapted to the patient [9].

Marks should be made on the mask, which can be supplemented by tattooed dots or marks on the patient's skin, to allow the mask to be repositioned during treatment. Information on the installation and immobilisation devices as well as photos must be included in the "Record & Verify" system.

For ENT conditions, apart from cases of proven allergy, dosimetry scans are performed with injection of iodine contrast agent after ensuring that creatinine clearance is well above 45 mL/min. For clearance between 30 and 45 mL/min, the use of a contrast agent is still recommended, but the patient should be slightly hyperhydrated before and after injection (e.g. 250 mL of intravenous saline solution). A two-phase injection of the iodine contrast agent is preferable (e.g. an injection of 45 mL of 2 mL/s). For tissue impregnation, it should be followed by a 45-second pause and a second 45-mL injection of 2 mL/s. For vascular opacification, acquisition should start at the end of the second injection. The dosimetry scan should be performed with 2-mm thick slices, an exposure rate constant of 100 to 120 kV and a sufficiently large field of view (FOV) to encompass the entire external contour. Patients should be advised to refrain from swallowing during the acquisition [10]. Artefacts due to dental implants can make it tricky to delineate target volumes and organs at-risk. To overcome this issue, metal artefact reduction algorithms can be applied during the acquisition of the scan. Medical physicists must be consulted when using these algorithms as they can affect the Hounsfield units on CT images.

A treatment-position PET-CT with the injection of an iodine contrast agent can be used as localisation imaging for larger tumours. For smaller tumours, a partial volume acquisition phenomenon may underestimate the volume of the tumour. Taking advantage of the superior contrast resolution for soft tissues, a treatment-position MRI is an attractive option for tumours of the nasopharynx, oropharynx and paranasal sinus [11]. In the absence of a dedicated machine with use of an immobilisation system during imaging (MRI simulation), it must be used sparingly given the inaccuracies in the recording of images on the simulation CT scan. Standard approaches to image readjustment under these conditions are based on rigid readjustments using transformations (rotation and translation) without elastic adjustment to avoid deforming the tumour.

4. Definition of target volumes and organs at-risk

Since the late 1970s, successive reports issued by the International Commission on Radiation Units and Measurements (ICRU) (reports 50, 62, 71, 78, 83, 93) have proposed various concepts to be used when defining target volumes and organs at-risk [12–18]. For target volumes, the concepts of gross tumour volume (GTV, macroscopic tumour volume) and clinical target volume (CTV, clinical-anatomical target volume) have been defined; for organs at-risk, it is the concept of organ at-risk. Selection and delineation of these volumes are a mandatory step in the dosimetric planning procedure. No dose can be prescribed, reported and recorded unless these volumes have been specified accurately. The various chapters on tumour sub-locations in the ENT region will present the recommendations for the selection and delineation of these different volumes in greater detail. Some general information is presented below.

4.1. Gross tumour volume

GTV is the macroscopic part of the tumour that is visible and/or palpable during the clinical examination and various imaging examinations. For ENT tumours there may be one (or more) GTVs for the primary tumour (GTV-P) and one (or more) GTVs for the metastatic lymph nodes of the neck (GTV-N). The GTV will always be delineated by integrating information from the clinical, fibroscopic and endoscopic examination and the various anatomical or functional imaging techniques. As previously mentioned, it is essential that the radiation oncologist in charge of the patient personally performs the clinical and fibroscopic examination. Endoscopic information will be collected under general anaesthesia. The localisation CT may be supplemented by an MRI, especially for tumours located near the base of the skull, the nasopharynx of the oral cavity and oropharynx. This MRI must be recorded jointly with the CT scan; however, merging the different images may not provide any greater accuracy in terms of the delineation of volumes, if the position of the patient is too dissimilar between the two examinations. The use of PET-CT to delimit the GTV ensures an automatic delineation closer to the actual tumour volume provided that automatic image segmentation algorithms are used [19,20]. Finally, it has been shown that all imaging methods (at least CT, MRI and PET-CT) tend to overestimate the macroscopic tumour volume evaluated compared with the volume of the surgical sample, and that PET-CT was the technique able to determine the actual GTV most consistently [21].

4.2. Clinical target volume

CTV is the volume that includes the GTV and tissue microscopically infiltrated by the tumour. Postsurgically, the CTV will include only the surgical excision site and potentially infiltrated adjacent tissues. Like the GTV, several CTVs can be defined including the primary tumour volume (CTV-P) and lymph node volume(s) (CTV-N).

Regarding lymph node CTVs, several recommendations are available for both the selection of at-risk lymph node areas and their delineation [22–25]. To summarise, lymph node infiltration will depend essentially on the location of the tumour and the presence or absence of macroscopically infiltrated lymph nodes. For patients with no metastatic lymph nodes or with a single metastatic lymph node (N0 or N1, classification of Union for International Cancer Control [UICC] American Joint Commission on Cancer [AJCC] 2018), selective treatment may be proposed. For patients with multiple macroscopic lymph node infiltrations (N2b, N2c, UICC/AJCC 2018)

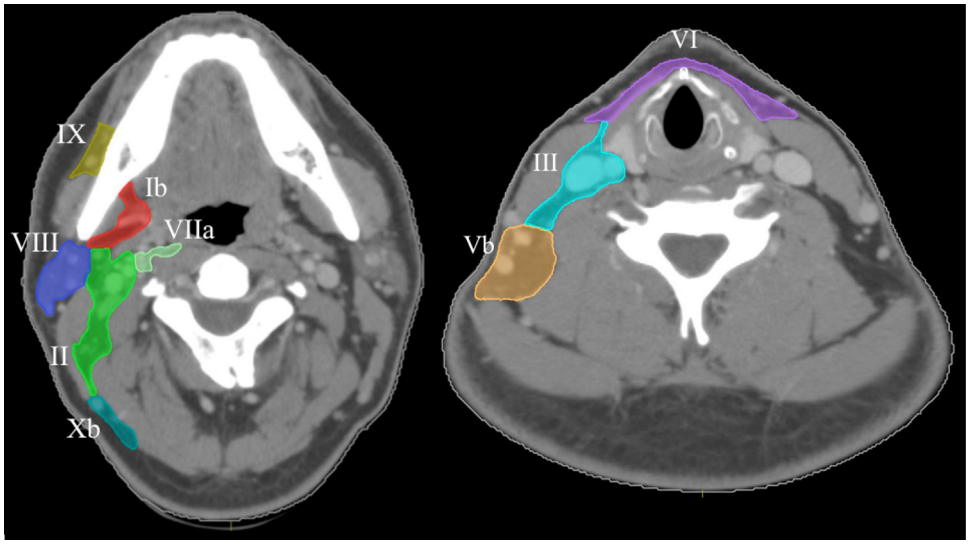

Fig. 1. Axial slice scans with contrast injection through the caudal portion of vertebra C2 (left) and through the caudal portion of vertebra C6 (right). Various nodal areas are represented: Ib: submandibular lymph nodes; II: upper jugular carotid nodes; III: middle jugular carotid nodes; Vb: lymph nodes of the posterior triangle; VI: anterior jugular nodes; VIIa: lateral retropharyngeal nodes; VIII: parotid nodes; IX: buccofacial nodes; Xb: occipital nodes.

or large lymph nodes (N2a, N3, UICC/AJCC 2018), it is recommended treating all lymph node levels of the neck at-risk. The lymph nodes to be treated will most often be bilateral; however, for tumours located in the tonsillar compartment, tumours of the lateral wall of the pyriform sinus, lateralised tumours of the oral cavity (e.g., retromolar trigone, gum, cheek, lateral edge of the tongue), and metastatic lymphadenopathies without a portal of entry, ipsilateral treatment in relation to the primary tumour is not only justified but highly desirable. For patients with an oropharyngeal tumour expressing the p16 protein, taking into account the lymph node-specific classification, no data are available to suggest a different selection of lymph node areas to be treated. The distribution of the lymph node areas to be treated will be presented in the chapters on the different tumour sub-locations. To delineate these lymph node areas, several consensus guidelines have been published by ENT cooperative groups and scientific societies (Fig. 1) [24].

In terms of the CTV of the primary tumour of the pharyngolarynx and oral cavity, guidelines have alternated between two schools of thought (anatomical and geometrical) until a recent integration of the two trends [26].

In short, the anatomical school recommended considering the different compartments of the ENT region (e.g., the parapharyngeal space, the carotid space, the pre-epiglottic compartment) as areas for possible macroscopic tumour infiltration. For laryngeal tumours, the supraglottic compartment is automatically be integrated into the CTV-P; for tonsillar compartment tumours, the CTV-P encompasses the parapharyngeal space in its entirety from the base of the skull to the hyoid bone. These recommendations were popularised in French literature by the publications of M. Lapeyre et al. for the various tumour locations [27–30].

The geometric school supported by Danish Head and Neck Cancer (Dahanca) advocates defining two concentric volumes of dissemination around the GTV-P; the first with a margin of 10 mm around the GTV-P to receive the prophylactic dose, the second with a margin of 5 mm around the GTV-P and to receive the therapeutic dose [31]. These margins were selected based on a small number of pathological studies defining peritumoral microscopic extension (see the summary in [32]). The recommendations were indirectly validated in a study showing a frequency of tumour recurrence after radiotherapy independent of the extension of the margins between GTV-P and CTV-P [33].

The integration of these two non-exclusive schools of thought has resulted in the development on an international consensus endorsed by many ENT cooperative groups and scientific societies [32]. To summarise, the consensus proposes an anatomical expansion of the GTV-P, as suggested by the anatomical school, but also suggests restricting it in the space by adopting a margin of 5 to 10 mm around the GTV-P, as suggested by Dahanca. Expansion of a tumour in the tonsillar cavity will include the soft palate, glossotonsillar sulcus, base of the tongue, and parapharyngeal space, but will be limited in the space taking into account the decreasing probability of microscopic infiltration relative to the distance from the GTV-P edge. Expansion of a right supraglottic laryngeal tumour will include the right paralaryngeal space, pre-epiglottic compartment, the anterior section of the contralateral laryngeal region, thyroid cartilage but will be limited in the space and not extend to the thyrohyoid muscles, and will not include the right pyriform sinus, postcricoid region or entire larynx. A volumetric comparison showed single to double differences in volumes between the two schools of thought, resulting inevitably in large differences in dose distribution and possibly the morbidity of treatments [32]. Following the publication of this international consensus it has now become the reference standard methodology to be used to define CTVs.

4.3. Organs at-risk

Organs at-risk are normal anatomical structures whose irradiation at too high a dose can result in disabling or even unacceptable morbidity. Radiosensitivity of such organs must therefore be considered when prescribing and planning the dose [17]. In principle, while all tissues outside the CTV are considered organs at-risk in the ENT region, the organs listed in Table 1 are usually delimited and taken into considering during the planning process. The location of the tumour determines which organs at-risk are to be delimited. The radiation oncologist may wish to delimit other organs at-risk such as, for example, the lips, frontal lobe and cerebellum, depending on the primary tumour involved.

For the delineation of organs at-risk in the ENT region, international guidelines adopted by the major cooperative groups have been published for reference [34]. It is important to mention that

Table 1
Main organs at-risk delineated in radiotherapy of the ENT region.

Organ class	At-risk organ
Organs of sight	Retina
	Optical nerves
	Chiasma
Organs of hearing	Inner ear
Swallowing organs	Superior, middle and inferior constrictor muscles
	Oesophagus
Speech/respiration organs	Larynx
	Trachea
Salivation organs	Parotid glands
	Submandibular glands
	Buccal cavity
Neurosensory organs	Spinal cord
	Brain stem
	Brachial plexus
Endocrine tissues	Pituitary gland
	Thyroid gland
Bone tissue	Mandible and temporomandibular joint

for some organs such as parotid glands, the entire gland must be delineated including its deep lobe.

4.4. Planning target volume

After determining the CTV, the various uncertainties in its positioning, linked to possible secondary internal movements, e.g., swallowing or breathing, or to a suboptimal or variable positioning of the patient on the treatment table during the numerous sessions, should be taken into account. In this context, the ICRU has defined a planning target volume (PTV), which is a "tool" to ensure the CTV receives the prescribed dose with a certain level of probability. The margins between the CTV and the PTV will therefore consider all the uncertainties recognised in the position of the CTV. In the ENT region, positioning uncertainties dominate those related to internal movements of the target, and only the former will be considered. Various guidelines have been published on the method of calculating the margin between CTV and PTV and the reader should refer to them [35]. In the ENT region, isotropic margins between 2 and 5 mm are selected, depending on tumour location, the immobilisation system used and the daily or non-daily use of repositioning imaging such as cone beam computed tomography (CBCT). Therefore, these margins must be defined by each unit and for each different type of equipment used. Whatever the margin used, it is not recommended that it should be less than 2 mm given the presence of residual uncertainties throughout the treatment procedure. Regardless of the margin used, in situations where PTV and an organ at-risk or planning organ at-risk volume (PRV) overlap, the ICRU recommends that the amplitude of the margin around the CTV should not be compromised, but stronger constraints used, or even "sub-PTVs" defined when optimising the dose.

4.5. Planning organ at-risk volume

Like the PTV, a margin will be applied around the organs at-risk to take into account the same uncertainties in the positioning of the patient. This is called the planning organ at-risk volume (PRV). Logically, unless significant internal movements exist compared to positioning uncertainties, a margin similar to that used around the CTV will be applied around the organs at-risk. However, the ICRU recommends only applying a margin around organs at-risk for "serial-like" organs such as spinal cord, brain stem and nerves (e.g., optic nerve, chiasma or brachial plexus). For other "parallel-like" organs such as parotid glands or constrictor muscles, the margin between the organ at-risk and the PRV may be zero.

5. Optimisation and dose–volume constraints

During volumetric modulated arc therapy (VMAT) planning, dose distribution to target volumes and organs at-risk is adjusted and prioritised through an iterative process called "optimisation". As illustrated in Fig. 2, this process includes:

- defining the planning objective, including defining the different volumes of interest discussed above and the dose constraints assigned to them;
- the procedure for calculating and optimising the dose to endeavour to fulfil the planning objective;
- accepting the different parameters having resulted in the accepted dose distribution and which, therefore, will become the prescription with the associated technical data.

In this context, the definition of dose–volume constraints for PTVs and PRVs is an essential step.

5.1. Dose–volume constraints in PTVs

The purpose of assigning dose constraints in PTVs is to maximise the probability that each voxel in the target volume will receive the prescribed dose. As the use of VMAT techniques requires volumetric dose planning, the ICRU guidelines recommend for such treatments a prescription established in relation to the median dose to satisfy homogeneity constraints. The metrics usually recommended for dose–volume constraints in the PTV are shown in Table 2. It is especially important to respect these metrics with ENT tumour radiotherapy due to:

- the highly curative role of treatments;
- the overlapping between the tumour and healthy tissues requiring no overdose inside and outside the PTV.

5.2. Dose–volume constraints in PRVs

The purpose of assigning dose-volume constraints in PRVs is to minimise as far as possible treatment morbidity. The dose to normal tissues considered acceptable should consider the clinical situation, the history of radiotherapy, the presence of prior morbidity and the administration of concomitant chemotherapy. Table 3 below summarises the risks of late toxicity and the maximum recommended doses for many healthy tissues in the ENT region as defined by the Quantitative Analyses of Normal Tissue Effects in the Clinic (Quantec) initiative [36–39].

It should be noted that all retrospective clinical data published underpinning estimations of toxicity risk mostly relate to patients treated with conformal radiotherapy with higher volumes of healthy tissue irradiated than after intensity-modulated radiation therapy (IMRT) and VMAT irradiation, and doses per fraction close to 2 Gy. It is therefore reasonable to consider that the frequencies mentioned represent a high estimation of risk. Finally, as a rule, it should be remembered that planning should always be maximised to reduce the dose to healthy tissues to well below the maximum recommended doses.

6. Irradiation techniques

6.1. Standard technique

The standard radiation technique for ENT tumours is conformal radiotherapy with intensity modulation and image guidance. Intensity modulation can be delivered either via IMRT with fixed arm angled beams (generally five to seven coplanar beams), or

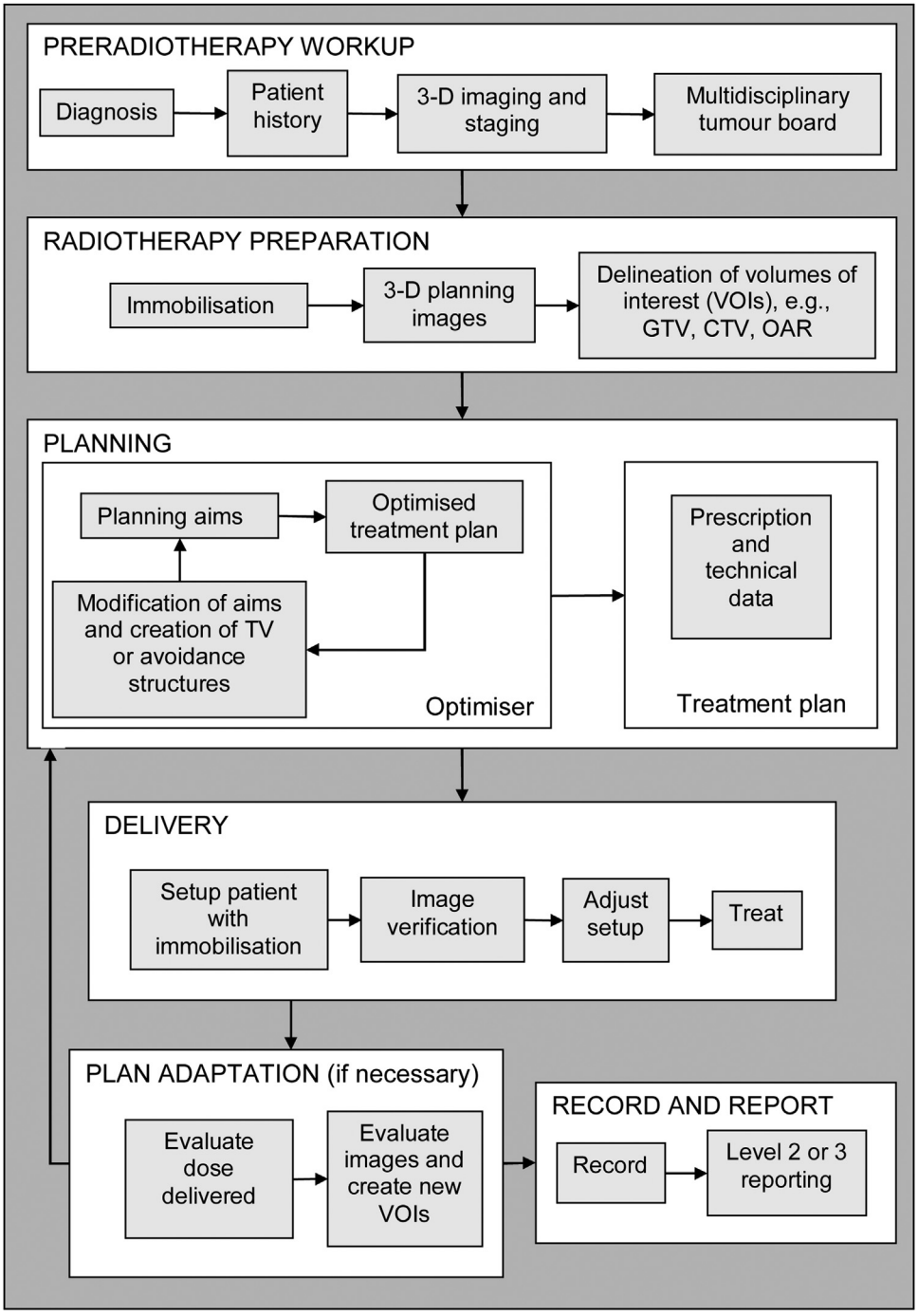

Fig. 2. Typical course of radiotherapy. GTV: gross tumour volume; CTV: clinical target volume; OAR: organ at-risk; TV: target volume.

Table 2
Dose–volume constraints for dose optimisation in the planning target volume.

Median dose: dose prescribed (Gy)
$D_{95\%} \geq 95\%$ of the dose prescribed
$D_{98\%}$ (dose close to the minimum dose) $\geq 90\%$ of the dose prescribed
$D_{2\%}$ (dose close to the maximum dose) $\geq 107\%$ of the dose prescribed

$D_{x\%}$: dose that covers $x\%$ of the volume.

via VMAT with one or more arcs (generally two arcs). The current trend is to increase the number of beams or arcs in view of the performance of the current machines, which deliver treatments increasingly rapidly. Helical tomotherapy can also be used. Intensity modulation techniques reduce xerostomia and dysphagia and improve the long-term quality of life of patients [40]. Intensity modulation techniques utilise fast-evolving reverse planning methods and new systems are emerging [41]. The use of multicriteria optimisation algorithms and/or expert systems facilitates and improves the quality of treatment plans. These optimisation techniques may be extremely beneficial for tumours in the ENT region [42–45]. Regardless of the optimisation algorithm used, the intensity modulation obtained can be complex and the conformity of the treatment delivered to the prediction must be checked, either by systematic pretreatment measurements or by monitoring complexity metrics [46,47].

Table 3
Risk of late toxicity for different organs and dose recommendations.

Organ	Toxicity	Dose level	Frequency	Recommendations
Brain	Symptomatic necrosis	D_{max} < 60 Gy	< 3%	$D_{2\%}$ < 60 Gy
		D_{max} < 72 Gy	5%	
Brain stem	Necrosis or neuropathy	D_{max} < 54 Gy	< 5%	$D_{2\%}$ < 50 Gy
		D_{max} < 64 Gy (vol < 1 mL)	< 5%	
Spinal cord	Myelopathy	D_{max} = 50 Gy	0.2%	$D_{2\%}$ < 50 Gy
Optic nerve/chiasma	Optic neuropathy	D_{max} < 55 Gy	< 3%	$D_{2\%}$ < 55 Gy
		$D_{max} \leq$ 60 Gy	3–7%	
Cochlea	Hearing loss	$D_{mean} \leq$ 45 Gy	< 30%	D_{mean} < 45 Gy
Brachial plexus	Clinical neuropathy	V_{70Gy} > 10%	13/23 (56%)	V_{70Gy} < 10%
		V_{70Gy} < 10%	38/329 (11%)	
Parotid gland	Xerostomia ≥ grade 2	$D_{mean} \leq$ 25 Gy	< 20%	D_{mean} < 25 Gy
Submaxillary gland	Xerostomia grade 4	$D_{mean} \leq$ 30 Gy	< 30%	$D_{mean} \leq$ 30 Gy
Pharyngeal constrictor muscles	Persistent dysphagia	$D_{mean} \leq$ 50 Gy	< 20%	D_{mean} < 45 Gy
Larynx	Hoarseness	D_{max} < 66 Gy	< 20%	D_{mean} < 30 Gy
	Pulmonary aspiration	D_{mean} < 50 Gy	< 30%	D_{mean} < 30 Gy
Mandible	Osteoradionecrosis	$D_{5\%}$ < 66 Gy	< 7% < 8%	$D_{5\%}$ < 70 Gy
		$D_{5\%}$ < 70 Gy		

D_{max}: maximum dose in a voxel; D_{mean}: mean dose; V_{70Gy}: volume receiving a dose of 70 Gy; $D_{5\%}$: dose in 5% of volume.

6.2. Prescription and reporting of doses

The ICRU 83 report recommends evaluating and reporting the coverage of the target volumes to, at least, four points of the dose–volume histogram: the dose close to the minimum $D_{98\%}$, $D_{95\%}$, the median dose ($D_{50\%}$) and the dose close to the maximum $D_{2\%}$. The dose is prescribed in relation to the median PTV volume and therefore $D_{50\%}$ is equal to the prescribed dose (D*x*: dose in *x*% of volume). It is also recommended checking the homogeneity of irradiation of the target volumes by calculating the homogeneity index [HI = $(D_{2\%} - D_{98\%})/D_{50\%}$], which must be around 0.

Doses in organs at-risk should be reported: $D_{2\%}$ reflecting a maximum dose for "serial-like" organs and, in "parallel-like organs", the mean dose as well as the fraction of the volume of organ V_D irradiated at a dose of interest D.

Planning objectives primarily serve to ensure the optimal coverage of target volumes with respect to the constraints given in Table 2 while endeavouring to preserve healthy tissues and respect the dose constraints for the organs at-risk indicated in Table 3.

Acceptance of the dose distribution is based, in addition to the quantitative criteria mentioned above, on a qualitative evaluation corresponding to the visualisation of the dose distribution across different planes.

6.3. Positioning control and image-guided radiotherapy

After positioning the patient with the immobilisation systems used during localisation imaging, image-guided radiotherapy (IGRT) should be used to ensure high-quality positioning at each session. This procedure reduces systematic and random errors and ensures an optimal repositioning of the patient at each session [48].

Two main types of onboard imaging (low- [kV] or high energy [MV] exposure) can be used, namely two-dimensional planar imaging (2D imaging) and volume imaging (3D imaging). The first enables an acquisition of planar orthogonal images and is optimal for bone structure adjustments. The acquisition is faster and less irradiating than 3D imaging. However, it is unable to evaluate variations in positioning due to patient rotation. The second type of imaging includes cone beam computed tomography (kV-CBCT) or megavoltage cone beam computed tomography (MV-CBCT), which, in addition to the visualisation of bone structures, also enhances the visualisation of soft tissues including, depending on their location and size, the primary tumour and invaded lymph nodes. The use of kV-CBCT and MV-CBCT allows rigid translation and rotation adjustment based on bone structures in relation to the reference image; however, checks must be carried out to ensure that no significant anatomical changes have occurred in the patient such as weight loss [49]. It accurately identifies translational and rotational movements. The definition of an area of interest on the bone structures in relation to the CTV will improve the automatic adjustment proposed by the registration algorithm [50]. However, this technique is more irradiating, and its acquisition takes 2 to 3 minutes longer than 2D imaging.

Recommendations on the frequency and type of imaging to be used were the subject of a recently published review [51]. The recommendations included the ability to individualise different structures, acquisition and analysis times, and additional exposure of onboard imaging.

In terms of imaging frequency, when a margin between 3 and 5 mm is used between CTV and PTV and/or with large random variations in positioning, daily imaging is recommended. This protocol will take into account systematic and random variations, thus ensuring an optimal positioning of the patient. For larger margins between the CTV and PTV, the use of the eNAL (extended no action level) protocol is justified. Daily imaging is required for the first three fractions to calculate any displacement to be applied to consider any systematic positioning errors. This displacement will be applied for the remainder of the treatment with weekly imaging performed for confirmation.

In terms of the type of imaging (2D or 3D), no real consensus is available in this area; however, the trend seems to favour an increasing use of 3D imaging throughout the treatment. Since a good correlation has been reported for translational movements between 2D and 3D imaging, an appropriate compromise could be to use volume imaging during the first week of treatment followed by daily planar imaging. Cone beam computed tomography could be performed once a week or more frequently, depending on the extent of rotational variations and anatomical changes.

6.4. Adaptive radiotherapy

Intensity modulation techniques ensure excellent isodose compliance around target volumes as well as high-dose gradients. Consequently, any anatomical changes in the patient may impact the dose delivered and thus deviate from the planned dose. This can increase the doses delivered to the organs at-risk and/or decrease the doses delivered to the tumour, which may lead to a risk of toxicity and recurrence. The acquisition of volume images (CBCT, high energy MV-CT scans) allows anatomical changes to be tracked during irradiation [52]. A variety of factors trigger changes in target volumes and organs at-risk (including tumour response, weight loss, involution of healthy tissues, etc.) and they are impossible to

predict during the initial treatment plan. For example, as the treatment of the patient progresses, radiosensitive structures such as parotid glands may migrate to high-dose regions [53] and target volumes may develop dose inhomogeneities with unintended cold spots [54].

In response to this situation, adaptive radiotherapy (ART) strategies have been developed [55,56]. ART consists of replanning treatment during radiotherapy either at predefined intervals or in response to major anatomical changes. In this context, ART can be referred to as anatomy-adapted adaptive radiotherapy (A-ART) as it is guided by anatomical changes occurring during treatment. At the same time, response-adapted adaptive radiotherapy (R-ART) with the use of diagnostic imaging during treatment (PET-CT or MRI) is also being developed. At present, no consensus is available on how to best incorporate A-ART into clinical practice; randomised studies demonstrating a clinical benefit have yet to be published. However, the fundamental issue consists in determining at what point in time a change in dose level reaches a clinically significant magnitude. R-ART has been the focus of recent studies and several prospective studies are expected over the next few years to determine whether such an approach is worth exploring. These adaptive approaches cannot currently be considered as therapeutic standards.

ART uses advanced image recontouring software that is both rigid and deformable to propagate contours and then accumulate the dose to provide an estimate of anatomical changes and their impact on the delivered dose. However, most of these systems remain a “black box” due to a lack of available documentation and it is difficult to evaluate the uncertainties associated with the software used. ART will require rigorous quality assurance procedures prior to its clinical implementation. Reference should be made to the recommendations contained in the following publications [57], which provide further help and guidance for the implementation of quality assurance for these processes.

Disclosure of interest

P. Giraud: relationships/activities with AstraZeneca, BMS (consulting fees), and Ipsen (honoraria for lecture/presentations or educational events); S. Boisbouvier: declares that she has no competing interest; V. Grégoire, P. Maingon, Y. Pointreau, L. Vieillevigne: did not disclose relationships/activities/interests.

Author contribution

The authors did not provide this information.

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Appendix 1.

Digital RecoRad™ tool: http://www.sfro-recorad.fr/

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