Cancer/Radiothérapie 26 (2022) 189–198

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

Clinical practice guidelines

Radiotherapy for oral cavity cancers

Radiothérapie des cancers de la cavité buccale

M. Lapeyre[a,*], S. Racadot[b], S. Renard[c], J. Biau[a], J.F. Moreira[d], M.C. Biston[e], Y. Pointreau[f], J. Thariat[g], P. Graff-Cailleaud[h]

[a] *Département de radiothérapie, centre Jean-Perrin, 58, rue Montalembert, 63011 Clermont-Ferrand cedex 1, France*
[b] *Département de radiothérapie, centre Léon-Bérard, 28, rue Laennec, 69008 Lyon, France*
[c] *Département de radiothérapie, Institut de cancérologie de Lorraine, avenue de Bourgogne, 54511 Vandœuvre-lès-Nancy, France*
[d] *Service de physique médicale, centre Jean-Perrin, 58, rue Montalembert, 63011 Clermont-Ferrand cedex 1, France*
[e] *Service de physique médicale, centre Léon-Bérard, 28, rue Laennec, 69008 Lyon, France*
[f] *Radiothérapie, Institut interrégional de cancérologie (ILC), centre Jean-Bernard, 9, rue Beauverger, 72000 Le Mans, France*
[g] *Département de radiothérapie, centre François-Baclesse, 3, avenue du Général-Harris, 14000 Caen, France*
[h] *Département de radiothérapie, institut Curie, 26, rue d'Ulm, 75005 Paris, France*

ARTICLE INFO

Keywords:
Radiotherapy
Brachytherapy
Oral cavity
Cancer
Neoplasm
Guidelines
French society of radiotherapy oncology

ABSTRACT

Intensity modulated radiation therapy and brachytherapy are standard techniques of irradiation for the treatment of oral cavity cancers. These techniques are detailed in terms of indication, planning, delineation and selection of the volumes of interest, dosimetry and patients positioning control. This is an update of the guidelines of the French Society of Radiotherapy Correspondence.

Mots clés :
Radiothérapie
Curiethérapie
Cavité buccale
Cancer
Recommandations
Société française de radiothérapie oncologique

RÉSUMÉ

La radiothérapie conformationnelle avec modulation d'intensité et la curiethérapie font partie des techniques d'irradiation de référence des cancers de la cavité buccale. Chaque technique est détaillée en termes d'indication, de préparation, de délinéation et sélection des volumes, de dosimétrie et de contrôle de position. Il s'agit de la mise à jour des recommandations de la Société française de radiothérapie oncologique (« Recorad ») pour cette localisation anatomique des voies aérodigestives supérieures.

1. Introduction

The oral cavity consists of several substructures such as the lips, the mobile tongue, the floor of the mouth, the hard palate, the gums and the oral mucosa (inner aspect of the cheek). Oral cavity cancers are primarily squamous cell carcinomas (95.3%). The average age at time of diagnosis is 60.3 years in male patients and 64.1 years in female patients (period 2000–2005). The main risk factors for lip cancers are ultraviolet radiation and for other substructures, alcohol use, tobacco, chronic trauma, a high nitrosamine diet, certain industrial solvents, and betel nut chewing for the oral mucosa, seen primarily in India. These cancers represent the 12th leading cause of mortality worldwide in males and 16th place in females. Lip cancers have an incidence of 0.74 per 100,000 in males and 0.17 in females. This rate can be very high (7.6 to 8.6) in some countries, such as in Spain or Australia, probably because of their abundant sunlight. For other sub-structures, the incidence is 7.92 per 100,000 in males and 1.85 for females. It reaches 10.3 in India related to excessive betel chewing. The probability of 5-year survival for all stages combined is 88 to 96% for lip cancer and 33 to 53% for other structures [1,2].

In 2017, the Tumour Node Metastasis (TNM) classification was changed for oral cavity cancers (*Union for International Cancer*

* Corresponding author.
E-mail address: michel.lapeyre@clermont.unicancer.fr (M. Lapeyre).

https://doi.org/10.1016/j.canrad.2021.11.012
1278-3218/

Table 1
Classification of clinical primary tumours (cT) or postoperative pathological tumours (pT) of oral cavity cancers and lip cancers (UICC 2017) (the size of the tumour is measured in its largest dimension).

Stage	Criteria
Tis	Carcinoma in situ
T1	Tumour ≤ 2 cm and infiltration in depth ≤ 5 mm
T2	Tumour ≤ 2 cm and infiltration in depth > 5 and ≤ 10 mm or tumour > 2 cm and ≤ 4 cm and infiltration ≤ 10 mm
T3	Tumour > 4 cm or infiltration in depth > 10 mm
T4a	
Oral cavity	Tumour invading the cortical bone of the mandible or the maxillary sinus or the skin[a]
Lip	Tumour invading the cortical bone, the lower alveolar nerve, the floor of the mouth or skin (chin or nose)[a]
T4b	Tumour invading the masticatory space, the pterygoid processes, the base of the skull or the area surrounding the internal carotid artery

[a] One superficial erosion alone of the alveolar bone is not sufficient to classify a tumour as stage T4a.

Table 2
Classification of clinical regional adenopathies (cN) and post-operative pathological adenopathies (pN) of cancers of the oral cavity and of the lip (UICC 2017) (size of the adenopathy and measured in its largest dimension).

Stage	Criteria
N0 (c/p)	No regional lymph node involvement
N1 (c/p)	Single ipsilateral metastasis ≤ 3 cm without extracapsular spread
N2a	
cN2a	Single ipsilateral metastasis > 3 cm or ≤ 6 cm, without extracapsular spread
pN2a	Single ipsilateral metastasis > 3 cm or ≤ 6 cm, without extracapsular spread or Single ipsilateral metastasis ≤ 3 cm with extracapsular spread
N2b (c/p)	Multiple ipsilateral metastases ≤ 6 cm without extracapsular spread
N2c (c/p)	Contralateral or bilateral metastases, ≤ 6 cm, without extracapsular spread
N3a (c/p)	Metastasis > 6 cm without extracapsular spread
N3b	
cN3b	Single or multiple metastases, with extracapsular spread (indifferent size)
pN3b	Single or multiple metastases, ipsi or contralateral(s), > 3 cm, with extracapsular spread

c: clinical; p: pathological. Infiltrated skin and/or deep fixation to the underlying soft tissue and/or neural involvement corresponding to extracapsular spread of the adenopathy.

Control [UICC] 8th version). The former criteria were saved such as the greatest dimension of the tumour (≤ 2 cm: T1; > 2 cm and ≤ 4 cm: T2; > 4 cm: T3), extension to adjacent structures with invasion of bony structures and of the maxillary sinus (T4a) and involvement of the masticatory space, the pterygoid process, the base of the skull or the sheath of the internal carotid artery (T4b). Another criterion was added which corresponds to the depth of tumour infiltration (≤ 5 mm: T1; > 5 mm and ≤ 10 mm: T2; > 10 mm: T3). Thus, a tumour of less than 2 cm in size (previously classified as T1), but with a depth of more than 5 mm infiltration becomes a T2 tumour, and if this infiltration is > 10 mm, it becomes T3. For adenopathies, the new classification modifies the node (N) stage in case of adenopathy with radiological criteria suggesting extracapsular spread. Before any treatment, the existence of at least one adenopathy with radiological signs of extracapsular spread is classified as cN3b, whatever its size. Postoperatively, a single adenopathy less than 3 cm in size with histologically demonstrated extracapsular spread is classified as pN2a and in case of multiple adenopathies with extracapsular spread, stage N becomes pN3b [3]. The TNM UICC 2017 classification is shown in Tables 1, 2 and 3.

Table 3
Classification according to stage of cancers of the oral cavity and of the lip.

Stage I	T1/N0	M0
Stage II	T2/N0	M0
Stage III	T3/N0 T1-3/N1	M0
Stage IVa	T4a/N0-1 T1-4a/N2a-2c	M0
Stage IVb	T1-4/N3a-3b T4b/N1-3b	M0
Stage IVc	T1-4/N0-3b	M1

Curative therapeutic management of non-metastatic cancers of the oral cavity is based on surgery, radiotherapy (external beam radiotherapy and brachytherapy) and medical systemic treatments. The standard technique of external beam radiotherapy is intensity-modulated radiation therapy (IMRT) [4]. Brachytherapy can be delivered at a pulsed dose rate (PDR) or high dose rate (HDR) [5]. For the last few years, the results obtained with IMRT in oral cavity tumours have been documented [6–10]. We are proposing an update of the radiotherapy reference for this tumour location [11] in the setting of "Recommendations for the practice of external beam radiotherapy and brachytherapy" (RecoRad^{TM} 2.0).

2. Indications for external beam radiotherapy and brachytherapy

The indications for external beam radiotherapy or brachytherapy for oral cavity cancers are determined at a multidisciplinary team. Many criteria are taken into account in addition to characteristics related to the patient such as age, overall condition and comorbidity. This involves primarily the tumour location, the TNM stage, the clinical presentation and tumour extension, CT-scan imaging, magnetic resonance imaging (MRI) and postoperative pathology criteria in case of initial surgery.

2.1. Indications according to stage

Conventionally, stages I-II tumours (T1T2N0) are indications for surgery [12,13]. Brachytherapy is an alternative option for superficial tumours of the lip, the tongue, the floor of the mouth and the oral mucosa. Postoperative external beam radiotherapy is indicated in case of unfavourable pathological criteria (see paragraph 2.3). If there is an indication for irradiation of the surgical bed without elective radiotherapy to the neck, it can be delivered by postoperative brachytherapy in the absence of contra-indications.

In patients eligible for surgery with stages III-IV advanced but non-metastatic cancer, surgery followed by external beam radiotherapy is the reference treatment. Postoperative chemoradiotherapy (cisplatin 100 mg/m^2 weeks 1, 4 and 7) is reserved based on histological examination (positive margin R1 (< 1 mm) and/or extracapsular spread) [14–17]. Weekly cisplatin (40 mg/m^2) is an option if a high dose is difficult to plan [18]. This option may become a standard if results of the Japan Clinical Oncology Group (JCOG) 1008 phase III study are confirmed [19].

In patients who did not undergo surgery who have non-metastatic cancer stage III-IV, concomitant chemoradiotherapy (cisplatin 100 mg/m^2 weeks 1, 4 and 7) is the standard treatment [20,21]. Combination with a targeted therapy (cetuximab) is an alternative in case of a contra-indication to cisplatin [22,23]. In the absence of possible chemotherapy, radiotherapy alone with altered fractionation is an alternative [24,25]. For bulky or rapidly progressive tumours or in case of multiple adenopathies or of bulky stage N3, induction chemotherapy (for example, docetaxel, cisplatin and 5-fluoro-uracil [TPF regimen]) can be

considered by a multidisciplinary team, followed by radiotherapy or chemoradiotherapy with carboplatin or cetuximab [26–28].

2.2. Specific aspects of neck dissection for oral cavity cancers

Criteria for management of the neck in oral cavity cancers have been published in 2018 at the congress of the American Society of Clinical Oncology (ASCO) [18]. For patients with lateralised cancer stage cT1N0, unilateral neck dissection is recommended. Abstention from neck dissection and ultrasound monitoring of the neck at close intervals is possible if the primary tumour is very superficial or of small size (< 1 cm). Unilateral elective neck dissection should be considered for other sites in stage cT2/4 disease. In patients with a primary cancer of the tongue or of the floor of the mouth, neck dissection should be bilateral in case of a neck classified as cN0 and a tumour stage cT3/4 or if the primary cancer approaches the midline or if the neck is classified as cN+ whatever the cT stage. In order to be significant, a pathology examination of a nodal dissection specimen should include at least 18 nodes per side. The "sentinel node" technique, as an alternative to neck nodal dissection, has been validated for cancers of the oral cavity stage N0 and has received a consensus [29].

2.3. Indications for postoperative radiotherapy and brachytherapy

Unfavourable pathology criteria requiring adjuvant radiotherapy are: the existence of disease extension in positive margin R1 ($\leq$ 1 mm), two or more positive nodes, a single positive node with extracapsular spread, a node of size > 3 cm, perineural infiltration, close margins or $\leq$ 5 mm, stages T3-T4 and the existence of lymphovascular emboli [13,30–32]. The existence of a single adenopathy without extracapsular spread and localised to the first cervical node can lead to consider surveillance in the absence of other unfavourable criteria. Cancers with positive frozen section microscopic tumour (R1) cut-through revised to negative (R0) carry a higher risk of local recurrence in comparison to those which are R0 at the outset [33,34]. Surveillance can be discussed in a multidisciplinary team meeting of specialists in the absence of other unfavourable criteria. For patients whose neck is classified as pN0, but with a number of nodes examined of less than 18 per side, management of the neck area should be considered as insufficient and can justify adjuvant radiotherapy [18]. Postoperative brachytherapy can be proposed when there is an indication to irradiate the surgical bed without elective radiotherapy to the neck (stage pT1-2N0 tumours presenting solely with criteria of local recurrence) [5]. A study is ongoing to investigate stereotactic radiotherapy in this situation [35]. The time between surgery and radiotherapy should be as short as possible as soon as healing is obtained, with a maximum of six weeks and not exceed 11 to 14 weeks total between date of surgery and end of radiotherapy [31,36–38]. The indications and modalities for postoperative chemoradiotherapy are described in paragraph 2.1.

3. External beam radiotherapy

3.1. Dental and nutritional management

For this location, as the result of systematic irradiation of the oral cavity, the salivary glands and the mandible, dental precautions prior to the start of irradiation are essential. Oral care interventions should be performed (at least ten days prior to initiation of irradiation for tooth extractions). It is also necessary to fabricate dental dams containing fluoride gel for patients who have teeth. Such fluoridated prophylaxis starts at the end of irradiation or as soon as healing of mucositis, and should be performed for life, 5 minutes per day, in order to limit the risk of dental caries. A nutritional assessment is to be performed prior to start of treatment and prophylactic gastrostomy tube placement is considered in case of concomitant chemoradiotherapy [39].

3.2. Data analysis and clinical examination prior to delineation

Analysis of all documents and imaging is mandatory: an endoscopy descriptive report, a diagram of the lesion (sometimes with photographs), initial imaging reports (at least a CT-scan of the head and neck and thorax with injection, magnetic resonance imaging (MRI) and, for infiltrating tumours, positron emission tomography (PET-CT-scan) after injection of (^{18}F)-fluoro-2-deoxyglucose, in particular for locally advanced tumours) [11,40]. The time elapsed between date of conduct of these investigations and date of preparation for radiotherapy should be taken into account in order to adapt delineation.

The radiation oncologist should be able to analyse the imaging available in order to assess exactly the tumour and nodal extension of the tumour and to detect a recurrence postoperatively. A suspect adenopathy is defined by a CT-scan based on morphological criteria: a transverse diameter (smallest diameter) > 10 mm (5 to 8 mm in the retropharyngeal space and 12 to 15 mm for the upper jugular node or level 2), central necrosis, a round rather than oval shape, loss of fatty material from the hilum, visible peripheral extensions evidencing an extracapsular spread and existence of more than three nodes combined of size between 6 and 8 mm [41].

Postoperatively, the pathology report should describe the size of the tumour, its depth of infiltration in mm, the margin of resection in mm (R0, R1 or R2), the existence of perineural and lymphatic infiltration, the total number of nodes analysed (ideally at least 18 per side) [18], the number, size and topography of metastatic nodes as well the existence of extracapsular spread.

Before starting delineation, the clinical examination should include examination of the patient in order to identify superficial extension of the tumour, difficult to observe in imaging and not fail to recognise the occurrence of tumour extension in comparison to the baseline examination. Postoperatively, the examination also enables to verify the absence of a clinical recurrence and good healing (wound-healing failure, necrosis, denudation of the mandible, site infection, and analysis of the position of the flap).

3.3. Dosimetric CT-scanning and immobilisation

Immobilisation is obtained by use of a thermoformed mask with five points of attachment on a patient installed in supine position with his/her arms alongside the body. An oral spacer can be used to conserve more readily the upper lip and the hard palate for certain locations (mobile tongue, floor of the mouth, lower lip). In order to stabilise the spacer throughout the duration of irradiation, it is preferable that it be configured in patients who are not totally edentate due to the need for very precise repositioning. Postoperatively, the identification of scars by a suture (copper or lead) can be useful, in particular, in case of adenopathies with extracapsular spread. Image acquisitions are performed using a dosimetric CT-scanner with injection whenever possible with thin sections of less than 3 mm thickness. An algorithm for correction of artefacts related to dental material can be applied in order to improve the accuracy of the delineation.

3.4. Radiotherapy technique

The standard radiotherapy technique is IMRT. It can be delivered either with fixed arm angulation beams (generally five to seven beams) or by a dynamic irradiation technique (volumetric

Table 4
Definitive radiotherapy. Proposed regimens for doses, volumes and fractionations depending on type of intensity modulated radiation therapy and main reminders and key points of radiotherapy.

	CTV-1 High risk	CTV-2 Low risk	CTV-3 Intermediate risk (option) (should be contained in CTV-2)
Sequential IMRT	70 Gy/35 fractions	50 Gy/25 fractions	/
IMRT with SIB	70 Gy/35 fractions 70 Gy/33 fractions	56 Gy/35 fractions 54 Gy/33 fractions	63 Gy/35 fractions 59.4 Gy/33 fractions
Delineation of CTVs-P	GTV-P + 5 mm	GTV-P + 10 mm with extension to be discussed according to compartments and areas of infiltration (consensus references 2018 and Gortec 2005), pathway of extrinsic muscles of the tongue if infiltrated, of nerves if infiltrated	Depending on dose to organs at risk Margin around CTV-P1 (5-10 mm) to be adapted according to anatomical barriers
Delineation of CTVs-N	GTV-N + 10 mm (GTV-N + 5 mm in case of a node < 3 cm and absence of doubt in imaging to be discussed)	Selection of nodal levels at risk according to references (Table 5)	In case of doubtful node (sum total of orthogonal diameters > 17 mm): node + 10 mm Or nodal level corresponding to GTV-N

CTV: clinical target volume; GTV: gross tumour volume; IMRT: intensity-modulated radiotherapy; SIB: simultaneous integrated boost; N: node; P: primary tumour; Gortec: Groupe d'oncologie radiothérapie tête et cou (head and neck oncology and radiotherapy group). Reminder of CT-scan morphological criteria of suspect neck adenopathies: transverse diameter > 10 mm (5 to 8 mm in retropharyngeal level (level VIIb) and 12-15 mm in level II), central necrosis, rounded rather than an oval shape, loss of fatty substance from the hilum, visible peripheral extensions evidencing an extra-capsular spread and existence of more than three nodes combined of size between 6 and 8 mm. Key points: maximum protection of the mandible and of the lips (apart from PTV). Taking into account of time between MRI diagnostic imaging repositioned and dosimetric CT-scanning (if > 4 weeks, consider a larger GTV depending on the clinical examination).

modulated arc therapy [VMAT]) with one or more arcs (generally two). Helical radiotherapy can also be used. Generally, rotational techniques enable to obtain a more advantageous dose distribution with higher dose gradients while reducing irradiation time compared to fixed beam IMRT. Two modalities for dose delivery exist: two-stage sequential normofractionated irradiation and single-phase irradiation known as irradiation with a simultaneous integrated boost (IMRT-SIB) which can sometimes have an advantage with slight acceleration of treatment. The main advantage of IMRT-SIB consists of a reduction in the number of very time consuming planning. Three-dimensional conformational radiotherapy should be abandoned apart from exceptional cases (for example haemostatic palliative care emergency).

3.5. Control of position by imaging during radiotherapy sessions

The quality of the patient's position should be verified either by two-dimensional (2D) orthogonal planar imaging with bone repositioning, or by three-dimensional (3D) volume imaging by cone beam computed tomography (low energy, kV-CBCT, or high energy, MV-CBCT) which enables visualisation of bone structures, but also of soft tissue. Currently, it is difficult to recommend use of one modality compared to another. However, the use of three-dimensional imaging sometimes makes it possible to verify the absence of major anatomical changes which may have an important impact on distribution of the theoretical dose. In all cases, training of staff is necessary. Guidance by daily imaging prior to each session is preferable [11,40].

3.6. Doses and delineation of target volumes

It is recommended to establish a programme of delineation specifying the different target volumes chosen and the dose levels which will be prescribed, as well as the organs at risk and their dose constraints. These choices should be based on available references and publications [30,40,42–47]. For target volumes, gross tumour volumes (GTVs) are defined (for unresected tumour), clinical target volumes (CTVs) and planning target volumes (PTVs). Organs at risk are also delineated and for some of them, a planning organ at risk volume (PRV) can be generated (so-called "serial" organs at risk and "parallel" small organs). In order to improve delineation of GTVs, image fusion with diagnostic imaging or with dosimetric imaging can be useful (MRI, CT-scan, or PET-scan which tends to be reserved for stage T3-4 tumours due to lack of spatial resolution for T1-2 tumours).

Two categories of CTVs are defined. High risk CTV (CTV1) corresponding to a primary tumour or the postoperative tumour bed (CTV-P1) and to the adenopathies or their surgical bed after neck dissection (CTV-N1). The second CTV is low-risk CTV treating peritumoural microscopic disease (CTV-P2) and microscopic nodal disease (CTV-N2). For the IMRT-SIB technique, a third so-called intermediate risk CTV can be proposed (CTV3). Intermediate CTV3 includes the area adjacent to the tumour or that of an adenopathy (corresponding level) and should be included in the low-risk CTV. Individualisation of CTV with intermediate risk is controversial because it has not demonstrated evidence of its oncological utility and can lead to an increase in the radiotherapy dose delivered to healthy tissue. [11,44].

Postoperatively, in addition to CTV1 and 2, a volume at very high risk has been determined empirically that can receive a higher dose and which corresponds to the area of slices in the section involved R1 (CTV-P/R1) and/or a surgical bed of adenopathies with extracapsular spread (CTV-N/CR1).

3.6.1. Definitive radiotherapy

3.6.1.1. Doses and fractionation. Several regimens are used [11,12,40,44]. CTV1 receives a dose of 70 Gy in 33 to 35 fractions (2 to 2.12 Gy per fraction). CTV2 receives a dose of 54 Gy (33 fractions of 1.64 Gy) to 56 Gy (35 fractions of 1.6 Gy). When delineated, the dose to be delivered in CTV3 ranges from 59.4 to 63 Gy in 33 to 35 fractions of 1.8 Gy. More accelerated regimens without chemotherapy are used more rarely (66 Gy in 30 fractions during six weeks (T1T2) or 70 Gy in 35 fractions with six sessions per week [25]). In sequential regimens, the dose is 50 Gy in 25 fractions in CTV1 and CTV2 followed by an additional dose of 20 Gy in CTV1. The different regimens are summarised in Table 4.

3.6.1.2. Delineation of GTV-P and N. GTV-P corresponds to a gross tumour visible in different imagings supplemented by a clinical examination. MRI is recommended for this location, in particular, for infiltrating tumours. In case of doubt related to non-optimal situations (clinical examination difficult to perform, unsatisfactory

imaging because of a patient allergic to contrast medium or an artefact, time between MRI diagnostic imaging and dosimetric CT-scanning of more than four weeks), it is preferable to enlarge the GTV.

For GTV-N, use of radiological criteria of malignancy mentioned in paragraph 3.2 are used (Table 4).

In cases of radiotherapy after induction chemotherapy, if the tumour has shrunk, GTVs will be delineated, taking into account gross tumour and nodal volumes delineated prior to chemotherapy, by including structures or regions initially affected [48].

3.6.1.3. Delineation of CTV-P1 and N1 (high risk). For the primary tumour, CTV-P1 includes GTV-P with a margin corresponding to immediate peri-tumoural extensions. This margin is 5 mm and should comply with anatomical barriers (bone in absence of infiltration) and exclude air. CTV-P1 is contained in CTV-P2 [40].

For adenopathies, CTV-N1 consists of GTV-N with a margin corresponding to the risk of extracapsular extension. This margin is 10 mm which can be reduced to 5 mm, in particular, in case of a smaller adenopathy (< 3 cm) and absence of doubt on the imaging. This margin should comply with anatomical barriers (bone) and exclude air [44].

3.6.1.4. Delineation of CTV-P2 (low-risk peritumoural extension). CTV-P2 corresponds to the region around GTV-P containing microscopic sub-clinical pathways of extension. These pathways correspond to the natural history of cancer and vary depending on anatomical barriers (fascia, bone), areas of preferential diffusion (fat, blood vessels, muscle fibres, nerves) and anatomical spaces and compartments. In order to obtain CTV-P2, an international consensus proposes a geometric approach which consists of adding a 10 mm uniform margin around the GTV-P (rule of 5 + 5 mm of the Danish Head and Neck Cancer Study Group [DAHANCA]) and then of reducing this automatic extension to exclude anatomical barriers (bone and fascia) and air. Strict application of the geometric method should be qualified in non-ideal situations (difficulty in performing the clinical examination, time greater than four weeks between diagnostic laboratory tests and dosimetric CT-scanning, artefacts, doubt in terms of tumour extension, location not described in a consensus). Most often, it is necessary to supplement this volume by the traditional anatomical method by widening the CTV-P2 to spaces and compartments with risk of contiguity, by use of a reference document on structures to include in oral cavity cancer. The 2005 reference document from the head and neck oncology and radiotherapy group (Gortec) on cancer of the oral cavity can be used [46]. Infiltration along nerves can be considered in case of gross or clinical involvement or based on the histology [49].

3.6.1.5. Delineation of CTV-N2 (low-risk nodal areas). Delineation of CTV-N2 involves the notion of nodal levels. Rules on delineation of levels I to X have been published [42]. Selection of nodal levels to be treated depends on their risk of involvement which is itself related to the location of the primary tumour, its lateral presentation and its local extension (stage T) as well as the nodal stage (stage N) and the topography of adenopathies. Proposals for selection of nodal volumes to treat for the primary tumour sub-locations are summarised in Table 5. They should be adapted on a case-to-case basis [43–45,47].

3.6.1.6. Delineation of CTV-3 (intermediate risk). Individualisation of CTV with intermediate risk is optional. This volume is included in CTV-2. The concept of CTV with intermediate risk is based on application of a safety margin around a high-risk CTV to cover an area of infiltration of subclinical disease in a higher quantity and requiring a higher dose to be delivered to the low-risk volume. The CTV-N3 can correspond to the nodal level of an invaded adenopathy. It can also be delineated around a node with a smaller size than that of a suspect adenopathy, but sufficient to create a significant risk of nodal recurrence, if a low-risk prophylactic dose is delivered to this level. This has been described when the total of the two orthogonal diameters of a lymph node at the limit of being pathological is more than 17 mm [49]. Regarding generation of a CTV-P3, this exposes to a risk of increasing the dose delivered to adjacent organs at risk (constrictor muscles of the pharynx, mandible, healthy area of the oral cavity) and the benefit/risk ratio for the patient should be taken into account.

3.6.2. Postoperative radiotherapy

3.6.2.1. Doses and fractionation. A randomised trial studied the dose to be delivered in the postoperative context. Results have made it possible to determine that it is necessary to deliver to the tumour site of the primary tumour, that is, the surgical bed (CTV-P1), a higher dose of 54 Gy (1.8 Gy per fraction), whatever the pathological criteria [31,50,51]. Excluding situations of surgical excision with positive margins (R1), doses of 57.6 and 63 Gy (1.8 Gy per fraction) produced identical results. For low risk neck areas (CTV-N2), the dose of 54 Gy (1.8 Gy per fraction) produced results identical to those with 57.6 Gy. For high-risk neck areas (CTV-N1), results were identical between 57.6 and 63 Gy and an increase in dose of 63 Gy did not provide any improvement. In very high risk cases, i.e. positive margins (R1), nodes involved with extracapsular spread (CR1), there was no difference between 63 and 68.4 Gy (1.8 Gy per fraction) [31,50,51]. Other studies have defined empirically a recommendation of 60 to 66 Gy in 30 to 33 fractions for volumes with very high risk [14–17].

Considering these results, it is possible to propose a dose of 60 Gy in 30 to 33 sessions on level of CTV-P1 and N1 (high risk) and 54 Gy in 30 to 33 sessions (equivalent to 50 Gy in 25 sessions) at level of CTV-P2 and N2 (low risk) [12,30]. It is possible to increase the dose to volumes with very high risk (positive margins or CTV-P/R1 and/or adenopathy with extracapsular spread or CTV-N/CR1) to order to reach a dose of 66 Gy in 33 sessions (or equivalent). These volumes should be limited to anatomical areas considered as at very high risk of recurrence (positive margins, surgical bed of excision of the adenopathy with extracapsular spread). The different regimens are summarised in Table 6.

3.6.2.2. Steps prior to delineation of postoperative CTVs. Definition of these volumes is difficult because of a change in the anatomy, loss of substance, flap placement, possible lymphoedema, lymphocele or haematomas and deformities of structure (remaining movable half tongue, half mandible, etc.). This makes a geometric approach of delineation for CTV-P impossible such as the one described in the consensus for primary tumours [40]. For delineation of CTVs, reinstallation of pre-operative GTV-P and N with repositioning of preoperative MRI and CT-scanning in dosimetric imaging is the prior step. Use of the diagram, the endoscopic description and the pathology report make it possible to supplement this step. If the time elapsed between surgery and pre-operative imaging is more than four weeks, it will be preferable to enlarge these volumes [30].

3.6.2.3. Delineation of CTV-P1 (high-risk tumoural surgical bed). CTV-P1 corresponds to pre-operative GTV-P with a margin of 10 to 15 mm [30]. This margin can be extended to 20 mm [52]. Another approach consists of adding a 10 mm margin around the surgical bed [52]. The limits of CTV should be adjusted to anatomical barriers if they are not infiltrated (bone, fascia, etc.) while excluding air [30,52].

In the presence of flaps, the region the most at risk of recurrence is the junction area between the flap and the native tissue opposite the initial primary tumour site. This area should be included in the high-risk CTV. Nevertheless, thickness of the flap to include remains

Table 5
Definitive and postoperative radiotherapy. Selection of nodal levels of oral cavity cancers for obtainment of CTV-N2 with low risk (for the retromolar trigone or the intermaxillary commissure, the levels selected correspond to levels of the anterior pillar (or the soft palate) to which are added levels of the posterior part of the inner of the cheek).

Primary tumour	Stage N	Levels to be included in CTV-N2	
		Ipsilateral[c]	Contralateral[a](absence of adenopathy in contralateral neck)
Mobile tongue	N0-N1 (in level 1-2-3)	I-II-III-IVa	No contralateral irradiation if T1-2 and > 1 cm from the midline I-II[2]-III-IVa if T3-4 or N+ or T1-2 and absence of dissection and < 1 cm from the midline or lymph node dissection N- with less than 18 nodes
	N2-N3	I-II-III-IVa[d]-Vab	I-II-III-IVa-Vab[e]
Floor of mouth	N0-N1 (in level 1-2)	I-II-III	No contralateral irradiation if T1-2 and > 1 cm from the midline I-II[b]-III if T3-4 or N+ or T1-2 and absence of dissection and < 1 cm from the midline or lymph node dissection N- with less than 18 nodes
	N2-N3	I-II-III-IVa[d]-Vab	I-II-III-IVa-Vab[e]
Buccal mucosa	N0-N1 (in level 1-2)	I-II-III-IX	No contralateral irradiation
	N2-N3	I-II-III-IVa[d]-Vab-IX	No contralateral irradiation I-II-III-IVa-Vab[e] if adenopathy ≥ 6 cm
Lower gum	N0-N1 (in level 1-2)	I-II-III-IX[f]	No contralateral irradiation if T1-2 and > 1 cm from the midline I-II[b]-III if T3-4 or if < 1 cm from the midline and no nodal dissection or nodal dissection N- with less than 18 nodes
	N2-N3	I-II-III-IVa[d]-Vab-IX[f]	No contralateral irradiation if T1-2 and > 1 cm from the midline I-II[b]-III if < 1 cm from the midline and no nodal dissection or nodal dissection N- with less than 18 nodes I-II[b]-III-IVa-Vab[e] if adenopathy ≥ 6 cm
Upper gumHard palate	N0-N1 (in level 1-2)	Ib-II-III-IX	No contralateral irradiation if T1-2 and > 1 cm from the midline I-II[b]-III if T3-4 or T1-2 and < 1 cm from the midline and no nodal dissection or nodal dissection N- with less than 18 nodes
	N2-N3	I-II-III-IVa[d]-Vab-IX	No contralateral irradiation if upper gum and T1T2 > 1 cm from the midline I-II[b]-III-IVa-Vab[e]-IX if hard palate or if upper gum and T3T4 or upper gum T1-2 and < 1 cm from the midline and no nodal dissection or nodal dissection N- with less than 18 nodes

CTV: clinical target volume; N: node. In patients with primary cancer of the tongue or of the floor of the mouth, nodal dissection should be bilateral in case of neck cN0 and tumour stage cT3/4 or if the primary tumour approaches the midline (≤ 1 cm) or in case of neck cN+ whatever the cT stage.
[a] In presence of an adenopathy in the contralateral neck (N2c), levels to be treated are identical to the homolateral level.
[b] Level IIb can be omitted.
[c] If adenopathy > 3 cm in level II, consider level VIIb.
[d] Level IVb included if involvement of level Iva.
[e] Level Vab can be omitted if involvement solely from level I and II in homolateral neck.
[f] Lower part of level IX (facial pedicle).

to be defined [52]. Schematically, a thickness of 5 mm (10 mm in case of an insufficient margin) of a flap opposite the initial tumour site can be included in the high-risk CTV [52].

To reduce the dose delivered to a voluminous flap, some authors propose to create a flap planning organ at risk volume ("flap PRV"), corresponding to the body of the flap decreased by a margin of 6 mm [53]. Recommendations define the methods of delineation of the main flaps in a post-operative context (pectoralis major muscle, musculomucosal facial artery, forearm free flap, anterolateral thigh free flap, free flap of the scapula and free flap of the fibula). Each flap is divided into two parts with its arteriovenous pedicle and the body of the flap [55]. This could subsequently enable dose adjustment in certain risk situations [54]. While awaiting results of future studies, a joint meeting with the surgeon can be useful in difficult situations.

Perineural infiltration of squamous cell carcinomas of the oral cavity most often are local microscopic areas of involvement which remain intratumoural. They are part of unfavourable criteria which carry an indication for post-operative radiotherapy. Nevertheless, apart from cystic adenoid carcinomas, prophylactic irradiation of pathways of tumour extension along nerves up to the base of the skull is not systematic. It can be justified in case of a voluminous tumour (T3T4) or clinical gross infiltration and in imaging. In this case, this volume tends to be treated in the CTV-P2. An atlas of delineation is proposed [49,52].

In case of invasion of muscle, the invaded muscle should undergo wide treatment opposite the area of invasion, but not necessarily up to its origin [52].

3.6.2.4. Delineation of CTV-N1 (high-risk nodal areas). CTV-N1 corresponds to pre-operative GTV-N with a 10 mm margin. CTV-N1 should be applied to all affected nodes in the pathology report, taking into account the surgical report and the preoperative imaging. The margin is applied by maintaining this extension within anatomical limits of the nodal level corresponding to the adenopathy [30,52]. When the node is in contact with a muscle, the CTV-N1 includes the muscle opposite the adenopathy. Fluid collections such as lymphoceles should also be included in CTV-N1 [30,43].

3.6.2.5. Delineation of CTV-P2 and N2 (low risk). CTV-P2 corresponds to a peritumoural volume at risk not treated with surgery

Table 6
Postoperative radiotherapy. Proposed regimens for doses, volumes and fractionations depending on type of intensity modulated radiation therapy and main reminders and key points of postoperative radiotherapy.

Postoperative location	CTV-P/R1 and CTV-N/CR1 Very high risk	CTV-1 High risk	CTV-2 Low risk
Sequential IMRT	66 Gy/33 fractions	60 Gy/30 fractions	50 Gy/25 fractions
IMRT with SIB	66 Gy/33 fractions 60 to 63.6 Gy/30 fractions	59.4 to 60 Gy/33 fractions 60 Gy/30 fractions	54 Gy/33 fractions 54 Gy/30 fractions
Delineation of CTVs-P	Positive margin (R1) Preoperative surgical bed of GTV-P R1 + 5 mm (to be adjusted to the pathology and surgical report)	GTV-P + 10 to 20 mm or surgical bed of GTV-P + 10 mm If flap: area of 5 to 10 mm depending on margin(6 mm of flap depending on size is possible).	Extensions around CTV-P1 to be discussed depending on compartment an infiltration according to location (reference Gortec 2005), pathway of nerve in case of infiltration, pathway of extrinsic muscles of the tongue and if at risk
Delineation of CTVs-N	Adenopathy with extracapsular spread (RC1) Surgical bed of GTV-N + 10 mm with perinodal region or nodal level involved in case of difficulty in identification.	Surgical bed of GTV-N + 10 mm or complete level N+ without CR; Include lymphoceles, haematoma, the muscular part in contact with the adenopathy and the pathway of the scar opposite N+	Selection of nodal levels at risk depending on reference Include pathway of the scar opposite level chosen

CTV: clinical target volume; GTV: gross tumour volume; IMRT: intensity-modulated radiotherapy; SIB: simultaneous integrated boost; N: node; P: primary tumour; Gortec: Groupe d'oncologie et radiothérapie tête et cou (head and neck oncology and radiotherapy group). R1: positive margins or ≤ 1 mm; N+: positive adenopathy; CR1: extracapsular spread or capsular rupture+. Reminder of criteria leading to consider postoperative radiotherapy: positive margins (R1), number of N+ ≥ 2, 1 N+ with extracapsular spread + (CR1), N+ size > 3 cm, perineural invasion, close margin ≤ 5 mm, stages T3-T4, lymphovascular emboli (optional: 1N+ without extracapsular spread in absence of other criteria; R0 margins obtained after resection of margin R1 in absence of other criteria). Key points: Neck pN0 after nodal dissection should include the number of nodes examined ≥ 18 (on each side). The time between surgery and radiotherapy should be ≤ 6 weeks and the total time day of surgery-end of radiotherapy ≤ 11 to 14 weeks. Taking into account time between repositioned diagnostic imaging and date of surgery (if > 4 weeks, consider a larger GTV depending on pathology data and the surgical report). Indications for postoperative chemoradiotherapy (cisplatin): margins R1 and/or N+ with CR1. Maximum protection of the mandible, bony free flaps and of lips (except PTV).

beyond CTV-P1. The use of the Gortec 2005 anatomical reference defining spaces and compartments at risk of contiguity in oral cavity cancers makes it possible to delineate it [46]. For tumours of the mobile tongue or the floor of the mouth, the extrinsic muscles of the tongue in contact with the tumour with risk of infiltration by the tumour should be included in their totality. The pathways of nerves can be discussed in case of perineural infiltration [49].

CTV-N2 corresponds to nodal levels not affected in terms of pathological description but considered at risk of residual microscopic infiltration. Rules on delineation of nodal levels are based on a reference already mentioned in chapter CTV-N2 for tumour sites [42]. Postoperatively, it is recommended to extend CTV-N2 to the subcutaneous area in contact with the surgical dissection scar opposite the affected adenopathies, in particular, those with extracapsular spread. The identification of scars can be facilitated by placement of a metallic suture during dosimetric CT-scanning. Selection of nodal levels to be included in CTV-N2 is based on the same proposals as those stated for tumour sites previously specified (Table 5) [30,43,45,47].

3.6.2.6. Delineation of CTV with very high risk (positive margins CTV-P/R1 or nodes with extracapsular spread CTV-N/CR1). For positive margins, CTV-P/R1 includes the per-tumoural bed around the preoperative GTV-P where the slice(s) of section(s) affected are located. A 5 mm extension around GTV-P adapted to the new anatomy can be proposed. The pathology report, preoperative imaging and the surgical report make it possible to supplement this volume. A collaborative discussion with the surgeon can be necessary in order to clarify these limits. It should be as limited as possible in order to minimise toxicity [30]. It can also involve the junction between the flap and the native tissue of contact.

For adenopathies with extracapsular spread, CTV-N/CR1 corresponds to the surgical bed of the adenopathy located by preoperative imaging [43]. An extension of 5 to 10 mm around the preoperative GTV-N facilitates positioning [52]. Infiltrated anatomical structures around an adenopathy should be included. In case of difficulty in locating these areas, the level opposite the adenopathy can be delineated.

3.7. Delineation of PTVs

This involves the volume in which the dose should be prescribed. It takes into account the uncertainties of the position and of positioning, the patient's movements and movements of the organ. Considering the efficacy of systems of immobilisation and use of daily image-guided radiotherapy, a 3 to 5 mm margin usually is added to the CTVs in order to obtain the corresponding PTVs.

3.8. Organs at risk and PRV

Delineation of organs at risk and dose constraints to be complied with do not have specificity for oral cavity cancers in comparison to other upper aerodigestive tract cancers. These constraints are to be complied with as strictly as possible and in case of combination with concomitant chemotherapy, it is necessary to make certain to limit the dose to the lowest possible dose [56,57]. Special attention should be paid to the oral cavity, the mandible and the lips when these structures are outside of the PTV.

4. Brachytherapy

4.1. Indication for brachytherapy

Brachytherapy for oral cavity cancers can be performed in superficial tumours less than 5 cm in size. It is used for tumour stages T1-T2 N0 and can be performed as a local boost after a first external beam radiotherapy for more advanced tumours. A two-week time interval is to be complied with between the first phase of external beam radiotherapy and the localised addition boost of brachytherapy. As the result of improvements in surgery, primarily by using the flap technique, improving functional results, the indications for brachytherapy have been progressively reduced. Furthermore, the conduct of elective neck dissection, in the same surgical time as removal of the primary tumour, enables lymph node exploration in order to adjust adjuvant therapy in case of a positive node. Nevertheless, brachytherapy continues to be preferred in tumour lesions for which surgical management would result in difficult

Table 7
Dose regimens and brachytherapy fractionations depending on dose rate used and clinical situation (definitive or post-operative brachytherapy) and main key points of brachytherapy.

	Definitive	Postoperative	
		R0 (close margin)	R1
Pulsed rate brachytherapy			
Exclusive	65–70 Gy	50–55 Gy	60 Gy
After first time radiotherapy	35–40 Gy (radiation dose: 40 Gy)	10–15 Gy (radiation dose: 50 Gy)	15–20 Gy (radiation dose: 50 Gy)
High dose rate brachytherapy (2 fractions per day with ≥ 6 hours intervals)			
Exclusive	45–55[a] Gy (4.5–5.5 Gy/fraction)	32–36 Gy (4 Gy/fraction)	36–40 Gy (4 Gy/fraction)
After first time radiotherapy	18–21 Gy (3 Gy/fraction; (radiation dose: 40–50 Gy)	16–20 Gy (4 Gy/fraction; radiation dose: 45 Gy)	20–24 Gy (4 Gy/fraction; radiation dose: 45 Gy)

a: for the tongue only. Key points: Possible indications: Superficial tumour < 5 cm. Systematic wearing of a leaded protection of the mandible or a spacer depending on case. Postoperative interval ≤ 6 weeks in case of postoperative brachytherapy. Time between brachytherapy and end of external radiotherapy ≤ 2 weeks. Contra-indications to brachytherapy: tumour less than 5 mm from the gum or retromolar trigon (or intermaxillary commissure), involvement of the hard palate.

functional sequelae such as lip cancers. Post-operatively, the traditional indication for brachytherapy is based on existence of unfavourable histopathological criteria exposing the patient to the risk of a local recurrence with no indication for elective irradiation of the neck. The time between surgery and brachytherapy should be at least 6 weeks if possible. Contraindications to brachytherapy for oral cavity cancers are tumours located less than 5 mm from the gum, impossibility to install a leaded protection of the mandible, involvement of the hard palate and infiltration of the intermaxillary commissure or the retromolar trigone. The check-up required to determine the indication for brachytherapy are identical to those necessary for planning of radiotherapy [5,58–60].

4.2. Implantation techniques

Before brachytherapy of the oral cavity, restoration of the patient's dentition is essential. In order to minimise the risk of radionecrosis related to proximity of the radioactive source to the mandible during treatment, a leaded protection of the mandible is produced with a radiotransparent resin copy in order to perform CT-scan dosimetry.

Needles and then catheters are inserted under general anaesthesia (or local anaesthesia for the lip) in the tumour and/or its periphery (2 to 5 mm) in conformity with guidelines of the Paris system (parallelism and equidistance between the needles or flexible catheters, with 10 to 15 mm optimal spacing) in order to obtain coverage of the planned target volume and optimum dose distribution. For the lips, use of needles without flexible catheters is the usual technique. After a first external beam radiotherapy, the implanted volume corresponds to the initial volume prior to irradiation. Post-operatively, the needles or catheters are inserted on either side of the scar, most often at a distance of 5 mm They are spaced apart by 10 to 12 mm, with the thickness of target volume being 10 to 20 mm [5,58–60].

4.3. Techniques of brachytherapy depending on dose rate

Currently, two techniques are used in routine practice. The pulsed dose rate or high dose rate techniques. For the two techniques, the method of implementation is identical. These two techniques use iridium-192 sources with different activities. These sources are delivered to the patient from a lead-lined container with connected catheters (source projectors). For PDR brachytherapy, the patient is managed during complete hospitalisation in a room equipped with radioprotection standards, located in a "protected" ward. 24-hour treatments are to be preferred insofar as possible, in comparison to 12-hour treatments, at a rate of one pulse every hour with prescription of an optimum rate of 0.5 Gy/h (0.3 to 0.7). For HDR brachytherapy, the patient can be hospitalised in a conventional ward and he/she undergoes sessions in the high-dose rate brachytherapy room (usually two fractions a day separated by more than six hours). The duration of hospital stay ranges from two to five days depending on dose delivered. Throughout duration of hospital stay (PDR) or solely during sessions (HDR), the needles or catheters implanted in the patient are connected to the source projector. The wearing of a leaded protection of the mandible (or sometimes, of a spacer depending on location of the target volume post-operatively) is systematic throughout the duration of treatment for PDR brachytherapy with possibility of one-time removal between two pulses during the day. For HDR brachytherapy, the wearing of a leaded protection of the mandible is used solely during the sessions [5,58].

4.4. Dosimetric and planimetric CT-scanning

Dosimetric planning CT-scan without injection of contrast medium with serial sections less than 3 mm in thickness is performed after implantation with placement of graduated markers in the catheters or the needles. The target volumes and organs are risk are delineated. The gross tumour volume is defined by the initial tumour located clinically and in the imaging assisted by position of the catheters. The clinical target volume corresponds to the gross tumour volume, increased by a margin of 5 mm. In a postoperative context, the clinical target volume is defined directly based on the scar and generally measures 10 to 20 mm in thickness. The planning target volume corresponds to the clinical target volume. The dummy sources are located in the CT-scan image and the length of activation of the sources in each catheter is determined. The dose prescribed is defined as the minimum dose in the clinical/planning target volume or a representation of the dose of 90% of volume at least 100% of the dose prescribed or of the volume receiving 100% of the dose prescribed at least 90%. Dosimetry can be started by identical activation of useful positions of the source in all catheters. Manual or automated optimisation can be performed to avoid significant overdoses or "under doses". The dose non-uniformity ratio (DNR = V150/V100 [volume receiving 150% of the dose prescribed/volume receiving 100% of the dose prescribed]) is verified in order to reach an optimum value less than 0.36 to 0.42. The total dose, the dose rate, the number of fractions or pulses per hour and per day are prescribed and reported, as well as the dose in the volumes (cumulative dose–volume histograms). The different dose regimens are listed in Table 7 according to the technique (PDR or HDR) and according to location (tumour site or postoperatively) [5,58]. Whatever the technique, the dose ratio should comply with recommendations of report 58 of the International Commission on Radiation Units and Measurements (ICRU). The type of optimisation should be specified as well as descriptions of treatments with the different parameters: mean central dose, minimal dose in the clinical target volume, indices of coverage of homogeneity and of uniformity, dimension of volumes, treated volume and irradiated

volume, high and low dose areas and doses in organs at risk [5,58–60].

4.5. Management during treatment and follow-up after brachytherapy

Throughout the duration of treatment, the patient uses a mouthwash regularly and feeding is provided via a nasogastric tube. At the end of the treatment, removal of the tubes or the needles is done in the operating room by the brachytherapy oncologist.

Acute reactions occur 8 to 10 days after the end of treatment and are manifested as mucositis localised to the target volume and last about six weeks. Monitoring by the brachytherapy oncologist is scheduled at around month two and then repeat monitoring is gradually spaced out to follow traditional follow-up of upper aerodigestive tract cancers [61].

Authors' contributions

M. Lapeyre: writing - original draft; J. Biau, M. - C. Biston, P. Graff-Cailleau, J. - F. Moreira, Y. Pointreau, S. Renard, J. Thariat: manuscript review and editing.

Disclosure of interest

J. Biau, M.-C. Biston, P. Graff-Cailleau, M. Lapeyre, J.-F. Moreira, Y. Pointreau, S. Renard, J. Thariat: did not disclose relationships/activities/interests; S. Racadot: declared having no relationship/activity/interest.

Acknowledgements

The authors wish to thank Dr. Xavier Liem (centre Oscar-Lambret, France) and Dr. Pierre Boisselier (Institut régional du cancer de Montpellier, France) for their careful reviewing and proofreading.

Appendix A. Links to external sites

Digital RecoRad™ tool: www.sfro-recorad.frhttps://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf

https://www.esmo.org/guidelines/head-and-neck-cancers/squamous-cell-carcinoma-of-the-head-and-neckhttp://oncologik.fr/referentiels/rrc/carcinome-epidermoide-de-la-cavite-buccale

References

[1] Ligier K, Belot A, Launoy G, Velten M, Delafosse P, Guizard AV, et al. [Epidemiology of oral cavity cancers in France]. Rev Stomatol Chir Maxillofac 2011;112:164–71.
[2] Gupta B, Johnson NW, Kumar N. Global epidemiology of head and neck cancers: a continuing challenge. Oncology 2016;91:13–23.
[3] Huang SH, O'Sullivan B. Overview of the 8th edition TNM classification for head and neck cancer. Curr Treat Options Oncol 2017;18:40.
[4] Alterio D, Marvaso G, Ferrari A, Volpe S, Orecchia R, Jereczek-Fossa BA. Modern radiotherapy for head and neck cancer. Semin Oncol 2019;46:233–45.
[5] Peiffert D, Coche-Dequéant B, Lapeyre M, Renard S. [Brachytherapy for head and neck cancers]. Cancer Radiother 2018;22:359–66.
[6] Bhide SA, Ahmed M, Newbold K, Harrington KJ, Nutting CM. The role of intensity modulated radiotherapy in advanced oral cavity carcinoma. J Cancer Res Ther 2012;8:S67–71.
[7] Sher DJ, Thotakura V, Balboni TA, Norris CM, Haddad RI, Posner MR, et al. Treatment of oral cavity squamous cell carcinoma with adjuvant or definitive intensity-modulated radiation therapy. Int J Radiat Oncol Biol Phys 2011;81:e215–22.
[8] Daly ME, Le Q-T, Kozak MM, Maxim PG, Murphy JD, Hsu A, et al. Intensity-modulated radiotherapy for oral cavity squamous cell carcinoma: patterns of failure and predictors of local control. Int J Radiat Oncol Biol Phys 2011;80:1412–22.
[9] Studer G, Brown M, Bredell M, Graetz KW, Huber G, Linsenmeier C, et al. Follow up after IMRT in oral cavity cancer: update. Radiat Oncol Lond Engl 2012;7:84.
[10] Quinlan-Davidson SR, Mohamed ASR, Myers JN, Gunn GB, Johnson FM, Skinner H, et al. Outcomes of oral cavity cancer patients treated with surgery followed by postoperative intensity modulated radiation therapy. Oral Oncol 2017;72:90–7.
[11] Lapeyre M, Biau J, Racadot S, Moreira JF, Berger L, Peiffert D. [Radiotherapy for oral cavity cancers]. Cancer Radiother 2016;20Suppl:S116–25.
[12] NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck; Version 2; 2020.
[13] Ettinger KS, Ganry L, Fernandes RP. Oral Cavity Cancer. Oral Maxillofac Surg Clin N Am 2019;31:13–29.
[14] Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck 2005;27:843–50.
[15] Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre J-L, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945–52.
[16] Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937–44.
[17] Cooper JS, Zhang Q, Pajak TF, Forastiere AA, Jacobs J, Saxman SB, et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2012;84:1198–205.
[18] Koyfman SA, Ismaila N, Crook D, D'Cruz A, Rodriguez CP, Sher DJ, et al. Management of the neck in squamous cell carcinoma of the oral cavity and oropharynx: ASCO clinical practice guideline. J Clin Oncol 2019;37:1753–74.
[19] Kiyota N, Tahara M, Fujii H, Yamazaki T, Mitani H, Iwae S, et al. Phase II/III trial of post-operative chemoradiotherapy comparing 3-weekly cisplatin with weekly cisplatin in high-risk patients with squamous cell carcinoma of head and neck (JCOG1008). J Clin Oncol 2020;38:6502.
[20] Blanchard P, Baujat B, Holostenco V, Bourredjem A, Baey C, Bourhis J, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. Radiother Oncol 2011;100:33–40.
[21] Pignon J-P, le Maître A, Maillard E, Bourhis J, MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4–14.
[22] Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 2010;11:21–8.
[23] Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354:567–78.
[24] Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 2006;368:843–54.
[25] Overgaard J, Mohanti BK, Begum N, Ali R, Agarwal JP, Kuddu M, et al. Five versus six fractions of radiotherapy per week for squamous-cell carcinoma of the head and neck (IAEA-ACC study): a randomised, multicentre trial. Lancet Oncol 2010;11:553–60.
[26] Geoffrois L, Martin L, de Raucourt D, Sun X, Tao Y, Maingon P, et al. Induction chemotherapy followed by cetuximab radiotherapy is not superior to concurrent chemoradiotherapy for head and neck carcinomas: results of the Gortec 2007-02 phase III randomized trial. J Clin Oncol 2018;36:3077–83 [doi:JCO2017762591].
[27] Blanchard P, Bourhis J, Lacas B, Posner MR, Vermorken JB, Cruz Hernandez JJ, et al. Taxane-cisplatin-fluorouracil as induction chemotherapy in locally advanced head and neck cancers: an individual patient data meta-analysis of the meta-analysis of chemotherapy in head and neck cancer group. J Clin Oncol 2013;31:2854–60.
[28] Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E, Gorbounova V, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007;357:1705–15.
[29] Schilling C, Stoeckli SJ, Vigili MG, de Bree R, Lai SY, Alvarez J, et al. Surgical consensus guidelines on sentinel node biopsy (SNB) in patients with oral cancer. Head Neck 2019;41:2655–64.
[30] Evans M, Beasley M. Target delineation for postoperative treatment of head and neck cancer. Oral Oncol 2018;86:288–95.
[31] Rosenthal DI, Mohamed ASR, Garden AS, Morrison WH, El-Naggar AK, Kamal M, et al. Final report of a prospective randomized trial to evaluate the dose-response relationship for postoperative radiation therapy and pathologic risk groups in patients with head and neck cancer. Int J Radiat Oncol Biol Phys 2017;98:1002–11.
[32] Ivaldi E, Di Mario D, Paderno A, Piazza C, Bossi P, Iacovelli NA, et al. Postoperative radiotherapy (PORT) for early oral cavity cancer (pT1-2, N0-1): A review. Crit Rev Oncol Hematol 2019;143:67–75.
[33] Ettl T, El-Gindi A, Hautmann M, Gosau M, Weber F, Rohrmeier C, et al. Positive frozen section margins predict local recurrence in R0-resected squamous cell carcinoma of the head and neck. Oral Oncol 2016;55:17–23.
[34] Patel RS, Goldstein DP, Guillemaud J, Bruch GA, Brown D, Gilbert RW, et al. Impact of positive frozen section microscopic tumor cut-through

revised to negative on oral carcinoma control and survival rates. Head Neck 2010;32:1444–51.
[35] Biau J, Thivat E, Millardet C, Saroul N, Pham-Dang N, Molnar I, et al. A multicenter prospective phase II study of postoperative hypofractionated stereotactic body radiotherapy (SBRT) in the treatment of early-stage oropharyngeal and oral cavity cancers with high risk margins: the STEREO POSTOP GORTEC 2017-03 trial. BMC Cancer 2020;20:730.
[36] Sanguineti G, Richetti A, Bignardi M, Corvo' R, Gabriele P, Sormani MP, et al. Accelerated versus conventional fractionated postoperative radiotherapy for advanced head and neck cancer: results of a multicenter Phase III study. Int J Radiat Oncol Biol Phys 2005;61:762–71.
[37] Ang KK, Trotti A, Brown BW, Garden AS, Foote RL, Morrison WH, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001;51:571–8.
[38] Graboyes EM, Kompelli AR, Neskey DM, Brennan E, Nguyen S, Sterba KR, et al. Association of treatment delays with survival for patients with head and neck cancer: a systematic review. JAMA Otolaryngol Head Neck Surg 2019;145:166–77.
[39] McClelland S, Andrews JZ, Chaudhry H, Teckie S, Goenka A. Prophylactic versus reactive gastrostomy tube placement in advanced head and neck cancer treated with definitive chemoradiotherapy: A systematic review. Oral Oncol 2018;87:77–81.
[40] Grégoire V, Evans M, Le Q-T, Bourhis J, Budach V, Chen A, et al. Delineation of the primary tumour Clinical Target Volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NCRI, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO, TROG consensus guidelines. Radiother Oncol 2018;126:3–24.
[41] Hoang JK, Vanka J, Ludwig BJ, Glastonbury CM. Evaluation of cervical lymph nodes in head and neck cancer with ct and mri: tips, traps, and a systematic approach. Am J Roentgenol 2013;200:W17–25.
[42] Grégoire V, Ang K, Budach W, Grau C, Hamoir M, Langendijk JA, et al. Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. Radiother Oncol 2014;110:172–81.
[43] Grégoire V, Eisbruch A, Hamoir M, Levendag P. Proposal for the delineation of the nodal CTV in the node-positive and the post-operative neck. Radiother Oncol 2006;79:15–20.
[44] Grégoire V, Grau C, Lapeyre M, Maingon P. Target volume selection and delineation (T and N) for primary radiation treatment of oral cavity, oropharyngeal, hypopharyngeal and laryngeal squamous cell carcinoma. Oral Oncol 2018;87:131–7.
[45] Biau J, Lapeyre M, Troussier I, Budach W, Giralt J, Grau C, et al. Selection of lymph node target volumes for definitive head and neck radiation therapy: a 2019 Update. Radiother Oncol 2019;134:1–9.
[46] Lapeyre M, Henrot P, Alfonsi M, Bardet E, Bensadoun RJ, Dolivet G, et al. [Propositions for the selection and the delineation of peritumoral microscopic disease volumes in oral cavity and oropharyngeal cancers (lymph nodes excluded)]. Cancer Radiother 2005;9:261–70.
[47] Lapeyre M, Miroir J, Biau J. [Delineation of the lymph nodes for head neck cancers]. Cancer Radiother 2014;18:572–6.
[48] Salama JK, Haddad RI, Kies MS, Busse PM, Dong L, Brizel DM, et al. Clinical practice guidance for radiotherapy planning after induction chemotherapy in locoregionally advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2009;75:725–33.
[49] Bakst RL, Glastonbury CM, Parvathaneni U, Katabi N, Hu KS, Yom SS. Perineural Invasion and Perineural Tumor Spread in Head and Neck Cancer. Int J Radiat Oncol Biol Phys 2019;103:1109–24.
[50] van den Bosch S, Dijkema T, Verhoef LCG, Zwijnenburg EM, Janssens GO, Kaanders JHAM. Patterns of recurrence in electively irradiated lymph node regions after definitive accelerated intensity modulated radiation therapy for head and neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys 2016;94:766–74.
[51] Peters LJ, Goepfert H, Ang KK, Byers RM, Maor MH, Guillamondegui O, et al. Evaluation of the dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. Int J Radiat Oncol Biol Phys 1993;26:3–11.
[52] Liu S-H, Chao KSC, Leu Y-S, Lee J-C, Liu C-J, Huang Y-C, et al. Guideline and preliminary clinical practice results for dose specification and target delineation for postoperative radiotherapy for oral cavity cancer. Head Neck 2015;37:933–9.
[53] Racadot S, Vérillaud B, Serre A-A, Le Guevelou J, Guzene L, Laude C, et al. [Impact of reconstructive or minimal invasive surgery on the assessment of current definitions of postoperative clinical target volume for head and neck cancers]. Cancer Radiother 2020;24:649–57.
[54] Bittermann G, Wiedenmann N, Voss P, Zimmerer R, Duttenhoefer F, Metzger MC. Marking of tumor resection borders for improved radiation planning facilitates reduction of radiation dose to free flap reconstruction in head and neck cancer surgery. J Cranio-Maxillo-Fac Surg 2015;43:567–73.
[55] Le Guevelou J, Bastit V, Marcy PY, Lasne-Cardon A, Guzène L, Gérard M, et al. Flap delineation guidelines in postoperative head and neck radiation therapy for head and neck cancers. Radiother Oncol 2020;151:256–65.
[56] Brodin NP, Tomé WA. Revisiting the dose constraints for head and neck OARs in the current era of IMRT. Oral Oncol 2018;86:8–18.
[57] Lapeyre M, Biau J, Miroir J, Moreau J, Gleyzolle B, Brun L, et al. [Concurrent chemoradiotherapy for head neck cancers. Should organs at risk dose constraints be revisited?]. Cancer Radiother 2020;24:586–93.
[58] Lapeyre M, Coche-Dequéant B, Moreira J-F, Le Bourhis J, Peiffert D. [Brachytherapy for head and neck cancers]. Cancer Radiother 2013;17:130–5.
[59] Mazeron J-J, Ardiet J-M, Haie-Méder C, Kovács G, Levendag P, Peiffert D, et al. GEC-ESTRO recommendations for brachytherapy for head and neck squamous cell carcinomas. Radiother Oncol 2009;91:150–6.
[60] Kovács G, Martinez-Monge R, Budrukkar A, Guinot JL, Johansson B, Strnad V, et al. GEC-ESTRO ACROP recommendations for head & neck brachytherapy in squamous cell carcinomas: 1st update - Improvement by cross sectional imaging based treatment planning and stepping source technology. Radiother Oncol 2017;122:248–54.
[61] Graff P, Blanchard P, Thariat J, Racadot S, Lapeyre M. [Post-treatment follow-up of head and neck cancer patients]. Cancer Radiother 2019;23:576–80.