



SEOM–TTCC clinical guidelines for the treatment of head and neck cancer (2025)

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Abstract

Squamous cell carcinoma of the lip, oral cavity, oropharynx, hypopharynx, and larynx comprises the ninth most common cancer in Spain. While alcohol and tobacco use have long been the primary etiological factors, the role of human papillomavirus (HPV) in oropharyngeal cancer is increasing. Diagnoses and relapses should always be discussed by an expert multidisciplinary team. For localized stages, surgery or radiotherapy should be used as single-modality treatments, while locoregional stages require combined modality approaches. In the case of recurrent or metastatic disease, curative intent should be considered for patients with local recurrence or oligometastatic disease, while systemic treatment is recommended for all other cases. These guidelines, developed by the authors on behalf of the Spanish Society of Medical Oncology (SEOM) and the Spanish Group for the Treatment of Head and Neck Tumors (TTCC), review available evidence and provide expert recommendations based on the current literature.

Keywords Head and neck cancer · Guidelines · Chemoradiotherapy · Immunotherapy

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Introduction

This Spanish Society of Medical Oncology (SEOM) guideline focuses on epithelial malignant tumors arising from mucosal surfaces of the lip, oral cavity, oropharynx, hypopharynx, and larynx. Nasopharyngeal, nasal cavity, paranasal sinuses, and salivary gland cancer, which follow a different natural history and have distinctive features, are not addressed in this guideline. Furthermore, the recommendations concentrate on squamous cell carcinoma (SCC), which is the most common histology in head and neck cancer (HNC); management of other types of HNC should be based on specific evidence for different histological types.

Alcohol and tobacco use are the main etiological factors for HNC in our area, although human papillomavirus (HPV) infection also plays a role, principally in oropharyngeal cancer [1]. HNC typically affects men due to earlier exposure to tobacco in this population. Nevertheless, incidence has been rising in women, attributed to increasing rates of tobacco smoking and the overall increase in HPV-related oropharyngeal tumors. Patients with HPV-positive oropharyngeal cancer have significantly better outcomes than those who are HPV-negative [2]. Other risk factors include radiation exposure, chronic infection, poor oral hygiene, poor nutrition, and betel nut chewing.

The worldwide incidence of HNC is highly heterogeneous, depending on the different distribution of risk factors. Oral cavity cancer is common in India, while HPV-related oropharyngeal cancer is more frequent in the USA and Northern Europe. In this regard, Southern Europe has a low burden of HPV-related oropharyngeal cancer, although incidence is rising in this area [3].

As for our area and according to data from the Spanish Network of Cancer Registries (REDECAN), the grouped incidence of lip, oral cavity, and pharynx cancer comprises the ninth highest cancer incidence for both sexes in Spain, with a crude incidence rate (CIR) of 22.7 cases per 100,000 inhabitants-year (95% confidence interval (CI) 18.8–27.0) in men and 9.0 (95% CI 7.9–10.3) in women. Laryngeal cancer has a CIR of 11.8 (95% CI 10.2–13.6) in males and 1.6 (95% CI 1.3–1.9) in females [4]. An epidemiological study in northeast Spain reveals that while the incidence of non-HPV-related oropharyngeal cancer is decreasing, as is the case of other HNC sites, oropharyngeal cancer due to HPV is increasing [5]. Almost two thirds of HNC are diagnosed in locally advanced stages, in which different therapeutic strategies can be used, requiring a multidisciplinary approach with different specialists to properly manage these patients.

In Spain, the crude combined mortality rate for lip, oral cavity, and pharynx cancer (both sexes) in 2022 was 4.9

cases per 100,000 inhabitants, while for laryngeal cancer, it was 2.6 per 100,000 inhabitants [6]. According to data from population-based cancer registries, 5-year relative survival was 61%, 49%, 41%, and 25% for laryngeal, oral cavity, oropharyngeal, and hypopharyngeal SCC, respectively [7].

Methodology

This guideline is based on a systematic review of relevant published studies and the consensus of ten treatment expert oncologists from TTCC (the Spanish acronym for the Spanish Group for the Treatment of Head and Neck Tumors) and SEOM (the Spanish Society of Medical Oncology), as well as an external review panel of two experts designated by SEOM. The Infectious Diseases Society of America-US Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines [8] has been used to assign levels of evidence and grades of recommendation (Table 1). The final text has been reviewed and approved by all authors.

Diagnosis and staging

Symptoms that should alert clinicians to a possible diagnosis of HNC include chronic odynophagia, swallowing problems, hoarseness, mouth ulcers that fail to heal, and/or neck masses.

A detailed clinical history should be performed, including comorbidities, symptoms, and toxic and sexual habits. Physical examination must be comprehensive and focus on the head and neck, including inspection, flexible fiberoptic endoscopy, and neck palpation. In addition, the patient's overall functional capacity should be assessed, considering performance status, airway patency, speech, dental health, nutrition, psychosocial condition, and the person's willingness to abandon smoking and alcohol consumption (IV, A). Assessment by a dentist is recommended, especially prior to radiotherapy (RT). Dental cleaning and potential tooth extractions may be necessary before treatment. Routine esophagoscopy or bronchoscopy is not recommended unless symptoms or diagnostic findings warrant it (IV, C).

Imaging is critical in HNC diagnosis and staging. Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) are essential for evaluating the primary tumor and regional lymph nodes (III, A). These modalities are complementary, and their indication should be discussed with a radiologist with experience in HNC. However, MRI outperforms CT in evaluating the tongue, skull base invasion, and intracranial extension. Identification of extracapsular nodal extension (ENE) is prognostic.

Table 1 Levels of evidence/grades of recommendation

Category, grade	Definition
<i>Grades of recommendation</i>	
A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit; does not outweigh risk or disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended
<i>Levels of evidence</i>	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts' opinion

Adapted from the quality and strength of evidence of the Infectious Diseases Society of America clinical practice guidelines [8]

Imaging should be conducted prior to biopsy to reduce artifacts from anatomical changes.

Chest CT should be performed to detect distant metastases and/or secondary lung tumors. Positron emission tomography (PET–CT) yields higher sensitivity and is particularly valuable in the following scenarios: for stage III–IV disease when definitive treatment is indicated; to diagnose carcinoma of unknown primary origin (II, A); to assess the response of the neck to RT or chemoradiotherapy 10 to 12 weeks after treatment [9]; and to identify early relapse or unclear findings from CT or MRI.

Routine blood tests should include a complete blood count, liver enzymes, serum creatinine, albumin, and TSH (thyroid-stimulating hormone) levels to establish baseline health status before treatment (IV, A).

Pathological confirmation by means of primary tumor biopsy or fine needle aspiration of lymph nodes is mandatory, although biopsy of the primary tumor is preferred. When nodal biopsy is required, complete resection is recommended to avoid extracapsular metastatic spread. Likewise, determination of HPV status in oropharyngeal tumors is mandatory (I, A). Pathological evaluation of surgical specimens must include tumor size, growth pattern, depth of invasion (DOI) (in oral cavity cancer), number and location of lymph nodes removed, presence of ENE, perineural and lymphatic infiltration, and surgical margins (R0–R1 resection) (I, A). Staging must be performed following the 8th edition of the AJCC staging system (TNM). The 9th edition of TNM has been recently published and it's expected to be used in clinical practice in the near future [10].

Treatment

Treatment of localized disease (Stages I–II)

Surgery and RT provide similar locoregional control and survival outcomes, although they have not been compared in randomized trials. Therefore, in the absence of high-level evidence, a multidisciplinary team should choose a single modality of treatment based on the patient's characteristics and wishes and on potential functional outcomes (Fig. 1).

Surgery is generally preferred over RT in the oral cavity (IV, B) [11]. In these cases, elective neck dissection (END) is recommended over therapeutic neck dissection because END increases overall and disease-free survivals (I, A) [12]. DOI is a crucial issue in oral cancers, and only tumors with DOI < 2 mm can be observed without neck dissection (V, C).

In oropharyngeal carcinoma, minimally invasive transoral surgery, such as transoral robotic surgery (TORS) or transoral laser microsurgery (TLM), achieve good results with less morbidity and should be prioritized over open surgery (IV, B) [13]. Evidence suggests that RT is an alternative with a lower tendency of long-term dysphagia (II,C) [14].

As for the oral cavity and oropharynx, sentinel lymph node biopsy (SLNB) obtains the same 5-year neck-relapse-free survival, disease-specific survival, and overall survival (OS) as END. Consequently, it can also be regarded as standard of care (I, A) [15].

Hypopharynx cancers often present in advanced stages (> 75% cases); thus, there is no strong evidence in

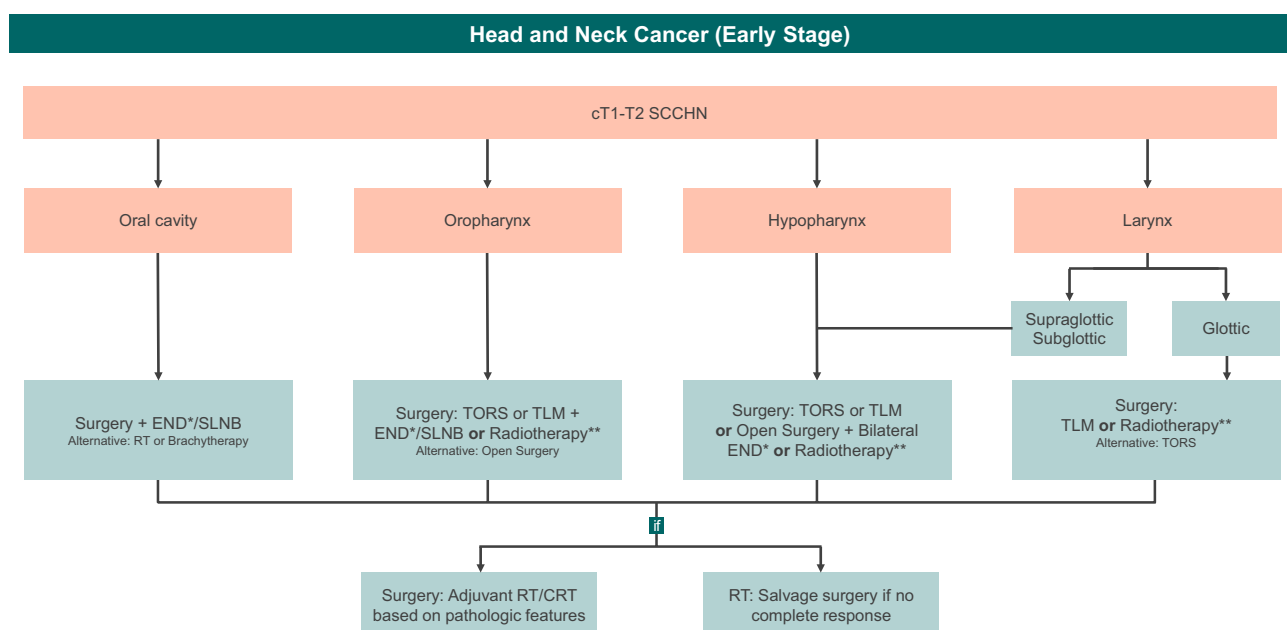


Fig. 1 Head and neck cancer (early stage). *Bilateral elective nodal dissection is recommended for midline, palate, and base of tongue tumors. ** Radiotherapy should include primary tumor and neck lymph nodes. END Elective node dissection; SLNB Sentinel lymph

node biopsy; SCCHN Squamous cell carcinoma of the head and neck; TLM Transoral laser microsurgery; TORS Transoral robotic surgery; RT Radiotherapy; CRT Chemoradiotherapy

early-stage patients. Comparable tumor control and survival rates have been achieved in patients with early-stage hypopharyngeal cancer with either surgery or definitive RT (IV, C).

In glottic larynx carcinomas, there is no clear OS difference between TLM and RT; however, there may be a trend in favor of TLM for disease-free survival and OS (IV, B). The same studies suggest a favorable tendency for RT if maintaining voice quality is the objective. These data must be discussed with the patient when choosing a treatment strategy. Intensity-modulated RT points toward superiority over conventional RT for local and regional control, although the difference is not significant (II, B) [16].

In supraglottic larynx cancers, TORS is a safe and effective option and may be superior to TLM (IV, B) [17]; however, there are no prospective data upon which to base a decision of whether to opt for conservative surgery, open surgery, or RT (II, B).

END, SLNB, or neck RT (if RT is chosen as primary treatment) is recommended for cT1-2N0 with the exception of cT1-2 glottic cancer (I, A) [18]. Tumors that arise in or near the midline and tumor sites that frequently have bilateral lymphatic drainage (base of tongue, palate, supraglottic larynx, hypopharynx, deep pre-epiglottic space) should be treated with bilateral END or neck RT.

Treatment of locoregionally advanced disease

Clinical stage III/IV is associated with high risk of both local recurrence and distant metastasis. Optimizing long-term disease control calls for combined modality approaches. Decisions regarding optimal sequencing require multidisciplinary input (I, A), considering factors such as the primary tumor site and extent of disease, individual patient factors (age, comorbidity, preferences for treatment type), as well as the functional consequences and morbidity of each therapeutic approach. The experience and technology available at the patient's medical institution also play a crucial role in decision-making (I, A) (Fig. 2).

Surgery-based treatment

In HNC, there is no universally accepted definition of unresectability; however, certain anatomical criteria are deemed unequivocal and classify the tumor as T4b. These include involvement of skull base, cervical vertebrae, prevertebral muscles, brachial plexus, mediastinal spread, involvement of nasopharynx, tumor fixed to the collarbone, and vascular encasement.

Multidisciplinary tumor boards can exclude patients from surgery due to low probability of achieving adequate

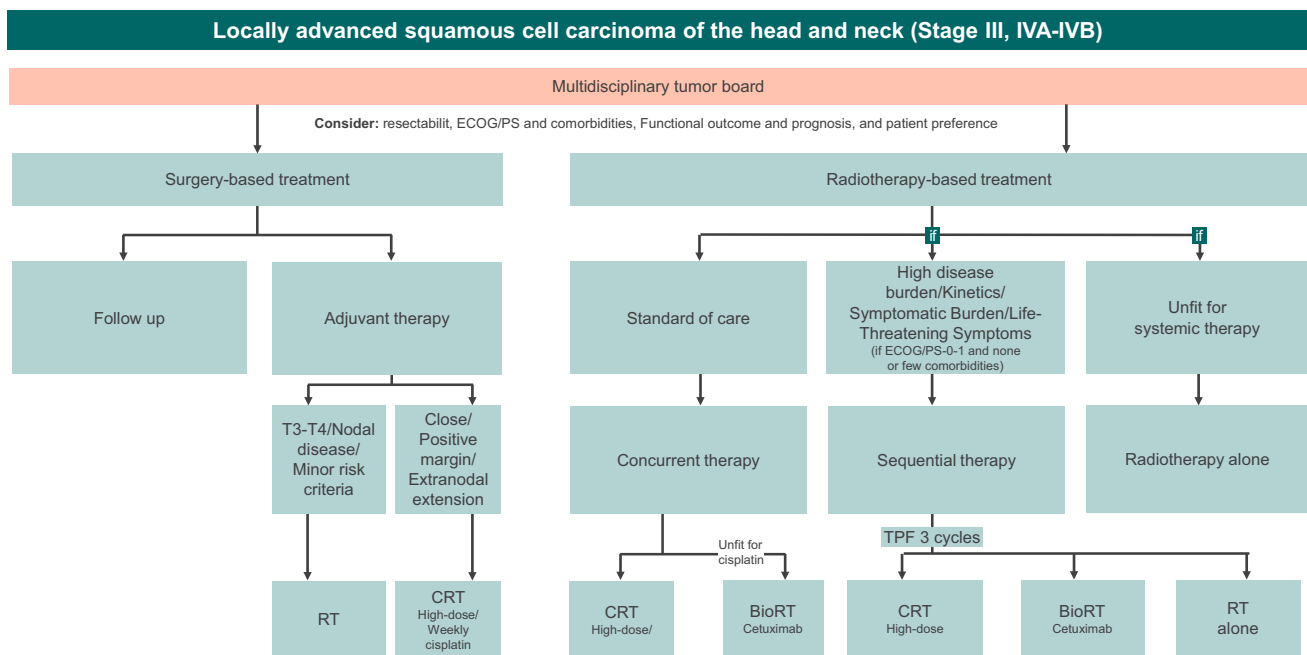


Fig. 2 Locally advanced squamous cell carcinoma of the head and neck (Stage III, IVA-IVB). *BioRT* Bioradiotherapy; *CRT* Chemoradiotherapy; *PS* Performance status; *RT* radiotherapy; *TPF* docetaxel/cisplatin/5-fluorouracil

margins, unacceptable functional and/or esthetic sequelae, meager expectation of cure, or comorbidities (I,A).

For locoregionally advanced oral cavity neoplasms, surgery is generally recommended as the initial approach. Simultaneous resection and reconstruction can be completed with acceptable functional outcomes. For cancers originating at other sites, functional preservation of speech, swallowing, and airway are vital factors that inform treatment decisions. Efforts are made to preserve these functions while minimizing the number of treatment modalities used to reduce treatment-related morbidity. Minimally invasive surgical techniques accomplish good functional and oncologic outcomes in appropriately selected cases.

The risk of nodal metastases varies by primary tumor site and factors such as size, histology, tumor thickness, and perineural invasion. When the probability of occult metastases exceeds 15–20%, the risk of neck recurrence without elective (prophylactic) treatment outweighs the morbidity associated with neck dissection [19]. For T3-4a N0 tumors, an ipsilateral or bilateral neck dissection is an option (except for oral cavity tumors, where it is mandatory). When neck nodes are palpable or histologically confirmed, all nodal levels should be dissected [20].

Adjuvant treatment Intensity-modulated radiotherapy (IMRT) 60–66 Gy is the preferred RT technique (I, A) [21].

RT alone may be considered when there are multiple positive neck nodes (without ENE), perineural, vascular, or lymphatic invasion, a pT3 or pT4 primary, or oral cavity or

oropharyngeal primary cancers with positive level IV or V nodes (I, A).

Concurrent chemoradiotherapy (CCRT) is recommended for tumors with high-risk pathological features such as affected margins and/or ENE extension (I, A) [22]. This involves three-weekly intravenous cisplatin 100 mg/m² on days 1, 22, and 43 (I, A) [22]. Weekly 40 mg/m² cisplatin can be a non-inferior alternative with better safety profile (I, B) [23]. Recently, the phase III NIVOPOSTOP trial has shown improved disease-free survival (DFS) in patients with high-risk resected HNC treated with adjuvant nivolumab plus standard-of-care postoperative chemoradiotherapy with three-weekly cisplatin *versus* postoperative chemoradiotherapy alone, though approval is pending (I, A) [24].

In patients unfit for platinum, consider RT alone (I, A). There is no evidence to endorse carboplatin in the adjuvant setting. Cetuximab improved DFS, but not OS in patients with intermediate-risk compared to RT alone [25].

Neoadjuvant treatment There is no evidence to support the use of induction chemotherapy (ICT) before surgery for resectable locally advanced HNC (I, A) [26]. Perioperative pembrolizumab (neoadjuvant for 2 cycles and adjuvant for a total of 15 cycles) in this setting has shown improved event-free survival compared to standard of care (surgery followed by (chemo)radiotherapy) in a phase III randomized trial. Based on these results, pembrolizumab was approved by the FDA in June 2025 and EMA in October 2025 for patients with resectable locally advanced HNC

whose tumors express PD-L1 by CPS (≥ 1), and is currently awaiting approval from the Spanish Agency of Medicines and Medical Devices (AEMPS) for standard clinical use in Spain [27] (I, A).

Radiotherapy-based treatment

RT-based treatment is recommended for patients with unresectable disease, those with resectable disease but poor functional outcomes, those whose prognosis does not justify mutilating surgery, or those who refuse this procedure.

Concurrent chemoradiotherapy Radiotherapy: IMRT or its variant volumetric modulated arc therapy (VMAT) are the recommended techniques (I, A), given the significantly reduced rate of xerostomia and improved quality of life without compromising locoregional control and survival rates [21]. Recommended dose fractionation schedules are 70 Gy in 35 fractions over 7 weeks and 65–66 Gy in 30 fractions over 6 weeks (I, A).

Chemotherapy: CCRT achieves better locoregional control and better OS compared to RT alone, as evidenced by several Phase III clinical trials and updates from the MACH-NC meta-analysis (I, A) [28]. The CT regimen exhibiting the greatest benefit is cisplatin-based, with recommended total doses $> 200 \text{ mg/m}^2$, administered as 100 mg/m^2 on days 1, 22, and 43 (I, A). Non-inferiority analyses have failed to demonstrate a benefit of other concurrent combinations, such as weekly cisplatin, over the standard regimen (II, B) [29]. Careful patient selection and continuous support are indispensable in light of the related acute and chronic toxicities. Efficacy decreases in patients over 70 years [28].

Cetuximab: Bioradiotherapy (an initial dose of cetuximab 400 mg/m^2 on day –8 followed by 250 mg/m^2 weekly concurrent) is an alternative in patients unable to receive cisplatin (I, A) [30]. Comparison studies and meta-analyses indicate that cetuximab is inferior to cisplatin when used concurrently with RT [31], even though most of the patients included were HPV positive [31].

Immunotherapy: It has not improved CCRT outcomes in this setting [32, 33].

Sequential therapy with induction chemotherapy (ICT) ICT enables rapid responses and predicts responses to subsequent therapies. Updated meta-analyses reveal no significant OS benefit, but lower incidence of metastasis with ICT [34]. Induction regimen TPF (three-weekly cisplatin 75 mg/m^2 , docetaxel 75 mg/m^2 , 5-fluorouracil $750 \text{ mg/m}^2/\text{d}$ continuous infusion 96 h) is the schema of choice [35] (I, A). ICT should be considered for patients with good performance status and organ function, given its associated toxicity, as large tumor volume and/or associated symptoms can compromise the patient's prognosis.

Post-ICT decisions should factor in response and tolerance. Cetuximab has not proven non-inferiority to cisplatin, making CCRT the recommended option whenever possible (I, A) [36].

Salvage neck dissection Salvage neck dissection should be contemplated in patients with complete response of the primary tumor, but persistent nodal disease on PET–CT at 12 weeks post-treatment (I, A) [9].

Approach to functional organ preservation

Organ preservation approaches have been applied for resectable laryngeal or hypopharyngeal disease. The organ preservation technique chosen must have an equivalent oncological benefit or be preferred by the patient.

When the tumor has destroyed the organ, functional organ-preservation approaches are inappropriate, and surgery is preferred. This typically occurs with very advanced laryngeal or hypopharyngeal cancers [37].

Salvage surgery is crucial to maintain survival rates when primary non-surgical treatments fail, but cases should be discussed beforehand by a multidisciplinary team.

Three options can be considered (Fig. 3):

1. Laryngeal preservation surgery and minimally invasive surgery followed by RT (or CCRT if risk factors for adjuvant CT) (I, A): Surgical advances provide options for larynx preservation in carefully selected patients. These surgical approaches have not been subject to head-to-head comparisons with CCRT [38].
2. CCRT: CCRT offers a significantly greater probability of larynx preservation compared to RT alone or ICT followed by RT alone (I, A). The standard regimen is cisplatin (100 mg/m^2 on days 1, 22, and 43). If cisplatin is not feasible, consider cetuximab concurrent with RT (I, A) [31, 37]. This approach is unsuitable for patients with large T4a lesions and/or poor pretreatment laryngeal function. For patients over 70 years, as well as those with comorbidities or suboptimal performance status, a thorough evaluation must be performed before offering this strategy.
3. ICT with TPF schedule: Tumor responsiveness to ICT provides predictive and prognostic information that can be advantageous when deciding if functional organ preservation is feasible, whether surgical resection is indicated, or more intensive CCRT should be administered. When compared to bioradiotherapy following ICT, CCRT achieved better local control. However, laryngeal preservation, laryngeal function, and OS were similar in the cisplatin and cetuximab arms [39].

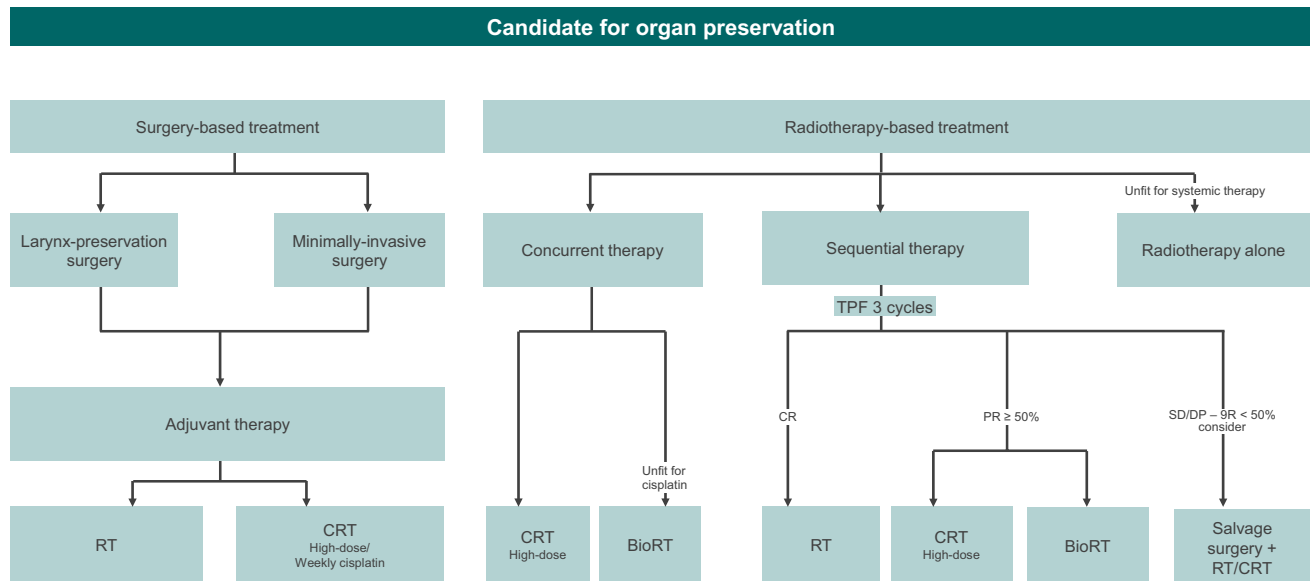


Fig. 3 Candidate for organ preservation. *BioRT*: bioradiotherapy; *CR* Complete response; *CRT* Chemoradiotherapy; *DP* Disease progression; *PR* Partial response; *PS* Performance status; *RT* radiotherapy; *TPF* docetaxel/cisplatin/5-fluorouracil; *SD* stable disease

If the patient fails to respond to ICT, prognosis is worse. Strategies based on salvage surgery should be discussed on a case-by-case basis by a multidisciplinary team (III, B).

Management of HPV-related oropharyngeal cancer

HPV status is a recognized independent prognostic factor in oropharyngeal squamous cell cancer (OPSCC), associated with a 58% reduction in mortality risk for HPV-positive *versus* HPV-negative tumors [2].

Diagnosis and staging

p16^{INK4a} overexpression is a surrogate marker for HPV involvement and is the most widely used one in clinical practice. Recent studies strongly recommend confirming HPV status in p16-positive patients using HPV-specific biomarkers, such as HPV DNA (IIA) [40]. HPV testing and p16 evaluation should be conducted concurrently in cancer staging, particularly in regions with a low attributable fraction (e.g., Spain), to ensure a comprehensive and accurate prognostic assessment.

Treatment

Staging of HPV-related OPSCC must follow the AJCC TNM 8th edition, while treatment decisions should be based on the AJCC TNM 7th edition.

- T1-T2, N0: initial treatment with either minimally invasive surgery (TORS, TLM) or IMRT (I, A). Patient characteristics and the treating team's expertise must be considered.
- T1-T2, single node involvement, disease ≤ 3 cm in selected non-smoking patients, with no adverse features (examples of adverse features include endophytic, ulcerated primary tumors; radiographic evidence of ENE or nodal matting; highly suspicious clustered or small lymph nodes; or retropharyngeal, level IV, or level V lymph node involvement): options including single-agent RT or surgery (IIC).
- T3-T4 or any T stage with one node > 3 cm, multiple involved nodes, or evidence of ENE: definitive chemoradiation alone rather than surgery (IIC). Cisplatin (100 mg/m² every 3 weeks) in combination with RT remains the standard of care, following the negative results of two phase III de-escalation trials [41, 42].
- Recurrent or metastatic disease: the clinical management does not differ from R/M HPV-negative HNC (I, A).

Surveillance

Following definitive chemoradiotherapy, PET imaging should be interpreted cautiously, as it may remain positive despite complete response [43].

A role for the use of circulating tumor HPV DNA in post-treatment surveillance has yet to be established and is currently under investigation.

Treatment of recurrent and metastatic disease

Patients with recurrent disease following primary treatment or newly-diagnosed metastatic disease (R/M) should be presented for discussion by the multidisciplinary tumor board. In the presence of oligometastatic (1–3 lesions) disease, treatment with curative intent should be considered (II, C) [44]. In cases of recurrence, salvage surgery and re-irradiation feasibility should be discussed. Systemic treatment should be considered in all other patients.

First-line treatment

Choice of treatment should consider both patient and disease characteristics, including Eastern Cooperative Oncology Group (ECOG)/performance status (PS), comorbidities, prior treatments, symptom and disease burden, tumor kinetics, PD-L1 expression as per the combined positive score (CPS) (required for pembrolizumab indication in first-line R/M) or tumor positive score (TPS) (required for pembrolizumab in the platinum-refractory setting), in addition to patient preference (expected toxicity, quality of life, etc.). PD-L1 expression should be preferably determined in the most recent tumor sample available. In pre-treated patients with recurrent disease, newly-obtained tumor tissue should be sought whenever feasible, weighing risk (i.e., bleeding) *versus* benefit [45].

Platinum-naïve/-sensitive disease

In cases of platinum-naïve disease or recurrent disease >6 months following a patient's last dose of platinum-based chemotherapy in the locally advanced setting, treatment recommendations are as follows (Fig. 4):

Patients with ECOG/PS <1:

- Tumors with PD-L1 expression of ≥ 20 by CPS [46]:
 - Pembrolizumab is the preferred option, particularly if low symptom load or low/slow disease burden/kinetics (I, A).
 - Pembrolizumab plus cisplatin/carboplatin-5-fluorouracil may be preferable when symptom/disease burden indicates greater importance of objective response (I, A).

● Tumors with PD-L1 expression of 1–19 by CPS [46]:

- Pembrolizumab plus cisplatin/carboplatin-5-fluorouracil is the preferred option (I, A).
- Pembrolizumab monotherapy may be considered based on patient characteristics (i.e., comorbidities contraindicating chemotherapy) and preference (I, A).

● Tumors negative for PD-L1 expression by CPS (<1):

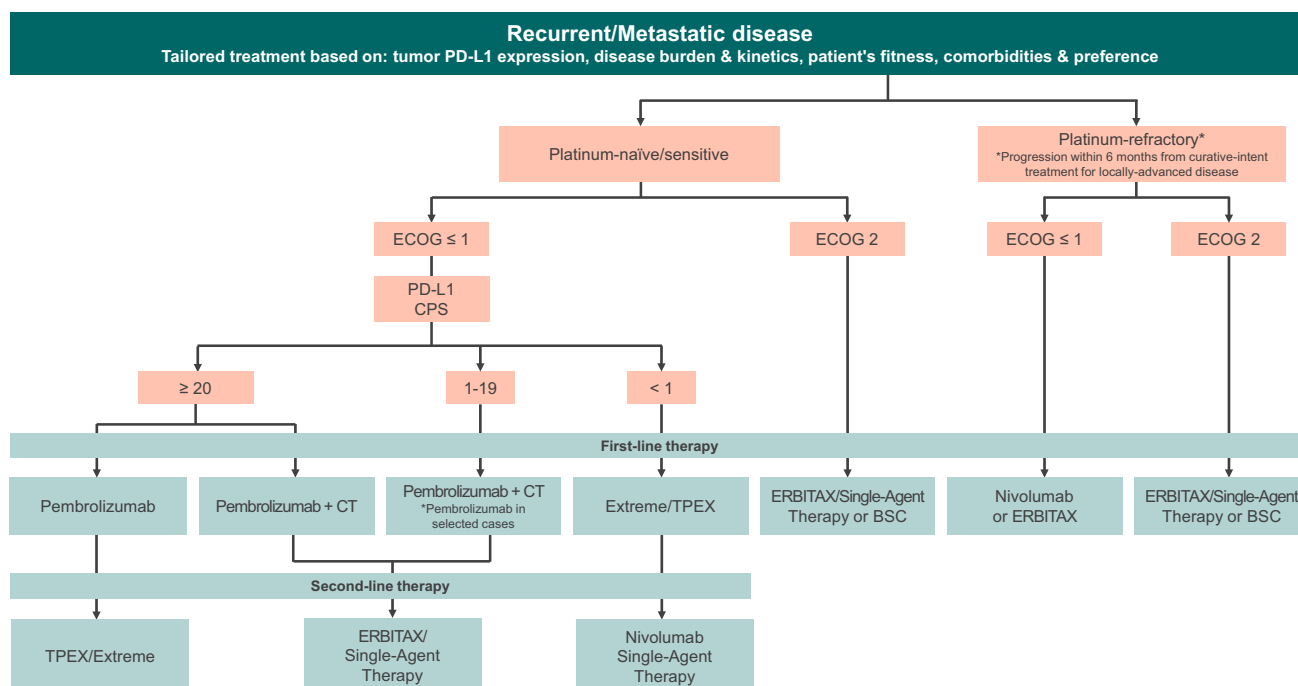


Fig. 4 Recurrent/metastatic disease. CPS Combined positive score; CT chemotherapy; BSC Best supportive care; TPEX cisplatin and docetaxel plus cetuximab

- EXTREME regimen (cisplatin or carboplatin and 5-fluorouracil plus cetuximab) (I, A) [47].
- TPEX (cisplatin and docetaxel plus cetuximab) when 5-FU is contraindicated (must be eligible for cisplatin) (II, B) [48].

Patients with ECOG/PS 2:

- Paclitaxel plus cetuximab (ERBITAX regimen) (III, C), single-agent chemotherapies (III, C), or single-agent cetuximab (III, C) [49, 50].
- Data on the efficacy of pembrolizumab in patients with R/M disease and ECOG performance status 2 are limited and has pembrolizumab not been approved for use in this population in Spain. Therefore, individualized use is recommended (IV, C) [51].
- Supportive care.

Patients with ECOG/PS ≥ 3 should only be offered supportive care.

Platinum-refractory disease

Patients who experience disease progression and/or recurrence within 6 months after the last dose of cisplatin-based chemotherapy should not be treated with cisplatin- or carboplatin-based chemotherapy doublets. Recommendations are as follows:

● Patients with ECOG/PS ≤ 1 :

- The preferred option is nivolumab (I, A) regardless of PD-L1 expression [52]. Pembrolizumab monotherapy can be considered if TPS $> 50\%$, noting that this use is considered off-label in Spain (II, A) [53].
- In cases in which anti-PD-1 agents are contraindicated (i.e., systemic immune-related disorders,) or not recommended (high disease burden and kinetics), paclitaxel plus cetuximab (ERBITAX regimen) (III, C) or single-agent chemotherapies should be considered.

● Patients with ECOG/PS 2:

- Paclitaxel plus cetuximab (ERBITAX regimen) (III, C), single-agent chemotherapies (III, C), or single-agent cetuximab (III, C) [49, 50].
- Data on the efficacy of nivolumab in patients with R/M disease and ECOG performance status 2 are limited; furthermore, this drug has yet to be approved in this patient population in Spain. Therefore, individualized use is recommended (IV, C) [54].

Second and subsequent lines of systemic therapy

There is limited prospective evidence regarding the efficacy of second-line therapies and beyond after the introduction of immunotherapy in the front-line setting. Subsequent regimens at progression will, therefore, depend on first-line treatment. As previously mentioned, choice of treatment should consider patient and disease characteristics, including ECOG/PS, comorbidities, symptom and disease burden, as well as patients' preference (expected toxicity, quality of life, others). If appropriate, patients should be offered or referred for clinical trials whenever available.

- For patients with prior pembrolizumab monotherapy: for patients with ECOG ≥ 1 and fit for platinum-based chemotherapy, EXTREME/TPEX regimens are preferred options. For ECOG 2 patients or those unfit for platinum, ERBITAX regimen should be considered (III, C).
- For patients with prior pembrolizumab plus platinum and 5-FU: ERBITAX regimen should be considered (III, C).
- For patients with prior EXTREME/TPEX: nivolumab (I, A) [52] or single-agent chemotherapy (taxane or capecitabine based on prior therapy received) are acceptable treatment options.
- Beyond second-line treatment: single-agent therapy with taxanes (docetaxel, paclitaxel) or anti-metabolite drugs (capecitabine or 5-FU, methotrexate) may be considered beyond second line depending on the patient's fitness (III C). Of note, second- and subsequent-line trials have tested different drugs with small sample sizes, and the heterogeneity of the study populations hinders the evaluation of the relative efficacy of each drug.

Recommendations for follow-up

Subjects treated for HNC should be monitored for a minimum of 5 years. The risk recurrence is estimated at between 40 and 60% for individuals with locally advanced disease, largely within the first 2 years after primary diagnosis. Prolonged follow-up in selected cases, especially because of the risk of second primary tumors, should be individualized. The incidence of second primaries, particularly tobacco-related ones such as lung, urinary tract, or other head and neck sites, is 2–4% per year and remains relatively constant over time. In addition to the specialists who have treated them, patients should be followed up by a multidisciplinary clinical team that includes clinical nurse specialists, speech and language therapists, dietitians, and other allied health professionals.

A proper clinical examination must include flexible nasopharyngolaryngoscopy. MRI and PET combined with CT imaging can be useful when recurrence is suspected.

Patients should be educated about recurrence appearance and detection. Persistent pain or the appearance of neck nodules should be investigated to exclude recurrent disease. Support with tobacco and alcohol cessation services should be offered to patients who present with these etiological factors.

There is no evidence that serological tumor markers provide any value in the follow-up of HNC patients.

The main follow-up recommendations for people treated for HNC are the following:

- Clinical follow-up including head and neck examination by flexible endoscopy should be performed every 2–3 months during the first 2 years, every 6 months for years 3–5, and annually thereafter (III, A).
- Imaging should be carried out if symptoms arise or in cases of abnormalities found on clinical examination (III, A). More intensive follow-up with semi-annual or annual CT scans should be individualized.

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Data availability Data sharing is not applicable to this article as no datasets were generated or analyzed.

Declarations

Conflict of interest Virginia Arrazubi reports Advisory Board, and Speaker from BMS and MSD and Speaker from Beigene, Lilly, Astellas and Organon. Marc Oliva reports Advisory Board, and Speaker from Merck; Other from Transgene and Guardant Health; personal fees from Obataca; Grant from Roche and Speaker from BMS. Pedro Pérez reports Speaker, and personal fees, non-financial support from MSD and Merck, and Speaker, Grant, personal fees, non-financial support from BMS. Jordi Rubió-Casadevall reports Advisory Board from Novartis, Sanofi, Merck and Lilly, and Speaker from IPSEN. Gemma Bruixola reports Speaker from Merck, BMS and MSD. Beatriz Cirauqui reports Advisory Board, Speaker, Grant from Merck, BMS and MSD, and Speaker from Pfizer. Antonio Rueda Domínguez reports Advisory Board, and Speaker from Roche, Takeda, Gilead and Merck; Speaker from MSD and BMS. Lara Iglesias, Alberto Carral and Beatriz Castelo have nothing to disclose.

Ethical approval Not applicable.

Informed consent The manuscript does not contain clinical studies or patient data.

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