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Review

Multidisciplinary management of head and neck cancer: First expert consensus using Delphi methodology from the Spanish Society for Head and Neck Cancer (part 1)

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ABSTRACT

Head and neck cancer is one of the most frequent malignances worldwide. Despite the site-specific multimodality therapy, up to half of the patients will develop recurrence. Treatment selection based on a multidisciplinary tumor board represents the cornerstone of head and neck cancer, as it is essential for achieving the best results, not only in terms of outcome, but also in terms of organ-function preservation and quality of life. Evidence-based international and national clinical practice guidelines for head and neck cancer not always provide answers in terms of decision-making that specialists must deal with in their daily practice. This is the first Expert Consensus on the Multidisciplinary Approach for Head and Neck Squamous Cell Carcinoma (HNSCC) elaborated by the Spanish Society for Head and Neck Cancer and based on a Delphi methodology. It offers several specific recommendations based on the available evidence and the expertise of our specialists to facilitate decision-making of all health-care specialists involved.

Introduction

HNSCC is the fifth most common malignancy worldwide and the eighth most common cause of cancer-related mortality [1,2]. Tobacco and alcohol abuse are the main risk factors, but in the past few years HPV infection has emerged as a new risk factor for a substantial percentage of HNSCC-especially in oropharyngeal cancer (OPC) [3]. Only one third of the patients present with early stage disease, while most of them will have locally advanced (LA) disease by the time of diagnosis [4]. In these patients, 5-year survival has remained invariable in the last decades [5]. Surgery and radiotherapy (RT) remain the primary treatment modalities for early tumors, while the addition of chemotherapy and targeted therapy (anti-EGFR monoclonal antibody Cetuximab) improve survival in locoregionally advanced disease [6,7]. However, despite the site-specific multimodality therapy, up to 60% and 30% of patients will develop local and distant recurrence, respectively [8]. Treatment selection based on a multidisciplinary tumor board decision repre-

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sents the cornerstone of head and neck cancer, as it is essential for achieving the best results, not only in terms of outcome, but also in terms of organ-function preservation and quality of life [9,10]. Evidence-based international and national guidelines for Head and Neck cancer are helpful but they often do not provide answers in terms of decision-making that specialists must deal with in their daily practice [10,11]. In this regard, an expert consensus might represent a useful tool. There is only one expert consensus on the multidisciplinary treatment for HNSCC, published by Lang in 2014, although its elaboration was not based on a "Delphi" methodology [12]. This is the first Expert Consensus on the Multidisciplinary Approach for HNSCC Treatment elaborated by the Spanish Society for Head and Neck Cancer that offers several specific recommendations based on the available evidence and the expertise of our specialists to facilitate decision-making of all health-care specialists involved.

Methods

The first "Consensus on the Multidisciplinary Approach for HNSCC Treatment" was endorsed by the Spanish Group for Head and Neck Cancer Treatment (TTCC) and the Spanish Society for Head and Neck (SECC), including medical, radiation and surgical oncologists.

The study was performed using the Delphi methodology; a systematic, interactive forecasting method which relies on a panel of experts integrated in this study by 25 specialists whose contributions were collected in the form of answers to questionnaires and their comments. The group of experts was led by the four authors of the article: MR and RA (medical oncologists), president and vice-president of the Spanish Group for Head and Neck Cancer Treatment (TTCC) respectively; GJ (radiation oncologist), president of the Spanish Group of Radiation Oncology for Head and Neck Cancer (GEORCC); and MM (ENT) Head of Head and Neck Cancer from the Spanish Society of Otorhinolaryngology (SEORL). The 25 experts participating were selected based on the following criteria: Opinion leadership in their own area, experience in the field (a minimum of 5 years-experience in Head and Neck cancer) and geographical location (to cover or the Spanish geography). A coordinator controlled the interactions among the participants by processing the information and filtering out irrelevant content. The result is a number of recommendations obtained from a decision-making process by a structured expert group, which are believed to be more accurate than those from unstructured groups or individuals. To that end, to achieve a consensus of agreement, in the case of questions based on a metric scale, the level of consensus required in each question must be equal to or greater than 68% in the first phase, and equal to or greater than 70% in the second phase in the "TOP 4" (meaning a minimum score of 7 points). The same rule applies for a consensus of disagreement that is achieved when in the second phase the "BOTTOM 4" meaning a maximum score of 3 points. In the case of nominal questions, a level of consensus equal or greater than 50% is required to achieve a consensus of agreement or disagreement.

A total of 57 questions were elaborated by the coordinators and distributed in 6 categories (C): 1. Laryngeal/hypopharyngeal cancer; 2. OPC and oral cavity cancer (OCC); 3. Response assessment after a non-surgical treatment; 4. Recurrent/metastatic disease; 5. Relapse and second primary tumors; 6. Cervical SCC of unknown primary site.

The study was developed in 3 phases. During the first phase, developed between February 12th and March 14th, 2016, the experts answered the 57 questions anonymously through an online questionnaire. Questions that did not reach the level of consensus required in the first phase were proposed for inclusion in the second phase, developed between April 13th and May 3rd. In this phase questions were answered again by 21 of the 25 participating experts. In the third phase, developed between June 8th and 20th, experts had to answer 4 additional questions proposed by the coordinators: 22 of the 25 initial experts participated in this phase. The coordinators were responsible for the analysis and identification of the divergent answers and did not respond the questions in any phase of the study. Finally, once elaborated the recommendations, experts validated every recommendation by voting in a face-to-face meeting.

This first article is focused on the following categories (C): early stage and locally advanced HNSCC (C1, C2) and evaluation of response after CRT (C3).

Results and discussion

C1. Laryngeal/hypopharyngeal SCC

See Table 1.

C1.A Early stage (stage I and II)

Clinical staging using diagnostic imaging is necessary to plan the optimal therapeutic approach, which should ensure the radical management of oncological patients [13]. Indirect laryngoscopy is the first step in the diagnosis and clinical evaluation of laryngeal cancer (tumor extension), however, it has limitations in the assessment of the implication of deep structures (anterior commissure, thyroid cartilage, and paraglottic spaces) that are discriminating for the extension of surgical resection [14]. This is especially relevant to offer partial resections or RT, which have demonstrated high rates of local control. CT and MRI are useful imaging tests with similar sensitivity to detect the extension of cartilage invasion and nodal involvement [15]. As a result, the panel of experts recommend an imaging test (CT or MRI) in the routine staging of early laryngeal/hypopharyngeal cancer.

Treatment of choice for an early stage laryngeal/hypopharyngeal cancer should be the most effective in terms of outcome according to the available evidence, and should not be influenced by further potential salvage therapies. When feasible, organ-preservation strategies including RT, partial laryngectomy (PL) or transoral laser surgery (TOLS) should be the initial therapeutic approach. Although there are no randomized trials comparing RT and conservation surgery, both strategies have shown similar rates in terms of local control (LC), progression-free survival (PFS) and overall survival (OS) [16]. In case of surgery, a margin of 2 mm is considered correct in early glottic cancer [17,18]. TOLS might achieve higher rates of local control and larynx preservation in some series and it has shown to improve overall survival when compared to RT in a meta-analysis of early-stage glottic cancer [19,20]. Adjuvant RT has not shown any benefit and might limit its further use at recurrence. Consequently, the experts agree that both modalities are valid in this setting, but recommend TOLS as treatment of choice for stage I/II laryngeal cancer. In stage I laryngeal cancer involving anterior commissure, that differs from the T1 reaching anterior commissure because of infiltration of cartilage, similar control rates can be obtained with open surgery, TOLS or RT, although some authors report that TOLS seemed to be associated with a higher risk of positive margins. [21–23].

Voice quality should also be considered when choosing the best treatment approach, especially in patients who need to preserve their voice for occupational purposes. Most studies suggest that RT improves functional outcomes and is better at preserving voice quality, especially in supraglottic cancers. Surgery of glottic cancer is associated with greater rates of dysphonia, which seem to be related to the extension of resection and the type of cordectomy

Table 1
Summary of recommendations for Laryngeal and Hypopharyngeal cancer.

Recommendation	Phase	Accepted consensus (% of agreement)
Routine staging of early laryngeal/ hypopharyngeal cancers should include an imaging test	1	YES (72)
Initial treatment of choice for laryngeal/ hypopharyngeal cancer should be the most effective according to available evidence, and should not be influenced by further potential salvage therapies	2	YES (76)
First treatment approach for an early stage laryngeal/hypopharyngeal cancer should include either surgery or radiotherapy, but not the combination of both	1	YES (80)
Transoral surgery is the recommended treatment for stage I/II laryngeal cancer	1	YES (88)
Adjuvant radiotherapy is generally not recommended		YES (72)
Treatment required for carcinomas located in the anterior commissure differs from the T1b glottis carcinoma	1	YES (76)
Voice quality should be considered when choosing the treatment for a stage I/II laryngeal/hypopharyngeal cancer	1	YES (88)
Radiotherapy should be the treatment of choice for patients diagnosed with an early stage glottis cancer who need to preserve their voice for occupational purposes	1	YES (92)
Patients with positive resection margins after surgery with radical intention for a laryngeal/hypopharyngeal cancer should be offered surgical:	1	YES
– Re-resection		(92)
– If not feasible, adjuvant radiotherapy is recommended		(68)
– Observation is not recommended		(68)
In patients with locally advanced supraglottic cancer either:		YES
– surgery (supraglottic laryngectomy)	2	(76)
– concurrent chemoradiotherapy	1	(88)
are validated options of treatment		
In patients with laryngeal/hypopharyngeal cancer, nodal disease burden (N) might change the initial therapeutic approach of the primary tumor, regardless of the T stage	1	YES (92)
In patients with a T3 laryngeal/ hypopharyngeal cancer, concurrent chemoradiotherapy (CRT) is recommended	1	YES (88)
Total or partial laryngectomy is an adequate treatment option in patients with a T3 laryngeal/hypopharyngeal cancer	2	NO (33)
Surgery followed by adjuvant radiotherapy/ CRT should be the treatment of choice for T4 laryngeal/hypopharyngeal cancer.	2	YES (81)
The treatment of choice when avoiding a pharyngolaryngectomy should be:		NO
concurrent CRT	2	(72)
induction chemotherapy (ICT)		(62)
Weekly Cisplatin at a dose of 40 mg/m^2 **should not be used** concurrent with radiotherapy	1	YES (95)
In case of ICT as a treatment of choice for locally advanced laryngeal/ hypopharyngeal cancer, a tumor reduction greater than 50% in the evaluation of response is needed to continue with the organ-preservation approach	1	YES (92)

[24]. As a result, the panel recommend RT as the treatment of choice in patients who need to preserve their voice for professional purposes.

Surgery should ensure the complete removal of the tumor with clear margins, as positive margins are an independent risk factor for high local recurrence, disease-free survival (DFS) and OS. Consequently, in the event of positive margins after surgery, further treatments should always be given. It is unclear whether re-resection or RT are the optimal treatment in this scenario. In patients with close or positive margins who received post-operative RT, fewer recurrences not statistically significant have been reported. Despite this, some authors as Crespo et al., suggest that surgical re-treatment is the preferred option to avoid the additional morbidity of RT and to reserve this treatment for the future [25]. The authors of this consensus recommend surgery as treatment of choice in case of positive margins, leaving RT as the alternative option when surgery is not feasible.

C1.B. Locally advanced (stage III/IVb)

Treatment for locoregionally advanced laryngeal and hypopharyngeal SCC entails high complexity as different variables must be considered: patient's performance status, comorbidities, patient preferences, tumor localization, stage and resectability. Therefore, a multidisciplinary tumor board is essential to choose the best therapeutic approach. The goals are to achieve the best results in terms of outcome and to preserve organ function when feasible. American and European guidelines recommend an organ-preservation approach as initial treatment of choice, which usually involves a combination of chemotherapy (CT) and RT, based on the Intergroup RTOG 91-11 trial, which established a new standard for larynx preservation (LP) by demonstrating the superiority of concomitant cisplatin plus RT for achieving LC and LP regarding other regimens, and with equivalent survival outcomes compared to surgery followed by RT ± CT [26–28]. On the other hand, some studies suggested that the decrease of survival recorded for larynx cancer in the mid-1990s may be related to changes in patterns of management (Hoffman et al., 2006). It must be considered that salvage surgery at recurrence after CRT entails a higher risk of major complications. Surgery (including total or PL) is a valid option but it is usually reserved to treat locoregional recurrences after conservative treatment or in patients who are not eligible or want to avoid chemoradiotherapy (CRT). In this regard, the experts recommend concurrent CRT as the initial treatment of choice for locally-advanced T3 laryngeal/hypopharyngeal cancer, though there was no consensus on whether total or PL is an adequate treatment option in this setting. However, in the case of supraglottic cancer, they agree that supraglottic laryngectomy is a valid alternative in selected patients.

It must be considered that locally advanced disease is defined not only by the primary tumor (T), but also by nodal burden (N). In selected patients with small primary tumors but high nodal disease, preservation surgery followed by adjuvant RT or CRT can achieve similar results in terms of disease control, although there are no randomized trials comparing both strategies [26,29]. Consequently, the authors of this consensus consider that nodal disease burden (N) might change the initial therapeutic approach of the primary tumor, regardless of the T stage.

Treatment for T4 laryngeal or hypopharyngeal cancer is a subject of discussion. There is no actual level I evidence to support non-operative organ preservation strategy. Patients with T4a disease and penetration through cartilage were not included in RTOG91-11. In the VALCSG trial, more than half of the patients with T4 disease underwent laryngectomy, and those randomized to laryngectomy had better survival [26,27,31]. Data from retrospective studies has given rise to controversy, with some reporting a decline in OS in patients treated with CRT, while others found no difference [26,30,32]. Therefore, the panel recommend surgery followed by RT as the treatment of choice for T4 laryngeal/hypopharyngeal cancer.

The role of induction chemotherapy (ICT) is still a matter of debate. The authors did not reach a consensus on whether

concurrent CRT or ICT followed by RT alone/CRT/bioradiotherapy should be the treatment of choice when a pharyngolaryngectomy is to be avoided. The EORTC trial 24891 published by Lefebvre in 1996 comparing surgery to ICT (cisplatin plus fluorouracil) followed by radiation as a larynx-preservation strategy showed that both treatments were equivalent in terms of survival and almost the half of patients in the induction arm preserved a functional larynx [33]. These results were maintained at 10 years of follow-up [34]. A meta-analysis published by Pignon et al. showed an absolute OS benefit of 5% when using ICT (cisplatin plus fluorouracil regimen) [35,36]. This benefit has been increased by the addition of taxanes to the regimen, which also improves complete response (CR) rates and decreases the incidence of distant metastases, as reported in two randomized trials and a meta-analysis [37–40]. However, the remarkable hematological toxicity of this regimen, and the publication of a recent meta-analysis that showed no statistically significant differences in OS, PFS or locoregional control, has given rise to this debate [41]. Clearly, tumor response to ICT has a prognostic and predictive value [38–40]. In this regard, the authors agree that in patients selected for ICT, a tumor reduction greater than 50% in the evaluation of response is needed to continue with the organ-preservation approach.

When it comes to CRT, weekly cisplatin at a dose of 40 mg/m^2 should not be used concurrent with RT, since there are no phase III randomized trials comparing this regimen to the standard regimen of three-weekly cisplatin at a dose of 100 mg/m^2. A recent meta-analysis comparing the efficacy and toxicity of both regimens found that weekly cisplatin was associated with less gastrointestinal toxicities but more grade $\geq$3 mucositis and chemotherapy related delay, with no differences in OS or LC [42].

C2. OPC and OCC

See Table 2.

C2.A Early stage OPC and OCC

Therapeutic options for early stage oropharyngeal squamous cell carcinoma (OPSCC) include both surgery and RT as single treatment modality. Both have shown equivalent LC and survival across the studies, but there are no randomized trials comparing both approaches [43]. In this regard, some authors suggest that two main factors must be considered when choosing the best treatment: HPV status and functional outcome following treatment and associated complications, especially late complications. HPV-related oropharyngeal tumors represent a distinct entity with different clinical and molecular features and treatment responsiveness [44]. They are usually associated to non-smoking younger patients, and show an overall better prognosis to any treatment for a given stage [3,44]. In consequence, there is a growing interest in the development of treatment deintensification trials to decrease treatment-related morbidity and functional impairment without compromising efficacy, although current evidence does not support less intense therapy compared with HPV-negative OPC. Intensity-modulated RT (IMRT) has improved radiation-induced late toxicity effects (xerostomia, trismus, osteoradionecrosis) so it might be a suitable option in early stage OPC [3,43]. Surgery approaches have also changed: classically, open head and neck surgery has been the state of the art procedure, with all the morbidity that it might involve (scars, malocclusion, compromised swallowing, chronic aspiration, and altered speech articulation); since the development of transoral endoscopic surgery, including transoral laser microsurgery (TLM) and transoral robotic surgery (TORS), which provide improved functional outcomes with minimal surgical morbidity, surgery might be also an adequate first treatment approach [45]. Moreover, surgery has the advantage to offer pathologic staging to selectively intensify high-risk patients for improved survival [46]. The experts did not reach a consensus on whether RT or surgery should be the treatment of choice for early stage OPC, however, RT was preferred over surgery as first treatment option for HPV-positive early stage OPC, while surgery was preferred over RT for HPV-negative OPC. As discussed in C1. A, in case of positive margins, surgical re-treatment is preferred over RT to avoid additional morbidity and to reserve this treatment for the future.

The role of adjuvant RT and CT is clear in locally advanced disease [46,50,51], but there is less evidence supporting its use in early stages. Post-operative RT has shown benefit in survival in early stage OPC when major adverse features (nodal metastasis, positive margins) are present [46,49], but its role is less clear in the presence of minor adverse features which include the degree of tumor differentiation, lymphovascular invasion, perineural invasion and, depending on the authors, tumor depth of invasion. The presence of this features, especially perineural invasion, are classical negative prognostic factors for DFS and OS [47,48]. There are no randomized trials evaluating the role of postoperative RT in this setting, however, small retrospective series have shown an improvement in survival when adding RT [49]. Therefore, the panel recommends adjuvant RT after resection of a stage I/II OPC if 2 or more minor adverse factors or if isolated perineural invasion are present in the resected tumor.

The addition of CT to adjuvant RT has been evaluated in two phase III randomized trials, the RTOG 9501 and EORTC 2293 [46,50]. Both trials were designed to evaluate adjuvant CRT in patients with locally advanced disease (stage III and IVa) that presented with major adverse features: extracapsular nodal spread and positive margins. However, in the EORTC trial, tumors with perineural invasion and few early stage tumors (T1-2 N0-1) were included. This study showed that the addition of systemic therapy improves DFS and OS. A retrospective analysis of both trials confirmed that adjuvant CRT improved the locoregional control rate, DFS and OS in patients that presented extracapsular nodal spread and positive margins [51]. As a result, the experts agree that patients with resected stage I/II OPC should receive adjuvant CRT when extracapsular spread is present in any of the lymph nodes resected. In the event the patient is not amenable for chemotherapy, then RT alone is recommended.

The oral cavity is a distinct site that possesses a complex functional anatomy and, despite its proximity to the oropharynx, tumors have a different etiology, management and outcome [52]. Surgery is often the first modality in sequential therapy because definitive high-dose radiation is associated with higher rates of osteoradionecrosis (ORN) compared with doses for postoperative adjuvant therapy [53,54]. Therefore, the panel of experts recommend surgery as treatment of choice for patients with early stage (I/II) OCC. Indications for adjuvant RT and CRT in OPC are applicable in OCC.

C2.B. Locally advanced OPC and OCC

To date, there are no prospective trials comparing surgery to definitive CRT in locally advanced OCC. Most of the data of organ preservation strategies in OCC come from clinical trials for locally advanced HNSCC in which very reduced groups of OCCs were included as clinicians were reluctant to enroll these patients due to the expectation of high toxicity and poor functional outcome. Few retrospective studies evaluated the results of the OCC cohorts from these trials showing similar efficacy in terms of survival when compared to surgery followed by perioperative RT or CRT, with PFS and OS rates ranging from 50% to 80% and 35% to 70% at 5 years, respectively [55–57]. Efficacy was maintained across stage III and IV and in patients with cartilage or bone invasion [55,61], but acute and late toxicity across the studies was remarkable, especially ORN, with rates ranging between 10% and 20% [53,54,62]. In two

Table 2
Summary of recommendations for OPC and OCC.

Recommendation	Phase	Accepted consensus (% of agreement)
Although there is no consensus, radiotherapy is preferred over surgery as first treatment option for HPV-positive stage I/II OPC.	2	YES (68)
Although there is no consensus, surgery is preferred over radiotherapy as first treatment option for HPV-negative stage I/II OPC.	2	YES (71)
In patients with early stage (I/II) oral cavity cancer, surgery is preferred over radiotherapy as first treatment option.	1	YES (92)
Re-resection is preferred over adjuvant radiotherapy in patients with stage I/II OPC with positive margins after radical surgery.	2	YES (71)
Adjuvant radiotherapy is recommended after resection of a stage I/II OPC if 2 or more adverse prognostic factors or if isolated perineural invasion are present in the resected tumor.	1	YES (64)
In patients with resected stage I/II OPC, adjuvant CRT is recommended when extracapsular spread is present in any of the resected lymph nodes. If the patient is not eligible for chemotherapy, then radiotherapy alone is recommended.	1 2	YES (84) (100)
Surgery is recommended over concurrent CRT in patients with locally advanced oral cavity tumors (stage III/IVA) that are resectable but subsequent reconstruction is expected.	1	YES (68)
In patients with locally advanced OPC and oral cavity cancer (Stage III, IVb) who undergo a non-surgical treatment approach, the following statements are indicated:		
• IMRT is the preferred radiotherapeutic modality.	1	YES (96)
• Concomitant CRT is recommended for stage III to IVB - N0-2a tumors. Three-weekly cisplatin at a dose of 100mg/m2 is the regimen of choice.	1	YES (92)
• Recommended treatment options for stage IVA-B N2b-c/N3 tumors are: - Concurrent CRT - ICT	1	YES (92) (76)
• If CRT is the selected treatment, three-weekly cisplatin at a dose of 100mg/m2 (during radiotherapy) is the regimen of choice.	1	YES (88)
• If ICT is the selected treatment, then continuance with bioradiotherapy (Cetuximab) is preferred over continuance with cisplatin-based CRT.	1	YES (80)
• In unfit patients (age 70 or greater, presence of comorbidities, poor performance status) the following are **not recommended** treatment options: - Concurrent CRT - ICT	2 1	YES (80) (81)

phase III trials, ICT did not improve rates of survival or distant metastases when compared to surgery plus postoperative CRT [60,61], but responders had improved outcomes, and some patients with T4 tumors might avoid total glossectomy [58,59]. However, level I data suggest that ICT has limited benefit, and CRT has not been evaluated in adequately powered studies that permit definitive recommendations, whereas surgery remains the standard of care. Consequently, the panel recommends surgery over concurrent CRT in patients with locally advanced oral cavity tumors (stage III/IVA) that are resectable but subsequent reconstruction is expected.

Conversely, for locally-advanced OPC (stage III-IVa-b), both American and European guidelines recommend CRT over surgery (10, quote ESMO guidelines). Radiation with concurrent cisplatin is the standard of care in this setting. As discussed above, cisplatin at a dose of 100 mg/m^2 every three weeks is the standard regimen, as there is no level I evidence to support other agents nor other schedules (see C1B). There is no current evidence to support less intense therapy for HPV-positive OPC either [63]. ICT remains a subject of discussion. Results from randomized trials comparing both strategies and a recent meta-analysis have failed to show a survival advantage of ICT in this group of patients, despite higher response rates and lower rates of distant metastases [40,64–66]. A recent review by Shert et al. evaluating the effectiveness of ICT in locally advanced OPC using data from American National Cancer Database found no improvement in OS [64]. Moreover, in subset analysis, HPV-positive patients did not seem to benefit from ICT. On the other hand, the poorest prognosis cohort – HPV-negative individuals with T4 and/or N3 disease – seemed to benefit from ICT [64]. Therefore, the panel of experts recommend concomitant CRT for stage III to IVB – N0-2a tumors. In the subgroup of patients N2b-c/N3, both concomitant CRT and ICT are recommended treatment options although CRT was supported by greater consensus.

Regarding sequential treatment after ICT, continuance with cisplatin plus RT entails high risk of acute and late toxicity, and might cause radiation breaks and incomplete treatments [64–66,69]. NCCN guidelines recommend sequential treatment with either carboplatin or Cetuximab [10]. The authors prefer Cetuximab over cisplatin-based CRT when ICT is given.

The panel agrees that concurrent CRT and/or ICT should not be recommended in unfit patients (age 70 or greater, presence of comorbidities, poor performance status) due to the high incidence of toxicity - higher rates of hospitalization during treatment and increased rates of acute mortality following CRT have been reported - and due to the lack of clinical benefit and possible negative impact on survival, as meta-analysis and subgroup analysis from prospective trials have suggested [67–69].

The recommendations for OPC are applicable to locally advanced OCC when unresectable or when a non-surgical treatment approach is chosen. Regarding the RT technique, the authors agree that due to the lower toxicity profiles reported in several trials, IMRT should be used [70,71].

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