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Defining the needs of patients with recurrent and/or metastatic head and neck cancer: An expert opinion

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ABSTRACT

The clinical and biological heterogeneity of head and neck cancer (HNC) is paralleled by a plethora of different symptoms that affect the patient's quality of life. These symptoms include, for instance, pain, fatigue, nutritional issues, airways obstruction, voice alterations and psychological distress. In addition, patients with HNC are prone to a high risk of infection, and may also suffer from acute complications, such as hypercalcemia, spine compression by bone metastasis or bleeding. Prolonging survival is also an inherent expectation for all patients.

Addressing the above needs is crucial in all patients with HNC, and especially in those with recurrent and/or metastatic (RM) disease. However, research on how to address patients' needs in RM-HNC remains scarce.

This paper defines patients' needs for RM HNC and presents an Expert Opinion on how to address them, proposing also some lines of research.

1. Introduction

Each year, more than 800,000 new cases of head and neck cancer (HNC) and 300,000 subsequent deaths are reported worldwide (Argiris et al., 2017; Bray et al., 2018). In most cases, the disease is localized at diagnosis and curative treatment is still possible. However, more than half of the patients with local disease experience relapse or present with metastatic disease (Bonomo et al., 2019).

Patients with HNC largely differ in terms of age, HPV status, socio-economical and cultural status, availability of caregivers, residual toxicities and comorbidities (Bonomo et al., 2019; Bossi et al., 2019a). High heterogeneity of HNC is also reported in terms of molecular signatures (Serafini et al., 2020; Oswald et al., 2020).

This clinical and biological heterogeneity of HNC is paralleled by a plethora of different symptoms that markedly affect the patient's quality of life, such as pain, fatigue, nutritional issues, airways obstruction, voice alterations and psychological distress (Bonomo et al., 2019; Oswald et al., 2020). Furthermore, patients with HNC carry a high risk of infection (Mirabile et al., 2015), and may suffer from acute complications, such as hypercalcemia, spine compression by bone metastasis or bleeding (Takes et al., 2012). In recurrent and/or metastatic (RM) disease, addressing these symptoms is crucial as they directly impact on the

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quality of life (Schorn et al., 2020). Finally, in patients with RM HNC, prolonging survival is the top expectation. Although attention to symptom care and to physical functioning is increasing, research on this topic remains scarce (Schorn et al., 2020; List et al., 2004; Tschiesner et al., 2013).

All those needs – addressing symptoms, limiting the risk of infections, handling the issues associated with acute complications, improving quality of life, prolonging survival – should be considered in the management of HNC, simultaneously taking into account the inherent heterogeneity of disease and affected patients. This paper defines patients' needs for RM HNC and presents an Expert Opinion on how to address them.

2. Methods

Some of the Authors (PB and the first five Authors; Steering Committee) decided to carry out a project that aimed to collect existing evidence on patients' needs in the setting of RM HNC, with a focus on squamous cell carcinoma, and how they can be managed in clinical practice. According to a preliminary literature search on most recent lines of research in the HNC setting, and based on the clinical experience of the Members of the Steering Committee, the following needs were identified as those requiring a broader consideration in the present manuscript: (i) pain; (ii) risk of infection; (iii) bleeding; (iv) nutritional issues; (v) voice and breathing; (vi) bone metastases; (vii) maintaining quality of life; psychological well-being; (viii) prolonging survival. However, other needs could also be commented upon in a more concise way, for the sake of completeness. The Steering Committee decided, for the sake of the present paper, not to focus on molecular characteristics or on the physician's perspective. Furthermore, other relevant issues (e.g., the so-called 'financial toxicity' of treatments) were not considered in the present manuscript, since they require to be discussed by a different approach.

Other international experts in HNC who were from different disciplines (medical oncologists, radiation oncologists, surgeons, experts of methodology) and from any region of the world and with a specific scientific interest in the above-mentioned needs were invited to join the Board by the Steering Committee. The assistance of an independent scientific consultancy agency (Polistudium srl, Milan, Italy) was also sought in order to guarantee the scientific accuracy, facilitation of meetings and preparation of materials. The entire project was supported by an unrestricted and unconditional grant from Merck Serono; they were not offered the opportunity to see or revise the output of the meetings or any other material and had no role in the submission process.

The participants attended two online meetings held on March 2020 and May 2020. During the first meeting, the Steering Committee discussed the aims of the project with the other participants. A comprehensive literature search on the identified needs was then conducted using MEDLINE, with different combinations of pertinent keywords. Full-text articles were collected and saved in a dedicated online repository, which was accessible by all participants. Each participant was then asked to: (i) select the most relevant papers for one specific need; (ii) identify further references from their personal collection of literature or other sources; (iii) draft a short section on the need, clarifying its importance and epidemiology in the setting of RM HNC, commenting on existing literature, and providing their personal opinion, based on evidence review and clinical experience on the topic, according to a predefined template; and (iv) summarize their expert opinion in a list of key points relevant to the specific need. Each contribution was then reviewed and harmonized with the others by the members of the Steering Committee. A draft of the manuscript was then circulated among all the participants, who were then offered the opportunity to add their own comments. The manuscript and related comments were then discussed during the second meeting. All relevant comments were included by the Steering Committee, and a final version of the paper was then circulated for final approval and decision to submit.

3. Patients' needs

3.1. Pain

Pain is one of the most frequent and revealing symptoms in HNC; its prevalence and mean intensity are the highest among different subtypes of cancers (Bossi et al., 2019b). Therefore, HNC patients have a higher demand for pain management, and its assessment and characterization should be performed at baseline and periodically, since pain is a rapidly evolving symptom. Pain is caused by the progression of the tumor itself, which is in a highly vascularized and innervated anatomical region, but also by the treatment of the tumor. Therefore, in addition to the RM setting, it is important to accurately evaluate the characteristics of pain and, hence, to discriminate between the different causes.

Pain induced by complications arising after curative-intended primary treatment is complex and multidimensional. Although this is outside the scope of this manuscript, it is important to mention that patients undergoing surgical procedures, radiation therapy, chemotherapy, such as platinum or taxanes, or patients receiving targeted treatments, such as cetuximab, may suffer from nociceptive and/or neuropathic pain at multiple locations, as a result of adverse effects of the primary tumor or complications related to the therapy (Bossi et al., 2019b).

Thus, at the time of regional or metastatic recurrence, the majority of patients have already been treated for their HNC and, in case of sequelae induced by treatment at the localized stage, are usually still present at the time of recurrence.

A precise assessment of the features of pain is essential for an effective management of the symptom. It is not only essential to make a precise diagnosis (location, intensity, underlying mechanisms), but also to monitor the efficacy of the treatment. To quantify the intensity of the symptom, validated quantitative scales may be used, such as the visual analog scale, the numerical rating scale or the simple verbal scale (no pain, weak, moderate, intense or extremely intense pain) (Dworkin et al., 2010). It is also necessary to distinguish between nociceptive and neuropathic pain. The latter is due to a peripheral or central nervous system lesion, leading to an alteration of the nociceptive transmission and/or control processes. Diagnosis of neuropathic pain is helped by a specific tool: the DN4 (Bouhassira et al., 2005).

Further to the specific anti-tumoral effects, systemic anti-tumoral therapies may also improve quality of life and tumor-related symptoms and can present an intrinsic painkiller effect (Filippiadis et al., 2017). Similarly, hypo-fractionated or short-course radiotherapy should be used for pain control, especially in case of symptomatic bone metastases.

Chronic pain is difficult to manage and requires a multidisciplinary approach. Psychotherapy and mind–body therapy can help and should be prescribed in addition to antalgics (Chaoul et al., 2014). To efficiently prevent chronic pain, the first symptoms should be addressed as early as possible. This is particularly true for patients with RM HNC, which have a high demand for pain management and, thus, requires supportive care to be implemented early and continuously throughout the course of the disease.

In addition, it is crucial to consider the multidimensional aspect of pain, the somatic, but also the physical, spiritual, psychological and social elements (Peyrade et al., 2013), which dictate a multidisciplinary approach for chronic and/or refractory pain.

3.1.1. Expert opinion

- Pain is a very frequent symptom experienced by RM HNC patients, who have the highest prevalence among all cancer types.
- Pain in patients with HNC is often multifactorial: it is caused by the disease itself; it may be the consequence of previous treatments

(mainly surgery and radiation), and it is sometimes also caused by the current oncological therapies.
- It is crucial to consider the multidimensional aspect of the pain – the somatic and psychological aspects of the symptom.
- Refractory pain should be managed by an expert multidisciplinary team.

3.2. Infections

Infection is a common life-threating complication in cancer patients, which contributes to suboptimal treatment compliance and higher morbidity and mortality rates (Freifeld et al., 2011; Montassier et al., 2013). Patients with RM HNC treated with first-line palliative chemotherapy, also when associated with cetuximab or pembrolizumab, present a 20–25 % risk of developing grade 3–5 neutropenia, with a reported rate of febrile neutropenia between 6 and 9% (Vermorken et al., 2008; Burtness et al., 2019) because of the therapeutic regimen and previous immunosuppressive therapies.

Furthermore, implantable devices (central venous catheter [CVC] and percutaneous endoscopic gastrostomy [PEG]), pre-existing oral pathologies, frequent mucosal and skin toxicity contribute to increased infection rates in these patients (Anatoliotaki et al., 2004; Lipitz-Snyderman et al., 2014). Moreover, most HNC patients have xerostomia, which heightens the incidence and severity of mucositis and dental caries, possibly leading to episodes of febrile neutropenia (JAEM et al., 2019). Furthermore, the addition of cetuximab to chemotherapy has been related with an increased risk of bloodstream infections (BSIs) (Vermorken et al., 2008; Gudiol et al., 2011; Qi et al., 2014), which is probably related to CVC (Marín et al., 2019) and treatment-associated adverse events, involving both skin and mucosa toxicity.

In the current era of widespread antibacterial resistance, the development of BSIs has become a major health problem worldwide and is particularly relevant for HNC patients since the presence of resistant bacteria has been associated with poor outcomes (Marín et al., 2019). BSIs in HNC represented 5% of the episodes registered in a monographic cancer center, with 60 % of infections occurring among RM disease (Anderson, 2019). Previous oral pathologies and continuous mucosal and skin disruptions justify that Gram-positive bacteria and, in particular, *Streptococcus pneumoniae* was the most frequent germ isolated in this setting (Gudiol et al., 2011). Higher mortality was associated with hypoalbuminemia and pre-existing comorbidities (Gudiol et al., 2011). Therefore, it seems important to identify those patients at higher risk of infection by a resistant strain, in order to benefit from early broad-spectrum empirical antibiotic therapy.

Dysphagia is another frequent chronic complication in patients with previous irradiation of the head and neck area (Funakoshi et al., 2014). Subsequent aspiration pneumonia incidence remains unknown, but advanced age, smoking, weight loss and lower cranial nerve palsies have been associated with multiple episodes of pneumonia and higher mortality rates in RM nasopharyngeal cancer patients (Berardi et al., 2015). Habitual alcoholic consumption, use of sleeping pills, poor oral hygiene, hypoalbuminemia before treatment and coexistence of other malignancies have been also identified as risk factors for aspiration pneumonia in patients with locally advanced HNC (Kawai et al., 2017).

Clinical nurses who are specialized in HNC can play a critical role by closely monitoring the CVC or PEG, in addition to individualizing the appropriate care of skin lesions, mucositis or diarrhea, which can trigger the onset of BSIs. Dental hygiene reviews are recommended in cancer patients before starting any drug (Levi and Lalla, 2018), as well as the 23-valent vaccination in patients who had not received any pneumococcal vaccine (Anon., 2020). Prophylactic granulocyte–colony-stimulating factor (G-CSF) use is indicated in high-risk neutropenic chemotherapy regimens (risk of febrile neutropenia >20 %), such as those including docetaxel, or according to individualized patient risk (Klastersky et al., 2016; Smith et al., 2015), and, in this sense, was used in up to 60 % of the patients treated with platinum–fluorouracil plus cetuximab in the TPExtreme trial (Guigay et al., 2019). However, the indication of G-CSF should always be individualized considering patient-specific risk factors (Crawford et al., 2017; Aapro et al., 2010). Prophylactic ciprofloxacin, even if employed in TPF induction schemes, may become questionable, given the lower incidence of BSI by Gram-negative bacilli and increasing resistance rates to this antibiotic (Schelenz et al., 2013).

3.2.1. Expert opinion

- Anatomical barrier disruption produced by the tumor or its treatment characterize the increase of infections by Gram-positive cocci in these patients.
- The risk of febrile neutropenia with cetuximab or pembrolizumab added to first-line chemotherapy is 6 – 9%
- Prophylactic use of G-CSF should be considered to prevent infections when using chemotherapy combinations with >20 % risk for febrile neutropenia, such as those including taxanes, or individualizing according to patient characteristics.
- Pneumonia is the main cause of infection in RM disease.

3.3. Bleeding

Bleeding events in patients with advanced HNC is often acute, severe, multifactorial and, sometimes, intractable and life-threatening (Zhao et al., 2014). For patients in the RM setting, these episodes should be managed by carefully balancing the impact of invasive procedures with the need to preserve quality of life and risk of death (approximately 10 % of subjects in case of catastrophic bleeding) (Mayland et al., 2020).

Predisposing factors have been identified, such as previous high-dose irradiation, uncontrolled wound infections, surgical complications, especially pharyngocutaneous fistula formation, poor nutrition, encasement of great vessels by the primary tumor and the use of anticoagulants for other comorbidities (McDonald et al., 2012; Li et al., 2019; Rumboldt et al., 2006; Frere et al., 2020). The choice of treatment, such as re-irradiation, systemic treatments combination and anti-angiogenetic agents, may also increase the risk of bleeding (McDonald et al., 2012; Cristina and Faivre, 2019). Therefore, an accurate evaluation of the patient history, clinical condition, and disease status is mandatory before defining the therapeutic protocol for each patient.

Among all the bleeding events in HNC patients, one of the most devastating complications is an acute carotid blowout event, which results from the rupture of the carotid artery or one of its main branches (McDonald et al., 2012). Carotid blowout syndrome is uncommon but can be rapidly fatal without prompt diagnosis and intervention, with mortality rates as high as 60 % and neurologic morbidity approaching 40 % (Chaloupka et al., 1996).

The standard of care for managing carotid blowout syndrome has changed over the past two decades with advances in interventional radiology. The traditional surgical approach has shifted to less invasive endovascular techniques. Although these treatments are believed to be efficacious; they potentially bring a significant risk of periprocedural stroke (Liang et al., 2016). Furthermore, risk of re-bleeding after stent placement is present even despite good initial rescue responses, especially for those who have severe tissue necrosis or wound infection (Pyun et al., 2007). For those complications, a concomitant or short-interval arterial trapping should be considered in some selected conditions (Liang et al., 2016).

Potential benefits and the risks of interventions for carotid blowout should be discussed with patients and caregivers, taking into account the expected prognosis and patient's wishes. Moreover, management options in case of massive bleeding, such as surgery, endovascular intervention with or without stent implantation, combined endovascular embolization with surgery, conservative drug control or palliative

sedation, should be openly discussed for HNC patients at higher risk, before starting any oncological treatment (Zhao et al., 2014; Ahmad, 2020).

3.3.1. Expert opinion

- Previous high-dose irradiation, uncontrolled wound infections, surgical complications, especially pharyngocutaneous fistula formation, poor nutrition, encasement of great vessels by the primary tumor and the use of anticoagulants should be considered as risk factors for bleeding.
- Bleedings in RM HNC patients may be caused by uncontrolled tumor growth, infection and treatment complications.
- The management for carotid blowout syndrome has changed to less invasive endovascular techniques.
- Potential benefits and risks of each intervention should be discussed with patients and caregivers whenever the risk of a carotid blowout is identified.

3.4. Nutritional issues

Approximately 40 % of patients with HNC suffer from dysphagia, with up to 40 % having a higher risk of asymptomatic aspiration (Cocks et al., 2016) and prevalence of malnutrition estimated at approximately 50 % of patients (Hébuterne et al., 2014). Dysphagia can also lead to the development with other conditions, such as sarcopenia (Silva et al., 2020). Metastatic disease is also associated with malnutrition, showing the highest impact in HNC among all malignancies (Hébuterne et al., 2014). Importantly, malnutrition and consequent weight loss have been reported as independent unfavorable prognostic factors for overall survival and objective response to systemic treatment (Argiris et al., 2004).

With respect to the mechanism of onset, mechanical obstruction and fistula formation in the upper digestive tract and functional dysphagia are caused by primary disease. Palliative radiotherapy and chemotherapy are associated with adverse effects, such as oral mucositis, pharyngitis, dry mouth and dysgeusia, which may lead to difficulty in oral intake.

The main purpose of nutritional support for patients with RM HNC is to prevent or limit weight loss, dehydration and infection, and to minimize treatment delays and unplanned hospitalizations, leading to improvement of treatment outcomes. Notably, improvement of quality of life rather than that of nutritional condition is the main goal for patients at the end of life. Therefore, selection of nutrition access is critical for each patient.

NCCN guidelines highly recommend assessment and continuous monitoring of nutritional status pre-treatment, during and post-treatment by multidisciplinary nutrition support team (Cocks et al., 2016; National Comprehensive Cancer Network, 2020). Assessment of the swallowing function through video-fluoroscopic examination and risk of aspiration through functional endoscopic evaluation of swallowing are simple and essential tools to establish whether oral intake is possible in the palliative treatment of HNC.

A comprehensive nutritional management should take patient's need into consideration, informing them about available alternatives, risks of aspiration pneumonia and tools to better deal with oral intake, such as methods to clear the airway after swallowing, choice of certain textures or use of thickened fluids (Cocks et al., 2016).

Multidisciplinary guidelines for patients with HNC receiving palliative and supportive care also discuss the basics of nutrition management in these patients (Cocks et al., 2016; Müller-Richter et al., 2017). The nutrition access for patients unable to swallow or have high risk in oral intake include enteral nutrition (EN), such as a nasogastric tube, PEG, radiologically inserted gastrostomy or percutaneous radiologic gastrostomy and, less commonly, parenteral nutrition. There is an algorithm for the use of parenteral nutrition and EN in the ASPEN clinical guidelines (Müller-Richter et al., 2017; Mueller, 2012; Druyan et al., 2012). If the prognosis is expected to be more than several months in patients without gastrointestinal tract impairment, early initiation of EN is the first-choice. The route of EN is largely determined by the anticipated duration of need for nutrition support. Generally, nasogastric tubes are used for short-term therapy (<4 weeks) and PEG tubes are preferred for long-term therapy (>4–6 weeks) (Mueller, 2012). Other factors affecting the choice of the route of EN are the ability to pass through upper digestive tract, potential complications, cost, cosmetic issues, quality of life and patient preference. PEG allows not just for nutrition and hydration, but also for medication even at home. Handling and maintenance of such medical devices should be well instructed to retain advantages and avoid complications.

Although a decision on nutrition access is frequently made based on patients' preference in the clinical practice, the treating clinician is responsible of guiding nutritional intervention, by sharing the burden of patients' difficult decisions. Necessity of invasive nutritional support should be re-considered especially for the patients at the end of life.

3.4.1. Expert opinion

- Malnutrition is highly prevalent and has a high impact on prognosis in RM HNC.
- An assessment of swallowing function by video-fluoroscopic examination or functional endoscopic evaluation of swallowing is recommended to estimate the risk of aspiration.
- To satisfy the patient's wish of oral intake and nutrition access, multidisciplinary intervention via collaboration between medical staff members is indispensable.
- Nutrition access depends on prognosis, technical indication, socio-economical factors and patient's need.
- Early initiation of EN is preferred for patients with an intact gastrointestinal tract if the prognosis is not in a short-term period.

3.5. Voice and breathing

Voice and speech are part of a person's identity and personality and represent the most important daily communication tools; therefore, deterioration of these functions can have an impact on well-being and quality of life (Jacobi et al., 2010). HNC patients frequently have voice and speech problems, due to direct tumor involvement, edema promoting airflow obstruction and vocal cord mobility impairment, or treatment-induced mucositis, fibrosis, swelling, lymphedema or atrophic changes in the vocal fold and pharyngeal soft tissue (Jacobi et al., 2010; Deng et al., 2016; Jeans et al., 2019). Speaking is also related to the lips, tongue, hard and soft palate and nasal cavity, and direct tumor invasion or sequelae in these structures can alter speech function (Nelke et al., 2014).

In a similar way, breathing problems and dyspnea may occur as tumor- or treatment-related symptoms in HNC patients (Deng et al., 2016), or in those with RM disease, for example in the lungs (Jeans et al., 2019). Nevertheless, many of these patients have a history of smoking and concurrent pulmonary disorders, such as chronic obstructive pulmonary disease (Gottlieb et al., 2015), which may negatively contribute to this scenario. Sleep-related breathing disorders (obstructive apnea) are also described in HNC patients, with a prevalence ranging from 76 to 91 % (Payne et al., 2005; Faiz et al., 2014).

These symptoms, as well as their treatment, are deeply interconnected – for example, the placement of a tracheostomy to treat airway obstruction can have a negative impact on voice quality. For patients with RM HNC these issues are magnified, as many have locoregional disease previous treated or not and/or lung metastasis, with a prevalence of 52 % for voice changes and 48 % for breathing problems. Moreover, according to patients, dyspnea and voice disorders are the symptoms with the largest impact in daily functioning (Lokker et al., 2013).

In this direction, a study analyzing the patients' experience in RM

HNC identified difficulty speaking or swallowing, localized pain and fatigue as important signs for treatment benefit evaluation from a patient's perspective (Degboe et al., 2017).

Patients facing breathing problems and dyspnea need rapid symptom relief, which may be achieved with rapid tumor shrinkage or airway obstruction management, possibly avoiding voice disorders by preventing, for example, the need for tracheostomy. Multidisciplinary management is essential, besides the head and neck surgeon, medical oncologist and radiation oncologist, other specialties, such as speech therapist and pulmonologist, can help optimize voice quality and pulmonary function, as well as work on rehabilitation. Early palliative care for symptom control is warranted (Schenker et al., 2016).

In patients presenting with metastatic disease at diagnosis, locoregional treatment may be considered, based on the extent of the disease and symptoms (National Comprehensive Cancer Network, 2020), and this approach can be useful in patients with voice and breathing problems related to direct disease involvement. Systemic treatment will still be the mainstay approach in this population and, for symptomatic subjects, opting for regimens with higher response rates is indicated. Carefully selected patients with locoregional recurrent disease can be offered rescue surgery and/or reirradiation if feasible (Mehanna et al., 2016; Iglesias Docampo et al., 2018).

3.5.1. Expert opinion

- Voice and breathing problems are prevalent in RM HNC patients and cause a significant impact on their quality of life.
- Adequate airway obstruction management, with local therapy when indicated, and high response rate systemic treatment, with platinum doublet plus pembrolizumab or cetuximab, should be employed.
- Multidisciplinary and palliative management are mandatory, involving specialists for function optimization, symptom control and rehabilitation. Early referral for a speech therapist, palliative care and, if indicated, pulmonologist is recommended.

3.6. Bone metastases

Following the lungs, bones constitute one of the most common sites of distant metastasis (10–31 %) in HNC (Takes et al., 2012), which is similar to many other solid malignancies. However, there is no comprehensive literature exclusive about bone metastases (BM) of HNC, and the diagnosis and management of these patients are analogue to other non-hematologic solid tumors causing BM; most commonly prostate, breast and lung cancer (Sze et al., 2003; Coleman et al., 2020).

BM affect patients' life through many problems, such as hypercalcemia and its associated symptoms, debilitating pain and especially pathologic fractures, frequently causing dramatic and immediate functional impairment via spinal cord compression and peripheral bone fractures. All of these consequences require quite rapid medical intervention.

The treatment of hypercalcemia involves fluid replacement, correction of electrolyte imbalance via intravenous infusions, promoting renal calcium excretion and decreasing bone resorption by vitamin D, adequate intake of calcium and administration of bisphosphonates or denosumab (Coleman et al., 2020; Minisola et al., 2015).

Symptomatic BM of HNC requires palliative radiotherapy with or without prior surgery. Other experimental local strategies, such as surgery only, cryotherapy and radiofrequency ablation without high-level evidence are out of the scope of this article. However, the landmark randomized study by Patchell et al. showed that the combination of decompressive surgery combined with post-operative radiotherapy (30 Gy in 10 fractions) was superior to radiotherapy alone in patients with spinal cord compression caused by BM, improving patients' walking ability and decreasing the need for corticosteroids and analgesics (Patchell et al., 2005). These results should be contextualized with HNC patients, whose prognosis is generally severe when BMs develop; therefore, the choice of surgery should be reserved for patients with no disseminated visceral metastasis, maintained motor function, longer disease-free interval and life expectancy. A nomogram generated to guide treatment options underlined these aspects as essential to define patient's prognosis (Rades et al., 2011).

Since radiotherapy is traditionally considered as the standard treatment, there is no randomized study challenging its added benefit following surgery for spinal cord compression.

In terms of pain relief, there is mounting evidence indicating equal clinical effectiveness between short-course, lower biologically effective dose and long-course, higher biologically effective dose radiotherapy, as witnessed by prospective trials and systematic reviews in other cancer settings (Hartsell et al., 2005; Chow et al., 2014, 2019), even if with a slightly higher rate of subsequent pathologic fractures and retreatment frequency after single fraction radiotherapy. This model could also be theoretically transposed to BM of HNC.

Pain flare is defined as temporary worsening of pain in the region of index BM and occurs in up to 44 % of patients irradiated for BM (McDonald et al., 2014). A randomized trial showed an improvement of pain flares with dexamethasone 8 mg 1 h prior to conventional single-fraction 8 Gy radiotherapy and then every day for 4 days compared with placebo (26 % vs 35 %, $p = 0.05$) (Chow et al., 2015). In an observational prospective study, the same regimen of dexamethasone is similarly effective before and after stereotactic radiotherapy, and a 4 mg dose is comparable to 8 mg in terms of reduction of pain flare (Khan et al., 2015). The recent double-blind, placebo-controlled, randomized DEXA study showed no difference in pain flare incidence or its mean duration, but dexamethasone postponed the occurrence of the pain flare compared with the placebo arm. Furthermore, patients in the protracted dexamethasone arm reported significantly lower mean pain scores on days 2–5 than in the single-day dexamethasone or placebo arms (van der Linden et al., 2020).

A recently published meta-analysis (SAFFRON) in patients with BM, showed that stereotactic radiosurgery (1 fraction) was superior to conventional radiotherapy in improving local control at 1 year, with an additional ~5% increase in local control for each 10 Gy increase in biologically effective dose. Nevertheless single-fraction stereotactic radiosurgery was associated with higher rates of subsequent vertebral compression fractures (Singh et al., 2020).

The ESMO evidence-based clinical practice guidelines for bone health in cancer provides comprehensive insight into the pathophysiology of the BM of various solid tumors and up-to-date algorithms for their management (Coleman et al., 2020).

3.6.1. Expert opinion

- BM manifests in up to 30 % of metastatic HNC cases, which may cause debilitating pain, hypercalcemia and spinal cord compression.
- In most of these situations, local metastasis-directed treatments should be added to systemic treatment. No data about the substitution of palliative radiotherapy with bisphosphonates or radionuclides exist for the BM of squamous cell HNC.
- In case of spinal cord compressions, surgery performed within 48 h improves functional outcome and increases the duration of patients' ambulatory state; these results could be extrapolated to HNC as well, even in absence of specific trials, but accurate patient selection should be performed.
- In uncomplicated spine or peripheral BM, stereotactic radiosurgery (e.g. 12 Gy for $\geq$4 cm or 16 Gy for $<$4 cm) may achieve the best local control and pain relief. Single fraction 8 Gy is an optimal option when conventional techniques are to be used. Except for a possibly increased need for re-irradiation, it is non-inferior and less toxic compared to longer courses of radiation.

3.7. Maintaining quality of life and psychological well-being

There has been a dramatic increase recently in the number of publications on health-related quality of life (HRQOL) in patients with HNC. This reflects the importance of the patient perspective as an outcome parameter in addition to survival, recurrence or physical function.

HRQOL is a multi-dimensional concept that encompasses the physical, emotional and social components associated with an illness. There are many different aspects to HRQOL, and these are assessed by a variety of questionnaires (Ringash and Bezjakn, 2001): performance, general or global, general cancer, HNC specific, function specific and others, such as satisfaction, personality and spirituality. Although questionnaires used to assess QoL are mostly used in the clinical trial setting, we also believe that in clinical practice the assessment of QoL is critical to investigate the needs of each single patient and his/her perception of disease and therapy.

Disease, treatment and site-specific patient-reported outcome (PRO) measures can be used alone, in combination with more general measures (e.g. the Short Form-36) or with clinical assessments. A large number of disease-specific PRO measures are currently available for the assessment of HRQOL in patients with HNC (Ojo et al., 2012; Vartanian et al., 2017). PRO measures vary significantly with respect to their development and validation and no one specific measure has been clearly identified as the gold standard to assess HRQOL in this population (Ojo et al., 2012; Vartanian et al., 2017).

Different PRO measures are commonly used in clinical trials (Table 1). Using a semi-structured interview guide, Degboe et al. (Degboe et al. (2018) showed, from a patient's perspective, the QLQ-C30 and QLQ H&N35 content are understandable and conceptually relevant, with some suggested additions.

Acute toxicities of therapy are associated with a marked symptom burden and reduced quality of life. It is now becoming clear that many patients will also experience substantial late effects and are at risk for poor long-term quality of life. Rogers et al. recently published the results of the HN5000 study on 2171 participants, showing the prognostic value of HRQOL measured using the EORTC QLQ-C30. As survival is the main priority for most people diagnosed with cancer, pre-treatment HRQOL is an additional factor to be included in risk stratification and case-mix adjustments (Rogers et al., 2020).

Although a throughout evaluation of treatment-related consequences on patients' quality of life is outside the scope of this work, it is important to note that sequelae induced by treatment at the localized stage are still present at the time of recurrence, and that HRQOL and PRO tools can be important instruments to measure the negative impact of these sequelae on patient's quality of life in the RM state.

Table 1
PRO measures commonly used in clinical trials.

PRO	Characteristic	Ref.
EORTC QLQ-HN43 (revision and update of EORTC QLQ-HN35) + QLQ-C30	35-item questionnaire designed (in conjunction with EORTC QLQ-C30) to measure functional status, well-being, symptoms and side-effects of treatment	(Bjordal et al., 2000; Singer et al., 2019)
The Functional Assessment of Cancer Therapy-Head and Neck Subscale (FACT-HN)	Proved sensitive to patient groups on the basis of treatment status (on vs off treatment) and global performance status (Karnofsky scores)	(List et al., 1990)
The University of Washington Head and Neck Cancer Questionnaire (UW-QOL)	Comparable to the Karnofsky and Sickness Impact Profile scales when tested for validity and reliability. Preferred test format of 97 % of patients	(Hassan and Weymuller, 1993)
The Vanderbilt Head and Neck Symptom Survey—Recurrent/ Metastatic (VHNSS-RM)	Card sort selected high-yield and high-impact items (contains 35 physical and 12 psychosocial issues)	(Jackson et al., 2016)
The 9-item Disabilities of the Arm, Shoulder, and Hand (Quick DASH-9)	Designed to improve practicality and eliminate item redundancy of the 30 item DASH. Improved practicality and completion time	(Gabel et al., 2009)

3.7.1. Expert opinion

- Quality of life is an important factor regarding HNC treatment and, for many, is essential for survival.
- Analysis of quality of life questionnaires is also very important in clinical practice for understanding and improving a patient's local and general condition also when disease recurs.
- As we continue to investigate new treatment regimens in the hopes of improving the survival of patients with HNC, it is important that we simultaneously continue to assess the biopsychosocial ramifications of therapy.
- Continued effort in this direction is needed in order to optimize treatment outcomes and quality of life for patients.

3.8. Increasing survival

In the palliative setting, the goal of increasing survival can be discussed with the patient at different timepoints. Treatment options should be evaluated on a case-by-case scenario by a multidisciplinary team taking in account TNM stage, previous treatment, comorbidities, symptoms, patient preferences and prognostic factors. Counseling and honest communication about the proposed treatment, potential secondary effects and chances to increase survival are important at this point, also given the relevance of increasing survival for patients (List et al., 2004).

3.8.1. Increasing survival in patients with recurrent HNC with or without metastatic disease

Only a minority of patients with isolated recurrent disease are suitable for salvage surgery procedures (Goodwin, 2000). Predictor models are useful to select patients suitable to salvage treatment (Hamoir et al., 2017). Patients with advanced stage tumors, concurrent local and regional failures and even recurrence outside of the larynx are poorer candidates for salvage surgery, with very poor 2-year overall survival (OS) rates when two or three predictive factors coexist. These patients might be amenable to intensity-modulated radiotherapy (IMRT) although this strategy can be associated with some toxicities. To better select patients suitable for reirradiation with IMRT or stereotactic body RT (SBRT), Ward et al. identified three prognostic subgroups with distinct and homogenous OS ($p < 0.001$): class I included patients >2 years from their initial course of RT with resected tumors (2-year OS, 61.9 %); class II included patients >2 years with unresected tumors or those ≤2 years and without feeding tube or tracheostomy dependence (2-year OS, 40.0 %), and the remaining patients formed class III (2-year OS, 16.8 %) (Ward et al., 2018).

In patients unsuitable for salvage treatments and those with metastatic disease, a systemic treatment could be proposed. The Extreme regimen (Vermorken et al., 2008) consisting of cisplatin or carboplatin with 5-FU and cetuximab followed by cetuximab has been the standard first-line treatment over the past years. More recently anti-programmed death 1 (PD-1) antibodies showed promising results after platinum-based chemotherapy or in the first-line palliative setting with increased OS and a better quality of life and symptom burden compared to standard existing treatments (Burtness et al., 2019; Cohen et al., 2019) especially in patients with increased PD-L1 expression. The KEYNOTE 048 study (Burtness et al., 2019), which compared pembrolizumab ± chemotherapy with the Extreme regimen in the first-line

palliative setting, showed that immunotherapy alone may be a choice for selected patients, with positive PD-L1 CPS, when increasing survival is the main aim, and the patient is asymptomatic or with minor symptoms, so not needing the contribute of chemotherapy in reducing tumor burden. This approach potentially leads to improved survival, reduced toxicities and increased quality of life. When increase in survival should be paralleled with increased probability of tumor shrinkage, chemotherapy should be added to immunotherapy, trading off toxicities for improved response.

3.8.2. Increasing survival in oligometastatic patients

Whereas polymetastatic disease is generally treated by systemic treatment, patients with limited number of metastasis involving single or few organs may benefit of metastasis-directed treatment modalities. However, the number of metastatic lesions manageable with ablative treatment options has not been well defined and is different from study to study. Pulmonary metastasectomy is a possible strategy to remove metastatic disease in patients with squamous cell HNC, with 5-year survival rates ranging from 29 to 59 % (Winter et al., 2008; Miyazaki et al., 2013). One should rule out the possible second primary tumors of the lung, to better define the therapeutic management. Surgical resection of liver metastasis of primary squamous cell HNC has been also documented in a small study showing overall median survival rates of 22.3 months and 5-year actuarial OS rate of 20.5 %; however, this opportunity should be critically considered, as the risk of rapid progression of liver metastasis exists (Pawlik et al., 2007). Therefore, all these strategies should be carefully evaluated considering burden of disease, disease-free interval and performance status, as patients' selection is crucial to gain a survival benefit.

Oligometastasis can also be treated by SBRT, which delivers high-dose, hypofractionated doses of radiotherapy in limited tumor volumes (Palma et al., 2019). Recently, a large randomized, multicentric, open-label phase II study conducted on 99 patients with a controlled primary tumor of any site and one to five metastatic lesions showed that palliative standard of care (SoC) plus SBRT was superior to standard of care alone in increasing OS (median 41 vs 28 months) (Palma et al., 2019).

SBRT and pulmonary metastasectomy seem to have similar outcomes in retrospective reports (Widder et al., 2013; Pasalic et al., 2020) and several prospective studies regarding SBRT are still ongoing especially in combination with other treatment modalities.

Preclinical trials and clinical reports also showed that the combination of SBRT and immunotherapy should be useful to increase immunostimulatory activity and thus enhance tumor activity on metastases outside of the irradiation field. This effect is known as abscopal effects and is still under investigation for different solid tumor types in clinical research protocols (NCT03539198, NCT03283605) (Choi et al., 2020).

3.8.3. Increasing survival in patients with upfront metastatic disease

In total, 10 % of HNC patients present with an upfront metastatic status. As locoregional disease can induce several symptoms impacting quality of life, treatment of locoregional disease despite metastasis should be useful.

Several retrospective studies have tried to determine if locoregional treatment also increases survival. Rambeau et al. reported that locoregional radiotherapy improved survival in 65 patients with upfront metastatic squamous cell HNC treated by platin-5-FU–cetuximab-based regimen (median OS 16.1 vs 7.5 months; $p < 0.01$) (Rambeau et al., 2019). OS showed a trend to an improvement if locoregional radiotherapy was performed as consolidation RT compared to upfront RT (median OS of 22.1 vs 15.5 months; $p = 0.11$) (Rambeau et al., 2019).

3.8.4. Expert opinion

- For patients with recurrent squamous cell HNC, the benefits of cure do not always justify an exceeding morbidity with poor quality of life; the individual patient's condition and preference should be strongly considered.
- The use of pembrolizumab alone showed a better toxicity profile than chemotherapy + cetuximab. Chemotherapy + pembrolizumab is associated with the same rate of AEs than chemotherapy + cetuximab.
- Anti-PD-1 antibodies in platinum-resistant patients increase OS with better side effects or toxicity profile compared to other standard treatments
- Oligometastasis can be treated by surgical metastasectomy or SBRT depending on tumor burden, disease-free survival and performance status
- Loco-regional treatment of patients with upfront distant metastatic disease increases survival and quality of life.

3.9. Other needs

The needs reported above do not cover the full spectrum of symptoms and issues the patient with RM HNC may complain about. In addition, lack of energy and fatigue, nausea and difficulty in swallowing have been reported as the highest priority disease symptoms by patients with advanced HNC (Oswald et al., 2020). Moreover, late toxicities from previous treatments may impact on the overall needs of this group of patients. In fact, after completion of curative therapy, the vast majority of survivors experience late adverse events, mainly fatigue, sticky saliva and xerostomia, subcutaneous toxicities, ototoxicity and neurotoxicity (Taberna et al., 2015). Moreover, late systemic toxicities are also frequently reported by HNC survivors, causing a worsened overall quality of life (Wulff-Burchfield et al., 2019). Therefore, even in the RM setting, one should consider that the late toxicities of previous treatments may represent issues for the patients, which overlap with the symptoms and needs due to the relapsing disease.

4. Tailored treatment

Treatment for RM HNC is a challenge due to the heterogeneity of the disease presentation, the variety of the patient's conditions and the different support the patients may receive from caregivers or social environment. Patients' needs and preferences, as previously depicted, represent a key factor to be considered when approaching RM HNC.

Luckily, in the last few years, different treatment options are becoming available, therefore allowing a more tailored therapeutic management, which reflects the multifaced presentation of disease (Lau et al., 2020).

When approaching a patient with relapsing HNC, one should consider several factors to define the best treatment for each patient, as described in Table 2.

Table 2
Main factors to be considered in therapeutic approach to recurrent/metastatic head and neck cancer.

Patient-related	Disease-related	Treatment-dependent	Others
• Performance status • Symptoms • Comorbidities • Organ function (kidney, liver, lung, bone marrow) • Patient's preferences	• Need of quick tumor response or not • Risk of acute complications (bleeding, airway obstruction) • Site of relapse (locoregional vs metastatic) • PD-L1 combined-positive score	• Residual toxicities from previous treatment(s) • Availability of (re) irradiation or salvage surgery	• Socio-economic environment • Availability of caregiver(s) • Availability of simultaneous palliative care

5. Lines for future research

Due to the inherent complexity of the disease, specific needs for patients with HNC should be carefully considered. However, at present, there are limited literature data regarding an approach to RM HNC matching patients' needs with therapeutic choices. The advent of immunotherapy as first-line treatment for relapsing squamous cell HNC is a first step for a tailored molecular strategy, with PD-L1 combined-positive score being a crucial analysis to select different treatment options, given also that treatment response is known to lower symptom burden in RM HNC (Hecht et al., 2020).

In our daily practice, we usually select treatment according to the patient's and the disease's characteristics. However, a prospective evaluation with a tailored treatment, embracing all the factors previously discussed, as well as patient's preferences and including molecular signatures is an area of research that could be implemented.

Such studies would be of the highest interest considering as endpoints the outcome of treatment, the response to the specific needs, the quality of life and the patient and caregiver's satisfaction, thus, greatly contributing to the improvement of RM HNC.

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Not applicable.

Declaration of Competing Interest

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