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Editorial

Emergency changes in international guidelines on treatment for head and neck cancer patients during the COVID-19 pandemic



On January 30, 2020, the World Health Organization formally announced that the novel coronavirus disease (COVID-19) caused by SARS-CoV-2 is a worldwide health emergency. Subsequently, all National Health Systems and each medical center faced the exceptional emergency and severe changes in their organizations. Consequently, there were various implications that needed to be addressed for oncology patients. In this sense, there are some practical and important issues in the management of head and neck cancer patients: (i) they are usually older and usually present with medical comorbidities (e.g., COPD and other tobacco-related diseases) that are associated with a higher risk of severe complications associated with COVID-19; (ii) high risk of SARS-CoV-2 exposure (transportation, daily radiation fractions, multiple consultations with multidisciplinary team members); (iii) cancer treatment can potentially and theoretically increase the risk of more severe complications of COVID-19 [1]. Of interest, the main risk factors for head and neck squamous cell carcinoma (HNSCC), tobacco and alcohol, also increase the risk for COVID-19 infection. One Chinese study reported an increased risk of cancer-related deaths associated with notorious difficulties of access to oncologic care. In addition, a nationwide analysis in China indicated that the risk of severe respiratory complications leading to admission to the intensive care unit, invasive ventilation, or death was much higher in cancer patients than in patients without cancer (39% vs. 8%, $p = 0.0003$). Moreover, patients who underwent chemotherapy or surgery in the past month had a numerically higher risk of clinically severe events than did those not receiving chemotherapy or surgery, irrespective of age, smoking history or co-morbidity (odds ratio 5.34, $p = 0.0026$) [2–5].

The majority of hospitals will be treating thousands of COVID-19 patients in the next few weeks and thus, there is an urgent need to preserve patient and staff safety. For this reason, the Center for Diseases Control (CDC) in the United States recommends that healthcare facilities interrupt elective care and restrict their activities to providing urgent and emergency visits and procedures. It is recommended that all elective and non-time sensitive procedures and admissions must be rescheduled [6].

There is a critical need to share skills and expertise to propose recommendations for the diagnosis and treatment of HNSCC patients throughout the COVID-19 pandemic. As healthcare professionals and HNSCC experts, we aim to offer emergency guidelines aiming to reduce the risk of patient harm, by reducing their risk of exposure to SARS-CoV-2, without compromising their treatment and outcome.

As a disclaimer, this is a general guideline and the following recommendations are suggested to help the multidisciplinary teams in the diagnosis and treatment of HNSCC patients, considering local constraints and epidemiological characteristics. It is important to mention

that local guidelines regarding COVID-19 (both at the national and institutional levels) must be followed to ensure the safety of patients, caregivers and health care professionals. In addition, a general rule, not to deviate from the standard of care in each clinical situation must be followed [7]. These proposed emergency guidelines may have to be modified in the future if new, significant evidence-based information becomes available.

- **Do not postpone or interrupt HNSCC treatment in SARS-CoV-2 negative patients unless there are significant clinical reasons that prevent the patient from being treated**

Multidisciplinary management continues to be essential for optimal decision making and treatment planning of HNSCC patients and, due to the inability to have in-person meetings, web-based meetings should be encouraged. HNSCC usually has a high proliferation rate and it is also associated with a significant tumor-associated symptom burden. Therefore, delay to initiate oncologic treatments or applying treatment interruptions can cause disease progression and may negatively impact survival outcomes [8–10]. Although the pandemic scenario is new, the risk of mortality due to COVID-19 is lower than the risk of cancer-related death [11]. While some patients with low-risk disease can be safely managed with a few weeks delay (one or two), this should be decided on a case-by-case discussion.

If possible, these patients must be tested before curative treatment, and before any hospitalization. This should be combined with a proper history, which in combination with the PCR-testing significantly increases the negative predictive value of the testing. Treatment of patients who are diagnosed as SARS-CoV-2 positive can be delayed by two weeks if necessary, to ensure safety for the patient, for other patients and for healthcare professionals, and to decrease the risk of treatment-related complications. One exception would be the last days of radiation therapy. In this situation, all precautions to ensure safety of other patients, caregivers and health care professionals must be ensured.

- **Flexible fiberoptic endoscopy should be done only if necessary, to make a decision on treatment**

Fiberoptic endoscopy examination is a high risk procedure for head and neck surgical oncologists and otolaryngologists because of the high nasal viral loads in COVID-19 patients [12]. This exam must be performed only for initial diagnostic or staging purposes and not for follow-up of asymptomatic patients. The recommendations for endoscopic examination vary because of the lack of availability of adequate Personal Protective Equipment (PPE) to the staff involved in patient

care in all institutions.

- **Multidisciplinary support must be kept during patient's treatment**

Nutrition assessments, swallowing evaluation and oral care are mandatory during HNSCC treatment. The use of prophylactic procedures (e.g., low-level laser therapy) in the oral cavity should be avoided for patients with high risk of mucositis (e.g., oral cavity and oropharynx cancers) due to the risk for healthcare professionals, and it may be considered as an analgesic procedure only in selected cases [13].

- **Treatment of early stage HNSCC patients should be individualized**

For patients with early stage HNSCC primaries located in the larynx, oral cavity or oropharynx, treatment options usually involve single-modality surgery or radiation therapy. These two approaches are normally associated with similar clinical outcomes [14].

In this context, surgery may be indicated in some scenarios due to the shorter treatment time, especially if the requirement of adjuvant radiation therapy is unlikely or a tracheostomy is not needed. Aiming to protect both the patient and health care professionals, all procedures on the upper aerodigestive tract should be performed after proper analysis of the case. Before surgery, patients must be confirmed to be negative on test for COVID-19, have no symptoms and have a negative Chest-CT (for COVID-19 infection). The mandate for a negative chest CT however, is based on institutional standards. Also, a contact with a positive-tested individual within the week prior would raise suspicion. If tracheostomy is required, then a non-surgical treatment should be considered if possible. Tracheostomy increases the risk of COVID-19 infection, risk of dissemination, risk of respiratory complications, and possibly risk of death. If surgery is not feasible (due to unavailability of operating rooms which are being used in many countries as ICUs) or the patient is inoperable or refuses the surgical option, then radiation therapy should be recommended.

Having said that, radiation therapy may be a better option for selected early stage patients with laryngeal or oropharyngeal carcinoma.

- **Concurrent chemoradiation with cisplatin is the standard of care for patients with locoregionally advanced HNSCC**

In those patients who are treated with concurrent chemoradiation, two high-dose cycles of cisplatin (100 mg/m² each cycle) should be administered, with the third cycle being suspended (survival benefit with a cumulative cisplatin dose of 200 mg/m² for HPV-unrelated tumors and in stage III HPV-related squamous cell carcinoma of the oropharynx has been documented). Only in cases with very bulky disease, and in patients who have not developed any toxicity to the two previous cycles, a third cycle may be considered. For patients with locally advanced disease who require concurrent treatment but are platinum-ineligible, the priority should be exclusive treatment with radiation therapy with individual assessment for concomitant cetuximab (understanding there is an increased risk of sepsis, need for weekly treatment, and increased skin/mucosal toxicity).

- **Induction chemotherapy should not be routinely used as an option to postpone upfront surgery or radiation therapy.**

Induction chemotherapy with the standard TPF (docetaxel, cisplatin, 5-FU) regimen has a significant risk of immunosuppression and when followed by cetuximab-radiation showed a higher risk of mortality compared with concomitant cisplatin-radiation [15]. Therefore, the risk of COVID-19 infection and subsequent severe complications requiring hospitalization may worsen the patient's prognosis. Therefore, it should not be considered as an option to postpone upfront

surgery or radiation therapy, but may be indicated in well-established clinical scenarios, like larynx preservation [16]. Other potentially defensible scenarios would include the need for rapid cytoreduction due to prolonged, unavoidable delays in receiving surgery or radiation, or to avoid imminent local issues (e.g. airway or central nervous system) that are not well addressed with surgery.

A subgroup of patients with severe COVID-19 might have a hyper-inflammatory syndrome characterized by a fulminant and fatal hypercytokinaemia with multiorgan failure. The indication of colony-stimulating growth factor (G-CSF) should be discouraged since G-CSF is supposed to induce cytokine storm, which could result in a hyperinflammatory status that could cause higher mortality in COVID-19 positive patients [17]. If induction chemotherapy is needed, alternative, less toxic regimens can be considered (e.g., paclitaxel 175 mg/m² and cisplatin 80 mg/m² I.V. every three weeks [18] or carboplatin AUC5 and paclitaxel 180 mg/m² I.V. every three weeks) [19].

- **Cisplatin with postoperative radiation therapy should be used only for patients with high-risk disease with major factors (extranodal extension and/or positive margins)**

Patients who are treated with surgery with curative intent, including radical resection with neck dissection of an advanced stage tumor may be at high risk of disease relapse. Although several factors have been related to an increased risk of locoregional relapse after head and neck surgery (e.g., stages T3/T4, lymphovascular space invasion, perineural invasion, positive/close resection margins, positive lymph nodes) [20–22], only extranodal extension and positive margins have been shown to negatively impact risk of relapse and mortality in randomized trials [23]. In the absence of these two high-risk pathologic features, adjuvant treatment in patients with otherwise deemed high-risk disease should be limited to radiation therapy only. The absolute reduction of 5-year relapse risk provided by the administration of concomitant cisplatin is 11% for patients with either of these two major factors. As mentioned earlier, at least two cycles of high-dose cisplatin during radiation (cumulative dose 200 mg/m²) seems advisable in these circumstances. Even in those patients who are at high-risk for recurrence (positive margin or extranodal disease), an individualized decision should be made with the patient.

- **Recurrent/metastatic disease**

The treatment objectives for patients with recurrent or metastatic HNSCC during the COVID-19 pandemic remain the same: optimize overall survival and quality of life, accomplish symptom control, and minimize toxicity. However, in the present situation it seems pertinent to avoid severe neutropenia, because there are data of a higher risk in neutropenic patients and SARS-CoV-2 infection [24]. To reduce frequent contact with the hospital, regimens with longer treatment intervals between cycles or the use of oral medication seems preferable. In the case of asymptomatic or pauci-symptomatic patients, consideration of short delays is warranted in case there is an infectious complication. In newly diagnosed, asymptomatic or pauci-symptomatic patients with limited disease, delaying the start of treatment for four to six weeks should be considered. Periodically assess the evolution of the patient by phone or virtual visits and to start the treatment if any symptom appears.

In general, chemotherapy and/or immunotherapy should be maintained. Patient's age and comorbidities, treatment tolerance and number of cycles already completed are variables that must be considered when deciding whether or not to continue treatment. There are no data regarding safety and/or efficacy of chemotherapy, cetuximab and/or immunotherapy in metastatic HNSCC patients during the COVID-19 pandemic. Therefore, clinical decisions should be individualized, as there is no direct evidence to support changing or withholding chemotherapy, targeted therapy, and immunotherapy in

these patients [5].

• **Hypofractionated radiation therapy may be considered for palliative care (shorter schedule as possible)**

In patients with incurable disease, best supportive care typically results in life expectancy of approximately 100 days, versus five months with palliative radiation therapy [25,26]. A variety of different dose schedules are reported in the literature for palliative radiation therapy in patients with locally advanced HNSCC. Although longer courses of treatment with higher total treatment dose may be related to marginally better results in retrospective data, the overall prognosis remain dismal. In this context, a shorter regimen of hypofractionated radiation therapy should be encouraged. These schedules may include delivery of 24 Gy in three fractions (D0-D7-D21) [26] or 25 Gy in five daily fractions [27]. Other schedule comes from RTOG8502 “QUAD SHOT” data. Prescription was for 3.7 Gy bid given over two consecutive days to a total of 14.8 Gy per cycle, each cycle every four weeks provided no local disease progression or significant toxicity [28].

• **Treated patients in follow-up**

The COVID-19 pandemic is overburdening health care systems worldwide due to extensive and rapid consumption of supplies necessary for acute care, the inability of supply chains to keep up with demands, and the losses and exhaustion of human resources [11]. Numerous hospitals and clinics will soon be unable to provide care to all cancer patients. Whenever possible for low risk patients, hospital face-to-face visits must be postponed or changed to virtual options [29].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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