Head and neck cancer radiotherapy amid COVID-19 pandemic: Report from Milan, Italy

Stefania Volpe MD [1]

[1]European Institute of Oncology IRCCS

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Abstract

Background: Management of head and neck cancers (HNC) in Radiation Oncology in the COVID-19 era is challenging. Aim of our work is to report organization strategies at a Radiation Therapy (RT) Department in the first European area experiencing the COVID-19 pandemic. Methods: We focused on 1) dedicated procedures for HNC, 2) radiation treatment scheduling and 3) healthcare professionals' protection applied during the Covid-19 breakdown (from 1st March to 30th April 2020). Results: Applied procedures are reported and discussed. Forty-three pts were treated. Image-guided, Intensity Modulated RT was performed in all cases. Median overall treatment time (OTT) was 50 (IQR: 47-54.25) days. RT was interrupted/delayed in seven pts (16%) for suspected COVID-19 infection. Two health professionals managing HNC pts were proven as COVID-19 positive. Conclusion: Adequate and well-timed organization allowed for the optimization of HNC pts balancing at the best of our possibilities pts' care and personnel's safety.

Daniela Alterio*[1], Stefania Volpe*[?1,2], Giulia Marvaso[1,2], Irene Turturici[1], Annamaria Ferrari[1], Maria Cristina Leonardi[1], Roberta Lazzari[1], Massimo Sarra Fiore[1], Giammaria Bufi[1], Federica Cattani[3], Camilla Arrobbio[1,2], Filippo Patti[1,2], Alessia Casbarra[1,2], Iacopo Cavallo[1,2], Fabrizio Mastrilli[4], Roberto Orecchia[5], Barbara Alicja Jereczek-Fossa[1,2]

1. Division of Radiation Oncology, IEO, European Institute of Oncology IRCCS, Milan, Italy
2. Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy
3. Medical Physics Unit, IEO, European Institute of Oncology IRCCS, Milan, Italy
4. Medical Administration, CMO, IEO, European Institute of Oncology, IRCCS, Milan, Italy
5. Scientific Direction, IEO, European Institute of Oncology IRCCS, Milan, Italy

* Daniela Alterio MD and Stefania Volpe MD equally contributed to the present work, and should be considered as co-first authors

Corresponding Author:

Stefania Volpe MD

E-mail address: stefania.volpe@ieo.it

Orcid ID https://orcid.org/0000-0003-0498-2964

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1. INTRODUCTION

Since the 20th February 2020, Italy is experiencing one of the most severe 2019 coronavirus-19 disease (COVID-19) outbreak worldwide, with the region of Lombardy being the first area in Europe hit by the pandemic. At present, Lombardy is the most affected areas in Italy, with 15.116 deaths and 82.904 cases as of 12th May 2020. Of these, 21.632 were diagnosed in the Milan area. Therefore, health care services across the Region are still facing and unprecedented challenges in limiting transmission rates in order to guarantee the continuity of care[1].

Cancer patients are often frail and immunocompromised, and therefore at risk of being more severely affected by COVID-19 infection[2,3]. Following the Regional resolution XI-2906 approved on the 8th March 2020, selected centers were designated as oncological hubs, meaning that they were called to host patients from hospitals in the frontline for COVID-19 emergency. Since our Institution was included among Lombardy oncological hubs, a set of procedures were implemented in order to guarantee a safe care and working environment.

Several reports and recommendations have been published on the management of head a neck cancer (HNC) from both an ethical and surgical perspective[4–6]. Moreover, a recent consensus by the American and European Societies of Radiation Oncology (ASTRO and ESTRO, respectively) was published to provide guidelines on optimal radiation treatment (RT) strategies during the pandemic [7]. Nevertheless, issues related to the management of HNC patients during RT have not been reported yet. Hence, aim of the current work is to report on technical aspects and the organization strategies applied in a Radiation Oncology facility operating in the first European area hit by the COVID-19 pandemic. As the 4th May represent the end of the lockdown phase in Italy, we wish to share our experience, and to provide some highlights on how everyday activities were re-organized to face an evolving epidemiological scenario, together with the short-term results of our efforts.Daniela Alterio*[1], Stefania Volpe*[?1,2], Giulia Marvaso[1,2], Irene Turturici[1], Annamaria Ferrari[1], Maria Cristina Leonardi[1], Roberta Lazzari[1], Massimo Sarra Fiore[1], Giammaria Bufi[1], Federica Cattani[3], Camilla

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1. Division of Radiation Oncology, IEO, European Institute of Oncology IRCCS, Milan, Italy

2. Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy

3. Medical Physics Unit, IEO, European Institute of Oncology IRCCS, Milan, Italy

4. Medical Administration, CMO, IEO, European Institute of Oncology, IRCCS, Milan, Italy

5. Scientific Direction, IEO, European Institute of Oncology IRCCS, Milan, Italy

* Daniela Alterio MD and Stefania Volpe MD equally contributed to the present work, and should be considered as co-first authors

Corresponding Author:

Stefania Volpe MD

E-mail address: stefania.volpe@ieo.it

Orcid ID https://orcid.org/0000-0003-0498-2964

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the Region are still facing and unprecedented challenges in limiting transmission rates in order to guarantee the continuity of care[1].

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1.1 Peculiarities of HNC clinical management

With a number of incident and prevalent cases in Lombardy of 1583 and 2687 in 2019, respectively, HNCs can be considered as relatively rare. Nevertheless, a recent national Italian survey among Radiation Oncology facilities has shown that the majority of COVID-19 positive oncological patients had a diagnosis of either lung or HN cancers and had their domicile in Lombardy[1].

For the Radiation Oncologist HNC patients in the COVID-era[8] the following peculiarities should be considered: 1) HNC are non-deferrable treatments[9,10], 2) increase in overall treatment time (OTT) negatively affects survival in curative-intent treatments[5,6] , 3) patients are generally elderly, heavy smokers as well as affected by several comorbidities [11–13] 4) as curative-intent RT is administrated in 25-35 fractions, patients are required to perform multiple hospital accesses, which may increases their risk of contagion[7], 5) the need of removing patient's surgical masks in different phases of RT favors environmental dissemination of droplets[5], 5) the frequent presence of a tracheostomy represents a further mean of viral spreading[14], 6) abundant mucous secretions with cough secondary to tumor- and treatment-related distress might further favor cross-infections, 7) high risk of developing ab-ingestis pneumonitis as a consequence of tumor and/or treatment-related swallowing impairment could make patients prone to pulmonary distress syndromes[15], and 8) the combined effect of RT and concomitant systemic treatments (mainly platinum-based chemotherapy) could result in myelosuppression, thus favoring infectious disease [16] .

2. MATERIALS AND METHODS

Data of HNC patients treated with RT at the Radiation Oncology Department of the European Institute of Oncology IRCSS (Milan, Italy) were reviewed. The considered time frame encompassed the early phase of COVID-19 pandemic in Lombardy (1st March to 30th April 2020). The impact of the pandemic was analyzed as: 1) dedicated Departmental procedures for HNC, 2) treatment scheduling (i.e.: delays, interruptions), and 3) healthcare professionals' protection was analyzed. As the current report focuses on outpatients treated with external beam RT, hospitalization and brachytherapy-related procedures are not described. Medical records from HNC patients were retrieved from electronic medical charts. This work was approved by the Ethical Committee of the European Institute of Oncology IRCSS (notification number IEO726). All patients signed a written informed consent for clinical research purposes.

3. RESULTS

3.1 Radiation Oncology Department- General organization

Eighteen Radiation Oncologists, 15 Radiation Oncology Residents, 11 Medical Physicists, 25 Radiation Therapists and 6 Nurses are currently working at our Department. On average, the number of outpatient treatments is approximatively 900 per week. In this time of emergency, and given the role of oncological hub, our efforts were directed towards maintaining an efficient clinical routine.

For this reason, the entire workflow was re-organized to minimize COVID-19 transmission among both the personnel and the patients. All measures were coordinated by a COVID-19 emergency team composed by the Chief of the Department, three Senior Radiation Oncologists, the Radiation Therapists Coordinator, the Nursing Coordinator and the Chief of the Medical Physics Unit, in compliance with the Institutional Recommendations.

The healthcare personnel was assigned a COVID-19 exposure risk class. Personal protective equipment (PPE) was provided accordingly: 1) low-risk of COVID-19 exposure (surgical mask, disposable gloves), 2) intermediate risk of COVID-19 exposure (surgical masks, disposable gloves, disposable gowns, medical caps) and 3) high risk of COVID-19 exposure (filtering facepieces- FFP2/KN95 and FFP3 masks, disposable gloves, disposable gowns, medical caps, goggles or face shield, aprons). The administrative staff and the medical physicists were assigned to the first group, the healthcare professionals (namely, physicians, Radiation Therapists and Nurses) without contacts with HNC patients to the second group, and the healthcare professionals with contacts with HNC patients to the third group. All staff members were required to use PPE for the whole working day, regardless of whether their activity encompassed any direct contact with patients.

A full list of the policies for the whole department is provided in**Supplementary Materials** .

3.2 Departmental COVID-19 dedicated procedures

Treatment scheduling was not modified and was followed our Institutional clinical practice: 6 weeks after surgery, 4 weeks after the last cycle of induction chemotherapy, within 4 weeks for exclusive radiation or concurrent chemoradiation).

The whole care path for HNC patients was re-planned according to temporal and special criteria, with the aim to maintain a safe working and treating environment. As previously detailed, patients were required to wear a surgical mask unless otherwise instructed by the personnel. A second surgical mask was provided to cover tracheotomies, if needed. A summary of dedicated procedures for HNC patients is provided in**Table 1** .

Time management in the COVID-19 pandemic encompassed scheduling all computed-tomography (CT) simulation scans and RT delivery in dedicated slots. The rationale beyond these measures was to optimize room sanitization and to easily provide all involved healthcare professionals with PPE.

All treatments are performed with mouthpiece-assisted head and shoulder thermoplastics masks (FirmFit Thermoplastics Masks CIVCO Radiotherapy Corporate Office 2303, Iowa, United States of America), to minimize intra- and inter-fraction movements during treatment delivery. Due to our immobilization device of choice, it was not possible for patients to keep surgical masks during irradiation. For safety reasons, patients were instructed to wear their surgical mask until they were correctly positioned on treatment couch. Subsequently, they were invited to remove the surgical mask and to insert their personalized mouth bites. The thermoplastic mask could therefore be applied by the Radiation Therapist, who performed the standard set-up procedures. The temporary removal of surgical masks by the Radiation Therapist managing HNC patients' set-up procedures were considered as a potential source of contamination, and an adequate PPE was provided accordingly (**Figure 1**).

Similarly, patients' surgical masks were removed at least once per week during medical consultations for oral cavity examination and toxicity assessment. A consultation room was reserved exclusively for HNC patients, and sanitized at the end of every working day. Clinical evaluations during the RT treatment were regularly performed. Follow-up consultations were organized according to the general Department procedures detailed in **Supplementary Materials** . In detail, follow-up evaluations for HNC patients were organized in the

form of telehealth surveillances, except for those requiring a physical and radiologic assessment of their gross tumor volume response following a curative-intent RT. In order to limit the accesses to our Institute, patients with no evidence of disease and good performance status were invited to stay at home and to reschedule their consultations.

All the above-mentioned procedures were progressively implemented according to pandemic development and in accordance with World Health Organization (WHO), National and recommendations and availability of Institutional resources[17] While COVID-19 phase II started in Italy on May 4th 2020, these procedures are still applied in our Department while this work is being written (10th March).

3.3 Impact of COVD-pandemic on HNC patients

Forty-three patients were included in the analysis. During the first two months of the COVID19 pandemic a slightly higher number of patients were treated at our Department as compared with the same period of 2019 (44 vs 36, respectively, +22%). This could be probably explained by the fact that as a hub center, some patients were referred from other Institutions. All patients received image-guided Intensity Modulated Volumetric Arch Therapy (VMAT). Two patients maintained their tracheostomy positioned at time of surgery. Patients' and treatment characteristics are provided in **Table 2** .

Postoperative RT was started after a median time of 58 (IQR 53-69) days for the 17 patients treated with surgery. Exclusive RT was initiated after a median time of 29 (IQR 20-42) days following the first clinical examination performed by the Radiation Oncologist (22 patients). For the 4 patients who had undergone induction chemotherapy, a median time to RT start was 24 (IQR 14-30) days from the last cycle.

Median OTT was 50 (IQR: 47-54.25) days. Overall, RT was interrupted/delayed in seven patients (16%) as a consequence of a suspected COVID-19 infection. Specifically:

- One patient presenting with fever was diagnosed with COVID-19- related pneumonia on March 4th after receiving 18 Gy out of the prescription dose of 70 Gy for cT1cN2M0 HPV-positive oropharyngeal cancer, TNM 8th edition[18]. The patient required hospitalization for intensive respiratory distress of COVID-19 related pneumonitis and was treated at an intensive care unit of a dedicated COVID-19 hospital. After a quarantine period the patient was proven negative at two consecutive nasal swabs (7th April). Due to a prolonged interruption of 57 days, after multidisciplinary discussion, a salvage surgery ± post-operative RT according to pathology specimen findings was proposed.

- Four patients had their RT interrupted following the onset fever. Nasal swabs tests were negative in all cases. RT breaks was 2 days for all patients.

- One patient interrupted curative RT for 23 days due to the quarantine measurements of her residence area. Treatment was interrupted at the dose of 62 Gy. OTT time was 105 days (further interruptions were needed for severe skin RT-induced toxicity).

- One patient with oral cavity cancer is experiencing a delay in the beginning of his adjuvant therapy. Following surgery, he subsequently developed COVID-19 pneumonia. Despite two consecutive swabs detected no sign of infection, the third one proved to be positive. Further two consecutive swabs performed recently demonstrated absence of COVID-19 infection. The patients is actually scheduled to start postoperative RT which will be performed after 71 days from surgery.

Overall, follow-up consultations were regularly performed until April 19th 2020**.** Telehealth surveillance subsequently performed for 21 patients. Among these three patients who had completed their RT course, were scheduled for a short-term consultation for a more comprehensive assessment (tracheostomy removal, toxicity evaluation and physical assessment of gross tumor response, respectively).

3.4 Impact on Health professionals

Overall, two health care professionals involved in the management of HNC patients (a Radiation Therapist and a Radiation Oncology Resident, 51 and 33 years old, respectively) were found to be COVID-19 positive

at nasal swabs. Both of them had been in contact with the patient diagnosed with COVID-19- related pneumonia. They have no comorbidities and clinical presentation of COVID-19 infection was mild in both cases (anosmia, diarrhea, fatigue and fever). No respiratory symptoms were reported and hospitalization was therefore not needed. In compliance with safety measurements, both of them were re-admitted to work after two consecutive negative nasal swabs.

Since pregnancy, has been recognized as a risk factor for developing a COVID-19 related severe acute respiratory distress syndrome[19], a Radiation Oncology resident in her seventh month of pregnancy was suspended from clinical practice and was assigned research works she could manage from home.

DISCUSSION

Radiation treatment management of HNC patients in the COVID-19 era is challenging. As Lombardy was the first European area affected form COVID-19 pandemic, guidelines and recommendation for RT in HNC patients were very limited at that time. Therefore, our Department approved extra-caution measurements to maintain adequate safety standards for both patients and healthcare personnel to minimize the risk of transmission. Our experience has shown that the designation as an oncological hub, together with internal procedures, allowed to preserve our standard of care while protecting health professionals treating HNC patients.

As COVID-19 likely binds to epithelial cells in the nasal cavities and the oropharynx[20], aerosolized droplets from infected patients determine a high risk of transmission during the whole HNC clinical workflow, from diagnosis (i.e. physical examination, trans-oral endoscopy) to treatment delivery (i.e. surgery, RT$\pm$ systemic therapy)[5]. During the emergency, it was difficult to identify a clear cut between our duty to provide optimal care and the one to protect healthcare professional and their families from infection[5]. Specifically, contamination reduction had to be balanced with the need of guaranteeing access to the best treatment options, as per national and international guidelines[6]. If an absolute solution to this ethical question is probably impossible to be found, the issue has been debated by some authors. Shuman et al advocate for a deliberate effort towards balancing exposure and maintaining moral and professional integrity in patient care[21].

An additional concern for HNC patients who undergo RT is the counterbalance between the benefit of a timely delivered treatment and the risk of contracting COVID-19 infection during the 7 weeks of an average curative-intent irradiation. In this regard, Bhattacharjee et al developed a multistate and hazard model to simulate the risk of death from disease progression vs the risk of death from COVID-19 infection in patients diagnosed with stage IV cancer of the oral cavity[22]. Given the risks of hospital admission, the authors suggest to defer treatment in this subset of HNC patients and to make efforts to minimize the chance of infection. While statistical models can provide reasonable solution to practical and ethical problems in the COVID-19 era, there was an unmet need for practice recommendations encompassing different clinical scenarios (i.e. curative vs adjuvant treatments, high-risk vs low-risk adjuvant settings). To this aim, a joint effort by the ASTRO and ESTRO has produced an expert consensus statement for five common cases of HN carcinoma[7]. While the reader is invited to refer to the full recommendations, we would like to focus on the need of adequately prioritizing treatment at the time of limited resources. Of note, as the authors claim, all measurements and recommendations need to be weighted according to the extent and duration of the pandemic across nations and regions, which are hardly predictable and constantly evolving[7]. As hospitals represent critical areas in the epidemiology of the disease: it is therefore straightforward to understand how critical it is to keep transmission rates as low as possible in all healthcare facilities. The rationale of oncological hubs instituted in March 2020 is to provide the best treatment options to the highest number of safely eligible patients, in order to preserve oncological outcomes of these populations. Our experience shows that these measures were effective in limiting cross infections for candidates to curative-intent RT for HNC. Overall, we did not experience a significant reduction in the number of treated patients, while maintaining high quality standards for delivered treatments.

In the context of HNCs, IMRT has proven to be superior to 3-dimensional conformal radiotherapy in reducing both acute and long-term treatment-related side effects (i.e. xerostomia, dysphagia) without jeopardizing

oncological outcomes[23–25]. Coherent with these results, we decided not to modify our planning strategies and to prioritize the maintenance of high-quality treatment standards for our patients. To this aim, set-up accuracy is an essential condition to ensure a safe and effective treatment delivery. Therefore, in order to assure an accurate set-up, our immobilization device is provided with a mouthpiece-assisted bite for every curative-intent treatment. A previous study from our Department showed that using this device maintain the set-up error within 5 mm in all directions[26]. As we did not test the outcomes of patients' positioning without a mouthpiece-assisted bite, we favored to maintain our standard immobilization procedures despite they could not allow patients to wear surgical masks. Accordingly, all Radiation Therapists managing HNC patients were considered at high risk of COVID-19 infection and equipped with personnel protection accordingly. Therefore, they were instructed to safely use PPE, as well as to adequately sanitize treatment rooms and any equipment in contact with patients. Results of our report highlight that to maintain a high quality standard of care, RT for HNC patients requires adequate personal protection as well as a department re-organization to optimize the room sanitization.

Considering that a percentage of individuals ranging from 13% to 30% were found to be COVID-19 asymptomatic, all HNC patients were considered as potentially COVID-19 carriers[6,27]. One of the limitations in our management was the impossibility to perform a swabs-based screening to all patients prior to the beginning of RT. A Chinese respective cohort study has underlined that the correct use of PPE prevented all 41 healthcare workers included in the analysis from being infected following the contact with COVID-19-positive patients[28,29]. Despite higher probability of contact with COVID-19 infected patients, Lombardy centers received, less PPE than the Italian average, most probably due to insufficient supply at the beginning of the outbreak. As an example, FFP2 and FFP3 provisions to the healthcare personnel were approximately 2 and 3 times lower in Lombardy than other regions, respectively[1]. Therefore, at our Department during the first weeks of the outbreak, priority for PPE assignment was given to those managing HNC patients. Arguably, this strategy probably contributed to reduce cross-infections between potentially COVID-19 positive HNC patients and health care providers. The relatively limited number of COVID-19 cases among health professionals in our Department could therefore be explained by contacts with asymptomatic carriers before rigorous self-protection measurements were introduced. Encouragingly, no other cases were diagnosed among our Colleagues recently. This might suggest that the high risk of cross-infection of HNC patients management was mitigated by the use of adequate PPE.

We are well aware that further protective measurements could have been taken. Possibly, the risk of viral dissemination could have been further reduced by defining two separate working shifts for health care professionals, as well as by creating separate areas for patients at higher risk for COVID-19 infection. Serological screenings for the whole staff have been executed only in a minority of swab-proven cases, while a systematic testing is programmed for the upcoming weeks. However, at the time of the outbreak available guidelines and/or recommendation were scares and admittedly, the pandemic urged us to quickly address unprecedented issues and to balance patients' and personnel's safety and oncological indications.

Overall, the peculiarities of our experience derive from our designation as an oncological hub in an area of severe COVID-19 outbreak, from the patients' volume and from the need (especially in the early phases of the emergency) of optimizing the use PPE. However, our aim is far from being either educational or didactic. The current work should in fact be considered as an early report of our management for HNC patients at the time of an unprecedented global health crisis. Nevertheless, we believe that it could be useful to provide our Fellow Radiation Oncologists with a set of indication covering Department organization in providing patients' and health professionals protection.

Conclusion: We presented the first report analyzing the beginning of COVID-19 pandemic in Europe with a dedicated focus on HNC patients candidate to curative radiation treatments. Results of the present work show that an adequate and well-timed organization (both in terms of national/regional and Institutional rules) permitted us to maintain a high quality radiation therapy standards of care, balancing the best clinical practice with healthcare personnel's safety.

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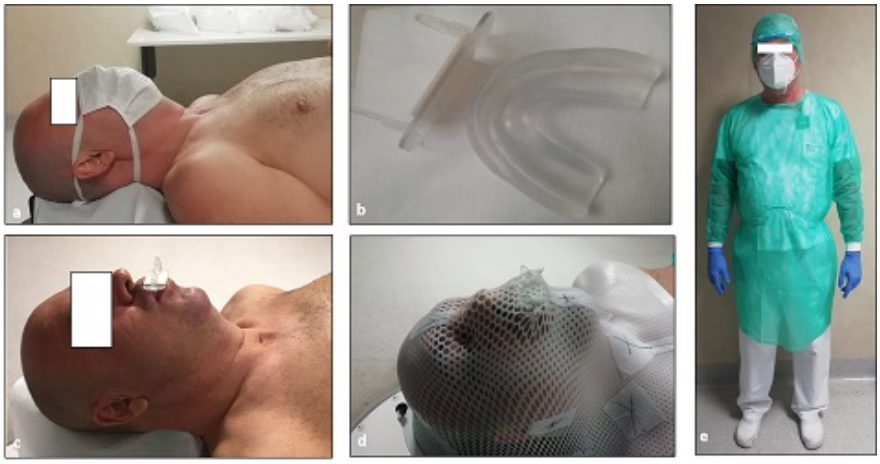

Figure 1: This is a caption

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