Practice recommendations for risk-adapted head and neck cancer radiotherapy during the COVID-19 pandemic: an ASTRO-ESTRO consensus statement

David J. Thomson, MA, MD, FRCR,[1] David Palma, MD, PhD,[2] Matthias Guckenberger, MD,[3] Panagiotis Balermpas, MD,[3] Jonathan J. Beitler, MD, MBA,[4] Pierre Blanchard, MD,[5] David Brizel, MD,[6] Wilfred Budach, MD,[7] Jimmy Caudell, MD, PhD,[8] June Corry, MD,[9] Renzo Corvo, MD,[10] Mererid Evans, MD,[11] Adam S. Garden, MD,[12] Jordi Giralt, MD, PhD,[13] Vincent Gregoire, MD, PhD,[14] Paul M. Harari, MD,[15] Kevin Harrington, PhD, FRCR,[16] Ying J. Hitchcock, MD,[17] Jorgen Johansen, MD, PhD,[18] Johannes Kaanders, MD, PhD,[19] Shlomo Koyfman, MD,[20] J.A. Langendijk, MD,[21] Quynh-Thu Le, MD,[22] Nancy Lee, MD,[23] Danielle Margalit, MD, MPH,[24] Michelle Mierzwa, MD,[25] Sandro Porceddu, MBBS, MD,[26] Yoke Lim Soong, MBBS,[27] Ying Sun, PhD,[28] Juliette Thariat, MD, PhD, MS[29] John Waldron, MD, MSc[30] Sue S. Yom, MD, PhD, MAS[31]

Affiliations

1. Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester and the Division of Cancer Sciences, The University of Manchester, UK
2. Division of Radiation Oncology, Western University, London, Canada
3. Department of Radiation Oncology, University Hospital Zurich, University of Zurich, Zurich, Switzerland
4. Department of Radiation Oncology, Emory University, Atlanta, GA, USA
5. Department of Radiation Oncology, Gustave Roussy Cancer Center, Villejuif, France
6. Department of Radiation Oncology, Duke Cancer Institute, Durham, NC, USA
7. Department of Radiation Oncology, University Hospital Düsseldorf, Germany
8. Department of Radiation Oncology, Moffitt Cancer Center, Tampa, FL, USA
9. Department Radiation Oncology Genesiscare, St Vincent's Hospital, Melbourne, Australia
10. Department of Radiation Oncology, Ospedale Policlinico San Martino and University, Genoa, Italy
11. Department of Clinical Oncology, Velindre University NHS Trust, Cardiff, Wales, UK
12. Department of Radiation Oncology, The University of Texas - M. D. Anderson Cancer Center, Houston, TX, USA
13. Department of Radiation Oncology, Hospital Universitari Vall d'Hebron, Barcelona, Spain
14. Department of Radiation Oncology, Centre Leon Berard, Lyon, France
15. Department of Human Oncology, University of Wisconsin, Madison, WI, USA
16. Division of Radiotherapy and Imaging, Institute for Cancer Research, London, UK
17. Department of Radiation Oncology, Huntsman Cancer Hospital, University of Utah, Salt Lake City, USA
18. Department of Oncology, Odense University Hospital, Department of Oncology, Denmark
19. Department of Radiation Oncology, Radboudumc, Nijmegen, The Netherlands
20. Department of Radiation Oncology, Cleveland Clinic, Cleveland, OH, USA
21. Department of Radiation Oncology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
22. Department of Radiation Oncology, Stanford University, Palo Alto, CA, USA

23. Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
24. Department of Radiation Oncology, Dana-Farber/Brigham & Women's Cancer Center, Harvard Medical School, Boston, Massachusetts, USA
25. Department of Radiation Oncology, University of Michigan, Ann Arbor, MI
26. Department of Radiation Oncology, Princess Alexandra Hospital, University of Queensland, Brisbane, Australia
27. Division of Radiation Oncology, National Cancer Centre Singapore, Singapore
28. Department of Radiation Oncology, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, PRC
29. Department of Radiation Oncology - Centre François Baclesse, University of Normandy, Caen, France
30. Department of Radiation Oncology, Princess Margaret Hospital, Toronto, Ontario, Canada
31. Department of Radiation Oncology, University of California San Francisco, San Francisco, California, USA

Statistical author:
David J. Thomson, MA, MD, FRCR
The Christie NHS Foundation Trust
Department of Clinical Oncology
Wilmslow Road, Manchester
M20 4BX. UK
Tel: +(44) 161 446 3361
Email: david.thomson@christie.nhs.uk

Corresponding author:
Sue S. Yom, MD, PhD, MAS
University of California, San Francisco
Department of Radiation Oncology
1825 4th Street, Suite L1101
San Francisco, CA 94143
Tel: (415) 353-7175
Email: sue.yom@ucsf.edu

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Running Title: COVID-19 head and neck recommendations

Abstract

Introduction

Due to the unprecedented disruption of health care services by the COVID-19 pandemic, the American Society of Radiation Oncology (ASTRO) and the European Society for Radiotherapy and Oncology (ESTRO) identified an urgent need to issue practice recommendations for radiation oncologists treating head and neck cancer (HNC), in a time of heightened risk for patients and staff, and of limited resources.

Methods

A panel of international experts from ASTRO, ESTRO and select Asia-Pacific countries completed a modified rapid Delphi process. Questions and topics were presented to the group, and subsequent questions developed from iterative feedback. Each survey was open online for 24 hours, and successive rounds started within 24 hours of the previous round. The chosen cutoffs for strong agreement (≥80%) and agreement (≥66%) were extrapolated from the RAND methodology. Two pandemic scenarios: early (*risk mitigation)* and late (*severely reduced radiotherapy resources)* were evaluated. The panel developed treatment recommendations for five HNC cases.

Results

In total, 29/31 (94%) of those invited accepted, and after a replacement 30/30 completed all three surveys (100% response rate). There was agreement or strong agreement across a number of practice areas including: treatment prioritisation, whether to delay initiation or interrupt radiotherapy for intercurrent SARS-CoV-2 infection, approaches to treatment (radiation

dose-fractionation schedules and use of chemotherapy in each pandemic scenario), management of surgical cases in event of operating room closures, and recommended adjustments to outpatient clinic appointments and supportive care.

Conclusions

This urgent practice recommendation was issued in the knowledge of the very difficult circumstances in which our patients find themselves at present, navigating strained health care systems functioning with limited resources and at heightened risk to their health during the COVID-19 pandemic. The aim of this consensus statement is to ensure high-quality HNC treatments continue, to save lives and for symptomatic benefit.

Practice recommendations for risk-adapted head and neck cancer radiotherapy during the COVID-19 pandemic: an ASTRO-ESTRO consensus statement

Introduction

The coronavirus (SARS-CoV-2) outbreak is considered a global pandemic by the World Health Organization.[1] Most infected people develop a mild respiratory illness, but based on an early census from the U.S. Centers for Disease Control, 20-30% of persons aged ≥ 45 years require hospital admission, and fatality rates range from 10-17% in persons aged ≥ 85 years, 3-11% among persons aged 65-84 years, and 1-3% among persons aged 55-64 years.[2] Those with cancer or receiving treatment for cancer are at enhanced risk of serious morbidity, including the need for ventilator support or death (HR 3.56, [95% CI, 1.65 to 7.69]).[3] The pandemic has strained cancer services, with routine outpatient appointments cancelled, elective surgeries postponed and resources diverted to the front line.

For the oncology clinician wishing to offer palliative systemic therapies there is a Hobson's choice: a high symptom burden from the cancer without treatment or an increased risk of a more imminent death from SARS-CoV-2 infection resulting from the exposure and stress of therapy. For curative-intent treatments, there are parallel and specific challenges facing the head and neck (HN) oncologist: (i) operating room closures, with increased requirement for non-surgical treatments, (ii) an altered risk-benefit ratio of chemotherapy and radiotherapy due to increased susceptibility for SARS-CoV-2 infection, (iii) a need to suppress coronavirus spread by minimizing travelling of patients for daily treatments and the exposure of hospital and radiotherapy staff, and (iv) a shortage of radiotherapy resources due to staff sickness or leave for family care entailing allocation of resources and triage of patients. The use of hypofractionated radiotherapy (radiation schedules that are shorter overall but give a larger

dose per treatment) could help address the latter two concerns, but these regimens may be unfamiliar to many radiation oncologists, and there is a risk of inappropriate application if these fall outside current international guidelines.

Due to this unprecedented disruption of health care services by the COVID-19 pandemic, the American Society of Radiation Oncology (ASTRO) and the European Society for Radiotherapy and Oncology (ESTRO) identified an urgent need to issue practice recommendations for radiation oncologists treating head and neck cancer (HNC), in a time of heightened risk for patients and staff, and of limited resources.

Methods

With endorsement of the ASTRO and ESTRO executive committees, a panel of international experts was identified to provide practice recommendations for HNC during the COVID-19 pandemic. Panellists were nominated in equal numbers from the two societies with select representation from a few affected Asia-Pacific countries. A modified rapid Delphi process was used to develop consensus recommendations. A systematic literature review was not performed due to the urgency and lack of information on the conduct of cancer treatment related to the COVID-19 pandemic. The organizers (DT, SY, DP, MG) presented the initial topics and questions to the group by electronic survey and subsequent questions were developed based on iterative feedback from the panellists. Questions were not asked again after agreement was reached. Each survey was open online for 24 hours and successive rounds started within 24 hours of the previous round. The chosen cutoffs for **strong agreement** (≥80%) and **agreement** (≥66%) were extrapolated from RAND methodology.[4]

Two scenarios, both of current and global relevance to the COVID-19 pandemic, were evaluated:

- Early COVID-19 pandemic scenario 1 – *risk mitigation*, given the potential for: (i) patient and/or staff infection due to repeat hospital visits, (ii) risk of more serious infection in those receiving radiotherapy and/or chemotherapy, and (iii) negative impact on strained healthcare resources from the management of the expected severe toxicities associated with intensive chemo-radiotherapy.
- Later COVID-19 pandemic scenario 2 – *severely reduced radiotherapy resources*: the additional consideration of a lack of resources, whereby some patients are unable to receive radiotherapy.

The panel was asked to develop treatment recommendations for five common clinical cases of head and neck squamous cell carcinoma (HNSCC):

1: Oropharyngeal SCC, T2 with multiple ipsilateral nodes < 3 cm, M0; this was subdivided into:

1a: p16 negative (OP-) and

1b: p16 positive (OP+)

2: Laryngeal glottic SCC, T1bN0M0 (GLOT)

3: Laryngeal SCC, T3N1M0 with impaired vocal cord mobility (LX)

4: Metastatic hypopharyngeal SCC, T4N1M1 – obstructed, bleeding, with several lung metastases (HXpal)

5: Resected oral cavity SCC, pT2pN2aM0; this was subdivided into:

5a: with positive margins (OC+) and

5b: with close but clear 3mm margins (OC-)

Supplementary questions concerned the conditions for delaying or interrupting radiation or chemotherapy for intercurrent SARS-CoV-2 infection, treatment prioritisation in case of severely limited resources, management in case of surgical operating room closures, and how HN oncologists are adjusting clinics to account for the attendant risks. For all cases, we assumed a representative HNC patient fit for chemotherapy and/or radiotherapy.

This consensus statement was developed through an agreement between the ASTRO and ESTRO, although given the urgency and differences in the societies' usual development processes, adjustments to the societies' usual procedures were allowed. The process was further endorsed by the Head and Neck Cancer International Group (HNCIG). Waiver of consent and exempt status was conferred by the University of California, San Francisco Institutional Review Board (#20-30633).

Results

In total, 29/31 (94%) of those invited accepted, and after a replacement nomination by ESTRO, 30/30 completed all three surveys (100% response rate). In the respective rounds, there were 80, 35 and five questions, taking on average a total of 73, 25 and five minutes to complete. The list of questions and panellists' responses are included in Appendix 1.

Treatment prioritisation

Panellists were asked if certain cases should be postponed in either the early or late pandemic scenario. There was **strong agreement** (for cases of OP-, OP+, LX, HXpal, OC+) or **agreement** (GLOT) not to postpone the initiation of HNSCC radiotherapy by more than 4-6

weeks in both the early and late scenarios. For OC- in the late scenario, there was no consensus.

Panellists were then asked to prioritise the cases. Compared to all other types of cancer within one's department requiring radiotherapy, there was **strong agreement** that OP-, OP+, and LX were very high (top 20%) or high (top 20-40%) priority. On average, GLOT and OC+ were also deemed high priority, while HXpal was of average (40-60%) priority. OC- was lower priority, and some (23%) would omit radiotherapy in case of severely limited radiotherapy capacity.

In a situation of severely reduced resources, we further asked for these cases to be ranked in order of treatment priority against each other. These were ranked by the panel from high to low as: OP+, OP-, LX, OC+, GLOT, HXpal, OC-. To further understand the trade-offs between treatment urgency and clinical priority, we asked respondents to set a policy by which a group of 20 patients would be treated before the other group could start. In this situation of policy determination, panellists prioritised LX over OP- (62%), OC+ over HXpal (63%), and HXpal over GLOT (73%).

Panellists were finally asked to prioritise factors that would matter most in starting radiotherapy either within the next one week or next 2-3 weeks. These rankings are shown by the highest to lowest weighted average from top to bottom (Figures 1a-b). In both scenarios of early and late pandemic, the three factors of active SARS-CoV-2 infection, symptomatic benefit, and potential for cure (as opposed to the specific % likelihood of cure) were the most important in triage for radiotherapy over the next one week (Fig. 1a). With an additional week or two of time before starting, active SARS-CoV-2 infection fell to the second highest weighted position behind symptomatic benefit (Fig. 1b).

COVID-19 Practice Recommendations: Treatment Prioritisation

Do not postpone the initiation of HNSCC radiotherapy by 4-6 weeks	**Strong agreement**
HNSCC radical radiotherapy is high or very high priority	**Strong agreement**
HNSCC post-operative radiotherapy for involved margins is high priority	Agreement
HNSCC post-operative radiotherapy for minor risk factors is lower priority	Agreement

Intercurrent SARS-CoV-2 infection

In the case of a patient testing positive for SARS-CoV-2 infection, there was **strong agreement** (OP, GLOT, OC) or **agreement** (LX, HXpal) to delay the initiation of radiotherapy until the patient had recovered. However, for all cases there was initially **agreement** *not* to interrupt radiotherapy (except for HXpal, where a single fraction could be used). We therefore sought to better understand the recommendation not to interrupt radiotherapy, and the interaction of this decision with SARS-CoV-2 symptom severity and timing during radiotherapy.

Panellists were instructed to assume that appropriate personal protective equipment (PPE) would be available and best practices would be implemented, such as treating the patient at the

end of the day in a designated vault, limiting exposure by utilizing minimal staff and properly sanitizing the vault.

Under assurance of these conditions, for patients testing positive with mild symptoms (cough but normal activity level), 63% of the panel voted to continue radiotherapy, 17% would only interrupt in the first or second week of radiotherapy, and 20% would interrupt in any week of radiotherapy until the patient recovered. In other words, there was **strong agreement** to continue radiotherapy in those with SARS-CoV-2-related mild symptoms who had completed more than two weeks of treatment. On the other hand, there was also **strong agreement** among panellists to interrupt radiotherapy in any SARS-CoV-2+ patient demonstrating more severe symptoms (cough, chest pain, and trouble breathing at rest requiring oxygen support) until the patient had fully recovered. Different centers reported varying policies on deciding when a SARS-CoV-2+ patient would be able to return including repeat negative testing as well as 10-14 day waiting periods.

For the minority who would interrupt radiotherapy even for mild symptoms, the top stated reasons included: (i) concern for worsening the patient's respiratory and general condition, (ii) increased likelihood of emergency admission and/or need for feeding tube insertion and (iii) risk of infecting other patients and staff. A few panellists expressed that protection of staff and other patients should be prioritised over treatment of a single patient, if unavailability of resources would endanger the many for the one.

COVID-19 Practice Recommendations: Intercurrent SARS-CoV-2 infection

For patients testing positive for SARS-CoV-2 infection:

Delay initiation of radiotherapy until recovery +/- SARS-CoV-2 test is negative	**Strong agreement**
Do not interrupt radiotherapy for mild SARS-CoV-2-related symptoms	Agreement
Do not interrupt after week 2 of radiotherapy for mild SARS-CoV-2-related symptoms	**Strong agreement**
Do interrupt radiotherapy for severe SARS-CoV-2-related symptoms	**Strong agreement**

Case-specific radiotherapy and chemotherapy practice

For each case, we asked participants to provide their center's standard radiotherapy dose-fractionation and how (if at all), this would be varied for scenarios of risk mitigation or severely restricted radiotherapy capacity (Table 1). In scenario 1 of early pandemic, there was **strong agreement** (OP and OC) or **agreement** (GLOT and LX) to stay with the same radiotherapy dose-fractionation. There was no consensus for HXpal. In scenario 2 of late pandemic, there was **strong agreement** to use a more hypofractionated schedule for all of the cases compared with the average standard approach.

Panellists stated that their usual standard concomitant chemotherapy schedules were cisplatin at 80-100 mg/m^2 every 3 weeks (60%) and cisplatin at 30-40 mg/m^2 once a week (40%). In early pandemic, there was **strong agreement** to continue the use of chemotherapy for all relevant cases where it would be applied (OP-, OP+, LX, OC+; Table 2) and **agreement** not to alter the schedules they used in standard practice. However, numerous panellists stated they

would consider switching from high-dose to weekly cisplatin. In the late pandemic setting, there was **agreement** to omit chemotherapy for OP+, and the majority (63%, near-agreement) would omit chemotherapy for HNC in general in this situation.

Given the recommendations to use more hypofractionated radiotherapy schedules, we sought to understand the maximum dose per fraction that panel members considered safe and acceptable to use with concomitant chemotherapy. There was **agreement** favoring use of concomitant chemotherapy only with conventional or mildly hypofractionated radiotherapy of ≤2.4 Gy / fraction (52%: 2.0-2.2 Gy / f; 21%: 2.2-2.4 Gy / f; 24%: 2.4-2.6 Gy / f; 3%: 2.6-2.8 Gy / f).

Of note, most panellists (63%, near-agreement) stated they did not consider induction chemotherapy to be a standard treatment for LX. A few (10%) supported induction as a standard treatment and a minority (27%) supported its consideration as a temporizing measure in times of pandemic. There was in the end a majority (63%) recommending against use of induction chemotherapy in either of the pandemic scenarios. Several panellists expressed concern about the SARS-CoV-2-specific risk that could be incurred from an extended period of myelosuppression.

COVID-19 Practice Recommendations: Radiotherapy and chemotherapy practice

In scenario 1, *risk mitigation*:

Do not alter standard HNSCC radical radiation dose-fractionation	Agreement
Continue to use concomitant chemotherapy	**Strong agreement**

Continue to use the standard concomitant chemotherapy schedule	Agreement
Do not use induction chemotherapy for locoregionally advanced larynx SCC	Majority, near-agreement

In scenario 2, *risk mitigation with severely reduced radiotherapy capacity*:

Use a hypofractionated radiation schedule	**Strong agreement**
Reserve concomitant chemotherapy for use with conventional or mildly hypofractionated radiotherapy (≤ 2.4 Gy / f)	Agreement
Do not use induction chemotherapy to delay initiation of treatment	Majority, near-agreement

Operating room closures and the management of surgical cases

In many afflicted regions around the world, operating theatre capacity has been curtailed or in severe pandemic scenarios, discontinued. However, many HNC are traditionally treated with primary surgery. In the case of absolute operating room closure, we asked about the panellists' recommended non-surgical treatment strategy for five cases typically managed by primary surgery.

A: Oral Tongue SCC, T2N0M0	Radical radiotherapy	Agreement
B: Oral Tongue SCC, T3N2bM0	Radical chemo-radiotherapy	**Strong Agreement**
C: Laryngeal SCC, T4aN2bM0, with tracheostomy	Radical chemo-radiotherapy	Agreement
D: Hard palate adenoid cystic carcinoma, T2N0M0	50% radical RT, 47% surveillance	No agreement
E: Sinonasal maxilla SCC T4aN1M0	Radical chemo-radiotherapy	**Strong Agreement**

In response to this question, a few panellists commented that they would not wait more than 2-3 months for surgery. Therefore, for oral cavity cancers, where primary radiotherapy is less effective and more toxic, we specifically asked what amount of time would be acceptable for a patient to wait for operating room availability rather than starting radical (chemo-)radiotherapy.

A: Oral Tongue SCC, T2N0M0	Wait up to 8 weeks	**Agreement**
B: Oral Tongue SCC, T3N2bM0	Wait up to 4 weeks	**Strong Agreement**

A few practitioners commented that in these conditions they might wait longer such as 12 or 6 weeks, respectively, to obtain surgery for these two cases.

COVID-19 Practice Recommendations: Operating room closures and surgical cases

Where faced with operating theatre closures and no capacity for HNC surgery:

(Chemo-)radiotherapy should be used for locoregionally advanced HNSCC	Agreement
Non-treatment is acceptable in certain cases of slow-growing cancers	No agreement
For early oral cavity cancers, consider waiting for surgical capacity, if this is predicted to be available within 8 weeks, and in this situation check on the patient every few weeks for progression	Agreement
For locoregionally advanced oral cavity cancers, consider waiting for surgical capacity, if this is predicted to be available within 4 weeks	**Strong agreement**

Adjustments to outpatient clinic appointments and supportive care

During the pandemic, there was **strong agreement** to modify the routine weekly in-person (face to face, in the same room) on-treatment reviews for patients receiving radiotherapy. There was also **agreement** to change the usual practice of conducting all new patient consultations in

person. For both situations, there was no consensus approach, as some (23%) had stopped in-person reviews altogether and others had reduced the frequency of in-person visits, replacing them with telephone (50%) or video (26%) consultations. A few panellists commented on concomitant reduction of dental, nutrition, or speech pathology services.

Panel members were in **strong agreement** not to increase the use of prophylactic placement of percutaneous endoscopic gastrostomy (PEG) feeding tubes; some commented that interventional radiology services were unavailable due to pandemic and PEG use was actually decreased. Over half (53%) of the panellists were no longer performing aerosol-generating procedures within the radiotherapy department (tracheostomy care, airway suctioning, flexible fiberoptic nasopharyngoscopy, nasogastric tube insertion).

COVID-19 Practice Recommendations: Appointments and Supportive Care

Where possible, reduce in-person (face to face, in the same room) consultations and replace with telephone or video for:

Routine weekly on-treatment reviews	**Strong agreement**
New patient consultations	Agreement

Discussion

The aim of this ASTRO-ESTRO practice recommendation was to provide urgent support for clinicians faced with managing HNC during the COVID-19 pandemic. There are a number of substantial recommendations, structured around typical cases in distinct pandemic scenarios, but treatment decisions in the real world must take into account all of the clinical factors relevant

at the time. These decisions are informed by local and national policies, and must be made within political, financial and regulatory frameworks. On a practical level, the ability to implement hypofractionated radiotherapy schedules will depend on the circumstances of the particular radiotherapy department, and the capability and capacity to do so (for example, knowledge of altered fractionation, critical structure dose constraints, and dosimetrist and physicist resources).

In the early, risk-mitigation scenario, neither the potential benefits of using hypofractionated radiotherapy to reduce frequency of patient attendance, nor the omission of concomitant chemotherapy to reduce risk of immunosuppression or treatment complications, were deemed sufficient justification to alter standard practices for locoregionally advanced HN cancer. However, our scenarios described a patient fit for a combined-therapy regimen. Patient-specific factors (such as age, fitness, comorbidities) were not addressed in this study. It has been recognized that the benefit of concomitant chemotherapy decreases with increasing age (especially for those >60 years' old).[5] Therefore, for older patients or those with comorbidities who are at higher risk of more serious SARS-CoV-2 infection,[6] and for whom concomitant chemotherapy will have less benefit, the use of chemotherapy should be restricted.

In the later scenario of severely reduced capacity (where some patients would need to go without radiotherapy), there was strong support for hypofractionated radiotherapy. For early larynx cancer (T1N0), 50 Gy / 16f was most commonly recommended,[7,8] and there are data for 55 Gy / 20f in T2N0 disease.[9,10] There is limited evidence to support the use of hypofractionated radical radiotherapy over 4-5 weeks for locoregionally advanced disease, but panellists suggested schedules including: 55 Gy / 20f,[11,12,13,14] 62.5-64 Gy / 25f,[15,16] and 54 Gy / 18f.[17,18] Most would not use concomitant chemotherapy in this setting, and there was agreement to restrict concomitant chemotherapy to schedules of ≤ 2.4 Gy / f. While there are data to support

the use of concomitant platinum chemotherapy with higher doses per fraction,[12,13,15] panellists expressed reservations about the potential lack of benefit (for example, no apparent local control or overall survival advantage from the combination of chemotherapy with accelerated radiotherapy),[19,20] and the risk of increased acute and late toxicities.

It is important to recognize the continuum between the early and late scenarios described in this statement. The prevalence of SARS-CoV-2 infection in a given community may reach a point whereby risk-mitigation strategies such as shorter fractionation schemes and the omission of concurrent chemotherapy must be considered prior to the actual onset of severely reduced capacity. Unfortunately, because predictors of how long a pandemic condition will last in a given geographic area are not exact, individual clinicians and policy-makers are forced to make complex decisions with considerable uncertainty; this is in fact a limitation on many recommendations in this consensus statement due to marked variability in the extent, duration, and characterisation of pandemic conditions across nations and regions. Decision-making within the context of continually evolving pandemic conditions is further challenged by the prolonged nature of a course of chemoradiation in the HNC population.

Panellists also wished to address the conditions under which a SARS-CoV-2+ patient might be treated. As resources permit, clinicians should adhere to formal, pre-specified screening and viral testing algorithms for HNC patients, because mucosal symptoms related to HN radiation may mimic mild infectious symptoms. For patients developing mild symptoms during radiotherapy and testing positive for SARS-CoV-2 infection, there was agreement not to interrupt treatment, especially if the patient had already completed the first two weeks of radiotherapy due to more limited ability to re-irradiate to a curative-intent dose and concerns about accelerated tumor repopulation later in the treatment course. The minority who wished to interrupt radiotherapy even for mild SARS-CoV-2-related symptoms cited concerns about the

tolerability of treatment and the increase in exposure of staff and resource burden on the department and hospital. On the other hand, there was near-unanimous agreement that a patient highly symptomatic with SARS-CoV-2 infection should be interrupted.

In the later pandemic situation of severely reduced radiotherapy resources, decisions about treatment prioritisation are required. When asked to determine the priority for each case compared with all other cancers and then amongst only the HNC cases, the average rankings were consistent, from highest to lowest priority: OP+, OP-, LX, OC+, GLOT, HXpal, OC-. However, when further tested as direct trade-offs choosing whether to start groups of 20 patients over the others, there were two areas of divergence. First, in these larger-scale policy terms, it was agreed HXpal should be prioritised over GLOT with the rationale that: (i) the treatment course could be delivered expediently by a single radiation fraction (note the increase from 4% to 30% of panellists who would use a single fraction in these late pandemic circumstances), which would result in important symptomatic benefit, and (ii) GLOT could wait for a period of time to start radiotherapy without risk of significant progression or change in the chance of cure. This approach is in keeping with the earlier finding where postponement of GLOT by 4-6 weeks was acceptable to more than 20% of panellists. Second, the majority (62%) now agreed LX should be treated before OP-. This was important to prevent potential airway obstruction (i.e., for symptomatic benefit), where both cases had a similar chance of cure. This preference was consistent with our finding that symptomatic benefit and chance of cure were two of the top three factors for panellists in determining which group of patients should start treatment within a week or 2-3 weeks in the face of severely reduced radiotherapy capacity. In terms of factors conditioning whether to initiate radiotherapy, the third most important factor was SARS-CoV-2 status, which reflects the strong agreement to delay the start of treatment in patients testing positive for SARS-CoV-2 infection.

An unfortunate consequence of the COVID-19 pandemic is the closure of operating rooms, due to a lack of protective equipment to counteract increased exposure risk, and redeployment of anesthesiologists and ventilators to critical care. There was consensus that HNC cases normally managed by primary surgery should generally be treated with radical (chemo-)radiotherapy rather than have no treatment. However, for cancers of the oral cavity, where radiotherapy is less effective and more toxic than surgery, there was agreement that waiting for up to 8 and 4 weeks for surgery was acceptable for T1-2 cancers and T3-4 cancers, respectively, with close clinical surveillance every few weeks to monitor for clinical progression.

A major effect of the COVID-19 pandemic is a shift in the risk-benefit ratio which typically governs HNC management. In the face of severely reduced resources, unaccustomed trade-offs may become necessary with the consequence of being forced to consider treatments that could carry a higher risk of late effects (hypofractionation) or could be suboptimal (without chemotherapy, nonsurgical), to ensure safety and therapeutic benefit for the greatest number of persons. These newly developed practice recommendations provide a global consensus and basic harmonisation of approach in the face of limited clinical data to direct these difficult, unfamiliar decisions. One tangible benefit already achieved was the rapid sharing and comparison of hypofractionation schedules considered “acceptable” by global HNC experts in times of extreme crisis such as COVID-19.

This urgent practice recommendation was issued in the knowledge of the difficult circumstances in which our patients find themselves at present, navigating strained health care systems functioning with limited resources and at heightened risk to their health from SARS-CoV-2 infection. The aim of this consensus statement is to ensure that high-quality HNC treatments continue, to save lives and for symptomatic benefit. The process was unusual in that several members of this panel participated even as they continued to deliver treatments facing serious

personal risks to themselves. This statement attempts to address the immediate impacts of the COVID-19 pandemic on HNC clinical practice; an understanding of future consequences (impacts on clinical research and scientific advance, health care systems' financial standing, health and psychological consequences for practitioners and patients) will require continued attention.

References

1.https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10pdficon (Accessed April 6, 2020)

2. https://www.cdc.gov/mmwr/volumes/69/wr/mm6912e2.htm (Accessed April 6, 2020)

3. Liang W., Guan W., Chen R., et al. **Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China.** *Lancet Oncol*. 2020; 21:335–337. doi:10.1016/S1470-2045(20)30096-6)

4. Fitch, K., Bernstein, S.J., Aguilar, M. et al. The RAND/UCLA Appropriateness Method User's Manual. Santa Monica, CA: RAND Distribution Services 2003.

5. Pignon J-P., le Maître A., Maillard E. et al. **Meta-analysis of Chemotherapy in Head and Neck Cancer (MACH-NC): An Update on 93 Randomised Trials and 17,346 Patients.** *Radiother Oncol* 2009; 92: 4-14

6. Chen N., Zhou M., Dong X. et al. **Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study** The Lancet 2020; 395: 507-513

7. Gowda R.V., Henk J.M., Mais K.L. et al. **Three Weeks Radiotherapy for T1 Glottic Cancer: The Christie and Royal Marsden Hospital Experience** Radiother Oncol 2003; 68: 105-11

8. Cheah N.L.C, Lupton S., Marshall A. et al. **Outcome of T1N0M0 Squamous Cell Carcinoma of the Larynx Treated With Short-Course Radiotherapy to a Total Dose of 50 Gy in 16 Fractions: The Birmingham Experience** Clin Oncol (R Coll Radiol) 2009; 21: 494-501

9. Ermis E., Teo M., Dyker K.E. et al. **Definitive hypofractionated radiotherapy for early glottic carcinoma: experience of 55Gy in 20 fractions** Radiat Oncol. 2015; 10: 203

10. Chera B.S., Amdur R.J., Morris C.G. et al. **T1N0 to T2N0 Squamous Cell Carcinoma of the Glottic Larynx Treated With Definitive Radiotherapy** Int J Radiat Oncol Biol Phys 2010; 78: 461-6

11. Tobias J.S., Monson K., Gupta N. et al. **Chemoradiotherapy for Locally Advanced Head and Neck Cancer: 10-year Follow-Up of the UK Head and Neck (UKHAN1) Trial** Lancet Oncol 2010; 11: 66-74

12. Benghiat H., Sanghera P., Cashmore J. et al. **Four Week Hypofractionated Accelerated Intensity Modulated Radiotherapy and Synchronous Carboplatin or Cetuximab in Biologically Staged Oropharyngeal Carcinoma** Cancer and Clinical Oncology 2014; 3, (2) DOI:10.5539/cco.v3n2p1

13. Jacinto A.A., Filho E.S.B, de Souza Viana L. et al. **Feasibility of concomitant cisplatin with hypofractionated radiotherapy for locally advanced head and neck squamous cell carcinoma** BMC Cancer 2018; 18: 1026

14. Mehanna H., Wong W-L., McConkey C. et al. **PET-CT Surveillance versus Neck Dissection in Advanced Head and Neck Cancer** N Engl J Med 2016; 374:1444-1454

15. Meade S., Gaunt P., Hartley A. et al **Feasibility of Dose-escalated Hypofractionated Chemoradiation in Human Papilloma Virus-negative or Smoking-associated Oropharyngeal Cancer** Clin Oncol (R Coll Radiol) 2017; 30: 366-374

16. Thomson D.J., Ho K.F., Ashcroft L. et al. **Dose intensified hypofractionated intensity-modulated radiotherapy with synchronous cetuximab for intermediate stage head and neck squamous cell carcinoma** Acta Oncol 2015; 54: 88-98

17. Agger A., von Buchwald C., Rørbæk Madsen A. et al. **Squamous cell carcinoma of the nasal vestibule 1993–2002: A nationwide retrospective study from DAHANCA** Head Neck 2009; 31:1593-1599

18. Stavas M.J., Shinohara E.T., Attia A. et al. **Short course high dose radiotherapy in the treatment of anaplastic thyroid carcinoma** J Thyroid Res 2014; 2014: 764281

19. Ang K.K., Harris J., Wheeler R. et al. **Human papillomavirus and survival of patients with oropharyngeal cancer** N Engl J Med 2010; 363: 24-35

20. Bourhis J., Sire C., Graff P. et al. **Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): An open-label phase 3 randomised trial.** Lancet Oncol 2012; 13: 145-53

Figure legends

Figure 1a. (left panel) In scenario 2 (severely reduced radiotherapy resources), which are your top three factors to inform the triage (prioritisation) of patients with head and neck cancer to start this week? Factors are ordered from highest to lowest weighted.

Figure 1b. (right panel) In scenario 2 (severely reduced radiotherapy resources), which are your top three factors to inform the triage (prioritisation) of patients with head and neck cancer to start within 2-3 weeks? Factors are ordered from highest to lowest weighted.

Table 1. Fractionation schedules for for five clinical cases: standard, early pandemic and late pandemic recommendations.

Clinical case	Standard approach: % agreement and favoured schedules*	Scenario 1 Early Pandemic - *risk mitigation* Change from standard: % agreement and favoured schedules*	Scenario 2 Late Pandemic - *severe shortage of radiotherapy capacity* Change from standard: % agreement and favoured schedules*
1: Oropharynx SCC T2N2bM0 p16 negative (OP-)	2.0-2.2 Gy / f (100%) **(strong agreement)** 70 Gy / 35f (63%) 70 Gy / 33f (17%) 65-66 Gy / 30f (13%)	No change **(strong agreement)**	**Hypofractionated** 2.41-3.0 Gy / f (70%) **(strong agreement)** 55 Gy / 20f (30%) 54 Gy / 18f (7%) 62.5-64 Gy / 25f (7%)
2: Larynx SCC T1bN0M0 (GLOT)	2.0-2.4 Gy / f: 80% **(strong agreement)** 63 Gy / 28f (52%) 70 Gy / 35f (14%) 66 Gy / 33f (10%) 50 Gy / 16f (7%) 55 Gy / 20f (7%)	No change (agreement)	**Hypofractionated** 2.41-3.2 Gy / f (70%) **(strong agreement)** 50 Gy / 16f (30%)
3: Larynx SCC T3N1M0 (LX)	2.0-2.2 Gy / f: 97% **(strong agreement)** 70 Gy / 35f (63%)	No change (agreement)	**Hypofractionated** 2.21-2.8Gy/f (80%) **(strong agreement)** 55 Gy / 20f (30%) 54 Gy / 18f (7%)
4: Hypopharynx SCC Palliative (HXpal)	Various (no agreement) 30 Gy / 10f (17%) 44.4 Gy / 12f (17%)* 20 Gy / 5f (13%) 32 Gy / 4f (7%) 8 Gy / 1f (4%)	Various (no agreement) 8 Gy / 1f (17%) 44.4 Gy / 12f (13%)* 20 Gy / 5f (7%)	**Hypofractionated** Various **(strong agreement)** 8 Gy / 1f (30%) 20 Gy / 5f (20%)

5: Oral cavity SCC Post-operative pT2pN2aM0, involved margins (OC+)	2.0 Gy / f: 87% **(strong agreement)** 66 Gy / 33f (53%) 60 Gy / 30f (30%)	No change **(strong agreement)**	**Hypofractionated** Various **(strong agreement)** 50 Gy / 20f (30%) 62.5 Gy / 25f (10%)

SCC: squamous cell carcinoma; Gy/f: Gray/fraction; % of panellists in agreement with dose/fraction range, followed by listing of the most commonly cited schedules arranged by % of panellists giving that response (latter does not add up to 100%).
*Panellists called this schedule “quad shot” but the exact schedule can vary; the most common version is 3.7 Gy given twice daily for 2 days, repeated for 3 cycles.

Table 2. Chemotherapy recommendations: standard, early pandemic and late pandemic approaches.

	Standard approach	Scenario 1 Early Pandemic - *risk mitigation* Standard therapy: % endorsement	Scenario 2 Late Pandemic - *severe shortage of radiotherapy capacity* Standard therapy: % endorsement
1: Oropharynx SCC T2N2bM0 p16 negative (OP-)	Concomitant chemotherapy	Yes: 93% No: 7% **(strong agreement)**	Yes: 50% No: 50%
1b: Oropharynx SCC T2N2bM0 p16 positive (OP+)	Concomitant chemotherapy	Yes: 87% No: 13% **(strong agreement)**	Yes: 23% No: 77% (agreement)
3: Larynx SCC T3N1M0 (LX)	Concomitant chemotherapy	Yes: 83% No: 7% **(strong agreement)**	Yes: 40% No: 60%
5: Oral cavity SCC pT2pN2aM0, involved margins (OC+)	Concomitant chemotherapy	Yes: 94% No: 6% **(strong agreement)**	Yes: 50% No: 50%

SCC: squamous cell carcinoma.

Figure 1

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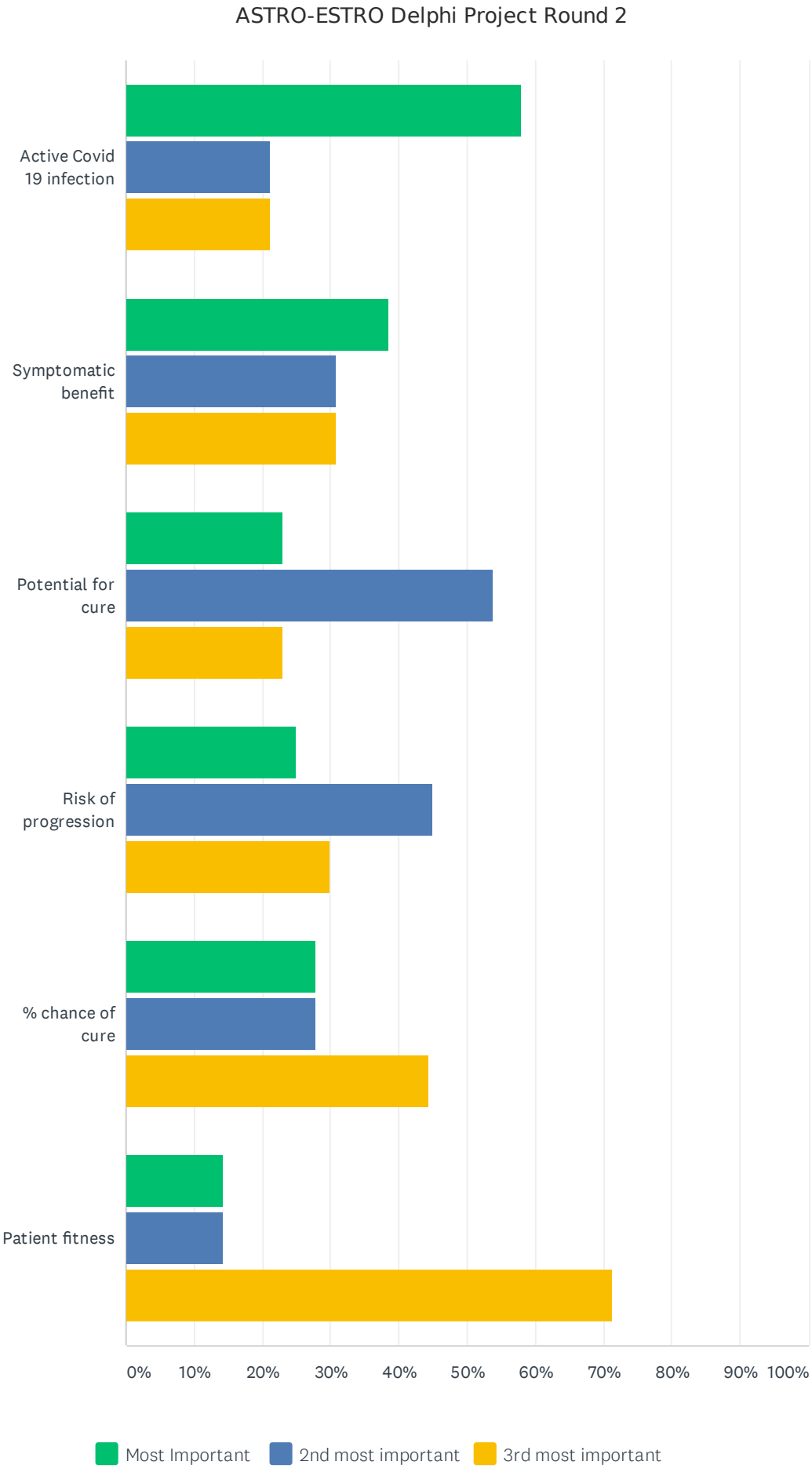

Figure 2

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