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Head and neck cancer and COVID-19

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This document considers potential adaptations to current practice that may be necessary due to the COVID-19 pandemic.

General advice

- Individual treatment centres will need to adapt their strategy based upon capacity and structure.
- Factors influencing decision making will change during the course of the COVID-19 pandemic; these include prevalence of infection and local radiotherapy resources.
- Discuss proposed changes to current treatment pathways with your head and neck MDT. This will mean that other unforeseen consequences of COVID-19 (e.g. lack of surgical capacity) are considered and that the MDT can communicate effectively with patients.
- Use the RCR H&N Forum as a way to discuss/seek advice from colleagues.
- ASTRO-ESTRO have published a useful recent consensus statement [1].
- Discuss any change to an individual treatment plan with the patient and document that discussion.
- Ensure treatment intent is clear in the patient record. In particular, ensure that patients having treatment with a high chance of cure and who become unwell have access to ITU support.
- Multidisciplinary support eg. attention to swallowing function and nutrition, remain very important pre-, during and post-treatment [2].

Curative treatment

Risks will be higher than usual, particularly for older patients and those with comorbidities who are at higher risk of serious COVID-19 infection. For example, patients with cardiovascular and metabolic illnesses have higher risks from COVID-19 infection.

- Curative treatment remains a high priority with many patients treated with the expectation of cure. Treatment should not be postponed.
- Consider hypofractionated radiotherapy regimens to reduce the number of patient visits to hospital, to reduce the duration of treatment in order to make successful completion of treatment more likely and to reduce overall burden to radiotherapy departments. 65Gy in 30 fractions is preferable to 70Gy in 35 fractions. Prior reported series from the UK demonstrate the efficacy and safety of hypofractionated radiotherapy with 55Gy in 20 fractions over 4 weeks [3]; this can be considered as an evidence-based option which would reduce treatment duration further.
- It is still reasonable to offer concurrent chemotherapy where indicated. However, this will increase overall risks of treatment. The absolute benefit of concurrent chemotherapy reduces with age [4] and older patients are at higher risk from developing a serious COVID-19 infection. In this group the increased risks of infectious complications may outweigh the benefit of chemotherapy. Decisions need to be individualised but consider omitting

concurrent chemotherapy in patients over 60 years old or in those with significant comorbidity.
- Accelerated fractionation without chemotherapy (e.g. six fractions per week [5]) may be an option but places an increased burden of twice-daily treatments on radiotherapy departments with limited capacity and may not be feasible.
- Consider cisplatin or carboplatin concurrently. Carboplatin is associated with lower rates of emesis or acute kidney injury [6], although randomised comparative efficacy data is lacking. Different centres are likely to have differing experiences of inpatient or outpatient cisplatin delivery and rates of subsequent admissions related to cisplatin; the ability to resource this may influence the appropriate choice of concurrent chemotherapy agent.

Curative treatment in the absence of usual surgery

Oncologists should work with MDTs to ensure surgical capacity maximised in local NHS Trusts and at Alliance level. Depending upon prevalent levels of COVID-19, undergoing surgery may carry a higher risk for patients than usual. A lack operating theatre capacity with the required critical care support and/or increased risks of surgery may mean that on occasion it is appropriate to treat patients with head and neck cancer non-surgically who would normally have been treated surgically. This is mainly relevant for squamous cell carcinomas for which non-surgical treatments may be curative e.g. oral cavity, paranasal sinus, locally advanced larynx cancer (may require tracheostomy). Multidisciplinary evaluation of surgical risks and discussion of possible alternative non-surgical treatment along with involvement of the patient in decision making is required [7]. If there is a realistic prospect of surgery becoming available, decisions are individualised but waiting up to 8 weeks for surgery for early stage disease and up to 4 weeks for locally advanced disease is reasonable [1].

Adjuvant treatment

Adjuvant treatment for patients with positive margins remains a high priority. It is important to consider appropriateness/type of treatment particularly for older patients and those with comorbidities who are at higher risk of serious COVID-19 infection.

- Consider omitting concomitant chemotherapy.
- A simultaneous integrated boost could be considered instead of concurrent chemotherapy for post-operative cases.
- Consider omitting adjuvant radiotherapy if the benefit is likely limited and may be outweighed by the risks e.g. patients with an RO resection and with minor risk factors who would normally have been considered at lower/intermediate risk of recurrence.

Palliative treatment

- Do not deliver palliative radiotherapy unless benefits clearly outweigh current risks.
- If delivering palliative radiotherapy, consider using short fractionation schedules (e.g. 25Gy in 5 fractions over 1 week, 20Gy in 5 fractions over 1 week, 30Gy in 6 fractions with IMRT over 2 weeks, or single 8Gy fraction depending upon clinical scenario).
- Consider not starting or delaying palliative chemotherapy/immunotherapy where the benefit is small and may be outweighed by the risks. Both chemotherapy and immunotherapy may increase the severity and mortality of COVID-19 infection; there remains considerable uncertainty regarding the impact of chemotherapy and immunotherapy upon the course of COVID-19 infection.

- Chemotherapy can still be considered for patients with good performance status and rapidly progressing disease. These patients with rapid progression are more likely to benefit from chemotherapy than immunotherapy.
- Pembrolizumab monotherapy is now an option in the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a combined positive score (CPS) ≥ 1. The NICE rapid guideline NG161, endorsed by NHS England, allows the use of pembrolizumab as first line monotherapy with the stated aim of reducing numbers of admissions and the risk of neutropenia (described in the interim treatment changes during the COVID-19 pandemic document [1]). This guidance does not include combination treatment with chemotherapy. Appropriate selection of patients for pembrolizumab monotherapy is challenging and needs to be based upon multiple factors including the CPS along with bulk of disease/speed of progression/symptom burden. Professor Kevin Harrington (The Institute of Cancer Research, London) has written the commentary in Appendix 1 to provide guidance for clinicians in decision making regarding the options of pembrolizumab monotherapy, chemotherapy or observation during the COVID-19 pandemic.
- For patients already having palliative chemotherapy/immunotherapy, consider stopping treatment or increasing the gap between cycles. It may be appropriate to stop palliative chemotherapy after 2-4 cycles when response is limited or stable disease. Single agent chemotherapy e.g. cisplatin may be considered rather than multi-agent therapy.

Infection prevention considerations

- Appropriate personal protective protective equipement (PPE) should be used according to local/national guidelines.
- Patients who have had a laryngectomy/have a tracheostomy have high levels of aerosol generation and radiographers have to get close to the patient for each fraction. Patients with who have had a laryngectomy/have a tracheostomy should only be treated when staff have appropriate PPE. Nasogastric tube insertion is also a potentially aerosol generating procedure and appropriate PPE is necessary.

Intercurrent COVID-19 infection

- If a patient tests positive for COVID-19 prior to radiotherapy commencing, the initiation of radiotherapy should be delayed until patient is recovered.
- If a patient receiving treatment develops *mild* COVID-19 related symptoms and tests positive, treatment should not be interrupted.
- If a patient receiving treatment develops *severe* COVID-19 related symptoms and tests positive, treatment should be interrupted until recovered.

Supportive treatment

- Consider modifying the structure of new patient, on-treatment and post-treatment reviews using telephone/video consultations to reduce in-person visits and face-to-face contact [2].
- However, particular care is needed to ensure adequate rehabilitation of swallow function etc. to minimise risks of long term enteral feeding dependency. Face-to-face reviews may be required for some patients to guide appropriate re-establishment of oral intake and prevent excessive duration of enteral feeding.

Response assessment

- Response assessment (clinical and imaging based +/- biopsy) is still required for patients who have received curative therapy for whom there would be a realistic prospect of surgical salvage if there was residual disease. For patients for whom there would be no option of surgical salvage (e.g. would decline, disease too advanced) then formal response imaging would not directly impact upon management and can be omitted.

Other resources of advice

ASTRO-ESTRO consensus statement [1].

ENT UK (https://www.entuk.org/entuk-guidelines-changes-ent-during-covid-19-pandemic) and BAHNO (https://www.bahno.org.uk/bahno_laryngectomy_guideance_during_covid-19_pandemic.aspx) have both published useful advice for management of head and neck cancer during the COVID-19 pandemic.

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Appendix 1

Commentary by Professor Kevin Harrington re: NHS England interim agreement to give eligible patients in England access to pembrolizumab for first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥ 1

NHS England (NHSE) is seeking to ensure patients are still able to receive anti-cancer treatment when it is required and are seeking to make the best use of NHS resources whilst protecting patients and NHS staff from the risk of infection. To help achieve that objective, NHSE is looking to offer alternative cancer therapies where clinically indicated to meet patient needs and reduce hospital admissions, increase the number of patients that are able to self-administer treatments at home and also reduce the number of patients on myelosuppressive therapies during the COVID-19 outbreak.

NHSE has brokered a partnership agreement with Merck, Sharp & Dohme Ltd (MSD) to supply pembrolizumab for untreated recurrent or metastatic squamous cell head and neck cancer[1]. Pembrolizumab was granted a European license for this indication in 2019 and was already undergoing National Institute for Health and Care Excellence (NICE) appraisal for use in the NHS, although this process (NICE HTA [ID1140]) is yet to be completed[2]. Pembrolizumab is indicated for monotherapy in the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥ 1[3]. This interim agreement between NHSE and MSD provides for use of pembrolizumab in England, **but only as a monotherapy** and for a **limited time period of an initial 3-months** as described in the interim treatment changes document attached to NICE rapid guideline NG161[1].

Although both the US FDA and EMA licences permit the use of single-agent pembrolizumab for first-line treatment of metastatic or unresectable recurrent HNSCC in adults whose tumours express PD-L1 with a CPS ≥ 1, it is important to stress that, in all other jurisdictions where this therapy has been approved in the first-line, treating physicians are also able to select the combination of pembrolizumab and chemotherapy[4] (for all-comers per FDA approval and in CPS ≥ 1 for EMA approval). The availability of both single-agent pembrolizumab and pembrolizumab-chemotherapy combination therapy allows experienced oncologists to select appropriate treatment for their patients based on factors such as CPS value, bulk of disease, site of disease (locoregional above the clavicle vs systemic), threat to critical structures (airway/swallowing apparatus/vasculature), presence or absence of symptoms and performance status. It is noteworthy that this agreement between NHSE and MSD **does not cover** the use of pembrolizumab in combination with platin/5-FU-based chemotherapy. As discussed below, this limited access to single-agent pembrolizumab may present clinicians and patients with challenges, as well as opportunities.

Regulatory authorities generally base decisions on drug approval on overall survival (OS) data derived from randomised studies, such as KEYNOTE-048[4]. In this regard, single-agent pembrolizumab was superior to EXTREME regimen for the CPS ≥ 1 population with a median OS of 12·3 vs 10·3 months, HR = 0·78 [0·64–0·96]. However, most of this benefit was driven by the approximately 45% of the study population with CPS ≥ 20 in whom

median OS was 14.9 vs 10.7 months, Hazard ratio (HR) = 0.61 [0.45-0.83 95%CI]. No specific data for the group of patients with CPS 1-19 were presented in the KEYNOTE-048 publication[4].

However, in the current context of exceptional access to single-agent pembrolizumab and in view of its relatively short-term goal of aiming to reduce hospital admissions and the number of patients on myelosuppressive therapies over the course of "an initial 3 months", oncologists may regard objective response rates (ORR) and progression-free survival (PFS) data as the most important guides when deciding whether, or not, to offer their patients single-agent pembrolizumab therapy during the current COVID-19 outbreak. Indeed, response to treatment or, at least, avoidance of progression have previously been recognised as indicators of the likelihood of deriving clinical gain from systemic therapy[5]. In this regard, ORR to single-agent pembrolizumab was 19% for CPS ≥ 1 and 23% for CPS ≥ 20, compared to 35-36% for the EXTREME regimen arms in KEYNOTE-048 [and approximately 20% for platin-5-FU in the historical control arm of the EXTREME study][6]. When comparing single-agent pembrolizumab to EXTREME regimen, PFS data reveal median values of 3.2 vs 5.0 months (HR = 1.13) for CPS ≥ 1 and 3.4 vs 5.3 (HR = 0.99) for CPS ≥ 20. Furthermore, inspection of the OS data reveals, for both CPS ≥ 1 and ≥ 20, that the survival curves cross at approximately 7-8 months – meaning that the single-agent pembrolizumab curve lies **below** the EXTREME chemotherapy curve in the initial treatment period.

It is also important to emphasise that the basic premise of the current decision – summarised briefly as immunotherapy good, chemotherapy bad – may be overly simplistic or even completely incorrect. Available preliminary data from China, Italy and the UK[7] suggest that there may not be a huge differential between the effects of immunotherapy and chemotherapy on the clinical course of COVID-19. Certainly, more data are likely to emerge in the coming weeks and months and these should be incorporated flexibly into any treatment selection process.

Taken together, and in the absence of specific information for the CPS 1-19 group, these data should lead treating oncologists to exercise caution in treating their patients with single-agent pembrolizumab during this early phase of the COVID-19 outbreak. As such, the following considerations may be helpful in guiding treatment selection for the first-line management of metastatic or unresectable recurrent HNSCC:

- For patients with CPS ≥ 20 and relatively asymptomatic/paucisymptomatic and non-bulky disease, single-agent pembrolizumab would appear to be uncontroversial and may well deliver benefit with relatively modest adverse effects.

- For patients with CPS ≥ 20 and symptomatic or bulky disease (especially above the clavicle), single-agent pembrolizumab may be a reasonable option but consideration should also be given to platin-5-FU-based cytotoxic chemotherapy (in units where this can be offered) or even palliative irradiation/re-irradiation.

- For patients with CPS 1-19 with asymptomatic/paucisymptomatic and non-bulky disease, a period of watchful waiting with regular telephone follow-up and repeated imaging (e.g. 6-weekly CT scans) may safely allow treatment to be delayed until the peak incidence of the COVID-19 outbreak has passed. This policy has the additional benefit that later in the course of the outbreak more data will be available on the consequences of systemic therapy (immunotherapy and/or cytotoxic chemotherapy) on the outcomes of COVID-19, allowing treating physicians to make more informed choices with their patients.

- The group of patients with CPS 1-19, with disease that is assessed as needing relatively urgent commencement of treatment, present clinicians with the most difficult decisions. There are three main choices: (i) to withhold all treatment because of concerns about patients contracting COVID-19 during repeated visits to hospital; (ii) to commence platin-5-FU-based cytotoxic chemotherapy in those units that are able to offer such treatment; and (iii) to commence single-agent pembrolizumab under the new scheme in those units in which cytotoxic chemotherapy is not currently offered. In the first situation, the patient, their family and the clinician are left in a terrible state of limbo, effectively observing and supervising symptomatic deterioration, disease progression and, ultimately, the patient's death. In situations (ii) and (iii) in which treatment is delivered, clinicians must explain that there is considerable uncertainty about the excess risks of chemotherapy or immunotherapy on the clinical course of a subsequent novel SARS-CoV2 infection. In the latter situation in which single-agent pembrolizumab is used, clinicians must also explain that there are concerns that a minority of patients may experience relatively rapid progression of disease and this may be associated with some patients experiencing worse survival outcomes relative to the underlying HNSCC.

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Conflict of Interest

KH discloses membership of MSD's Global Scientific Advisory Committee for head and neck cancer and has received research grant income, speaker's fees and honoraria for Advisory Board membership from MSD. All fees were paid to The Institute of Cancer Research.

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