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ESOPHAGEAL ONCOLOGIC SURGERY IN SARS-CoV-2 (COVID-19) EMERGENCY

IMPORTANT NOTE: This document is not intended as guideline, but has been drawn up to help cope with the temporary emergency and manage the surgical priority. These suggestions are subjected to change based on the pandemic evolution and must be adapted to the local situation in terms of resources and incidence of infection. In ALL centres, decisions should be made through an MDT process. Ensure each patient is considered on an individual basis by the MDT and record the reasoning behind each decision.

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1 Introduction

The rapidly expanding coronavirus disease 2019 (Covid-19) acute respiratory infection has changed many aspects of daily life. The outbreak was declared a public health emergency of international concern on 30 January 2020 by WHO. The dramatically raising number of general population and health care professionals infected in Western Countries is profoundly changing daily clinical practice. Resources of health care systems across Europe and globally have been temporarily reallocated to cope with the pandemic. As no vaccine is effective to date, social distancing has been promoted in order to decrease the diffusion and reduce the preventable deaths from overloading the public health system. All non-urgent procedures such as elective surgery and diagnostic testing have been markedly impacted . In this particular environment the lack of availability of operating theatres, endoscopic suites and infusion sessions, radiation planning or planned hospital admissions has forced the entire oncologic community to carefully consider how to deliver best care to cancer patients during this crisis.

Additional risk among oncologic patients in the Covid-19 era

It is well-known that elderly patients and those with comorbidity have been most victim to the most serious respiratory effects of Covid-19 . Cancer patients are vulnerable, and the balance between fear of immunosuppression, with the threat of Covid-19, and a compromised cancer outcome due to either delays in treatment or the use of suboptimal alternatives is a matter of great concern taking place daily in MDTs throughout the world. The Chinese experience to date highlights these concerns, in particular the added risk of Infection due to cancer-associated or treatment-induced therapy, as well as poorer outcomes from infection itself with higher risk of severe events. Patients who underwent chemotherapy or surgery in the prior month had a clinically severe form in 75% of cases, with an odds ratio of 5.34 ,{95% CI 1.80–16.18; p=0.0026} [1]. Therefore, the risk of acquiring Covid-19, and its implications with respect to mortality in particular, is highly relevant at this time in treatment planning and informed consent [2].

Esophageal Tumors

Surgery of esophageal cancer in particular is associated with a higher risk of mortality compared with most other cancer surgeries, up to 5% even in the best high volume centers. Moreover, the rate of postoperative major respiratory complications is high, at approximately 25%, hence a severe acute respiratory syndrome, from Covid-19, would present a major risk to life, particularly if respiratory and intensive care resources were unavailable or suboptimal. [3-8].

A key question consequently, uncertain at this time, is the timing of progression of an esophageal cancer that can be treated with curative intent from the initial clinical presentation and staging. We acknowledge the insufficiency of data on this topic, and suggest that doubling time and metastatic potential is likely to be highly variable across the spectrum of tumor biology seen in esophageal cancers, and most estimates in this context are speculative .

As the pandemic is going on, with no clear signs of abating, and no vaccine likely for approximately a year, difficult decisions will have to be made, in part depending on patient factors and preferences, with the access to safe treatments, including chemotherapy, radiation therapy, and surgery being paramount within local and regional structures, as well as population prevalence and position on the curve of COVID-19 infections, and the key element of critical care facilities.

2 Emergency Cases

This includes bleeding and perforations, as well as obstruction.

2.1. For bleeding, consider the endoscopic and/or interventional radiology options first, including embolization or hemostatic radiotherapy in selected cases.

2.2. In cases of perforation, if the patient shows relevant co-morbidity (cardiovascular disease, previous respiratory condition, end-stage renal disease, moderate-severe liver disease, diabetes, obesity), low performance status (ASA score >3, ECOG PS \geq 2 or Karnofsky \leq 60%) and/or organ dysfunction is present, and critical beds are limited due to a high volume of Covid-19 positive patients, always try conservative measures first.

2.3. Esophageal obstruction can be managed endoscopically in line with local endoscopic protocols

3 Elective Cases

Given the implications of serious respiratory distress in response to Covid-19 in the postoperative course, every patient scheduled for elective upper gastrointestinal cancer surgery, should be triaged and investigated with proper testing

3.1. Covid-19 positive or suspected patients

For Covid-19 positive patients or those with symptoms every intervention should be delayed. Every case should be discussed in a multidisciplinary setting assessing the timing of future intervention, and patients should be made aware of the additional surgical risk posed by Covid-19. In addition, more intensive surveillance or treatment should be considered when patients with cancer are infected, especially in the elderly or those with other comorbidities. In asymptomatic positive patients, the same principle should apply, and surgery delayed until the patient test is negative.

3.2. Covid-19 confirmed negative patients

Due to the high respiratory risk of esophageal surgery, and the implications of Covid-19 infection, together with the higher chance of abnormal presentations of the infection due to tumor or treatment-related immunosuppression, there is a compelling case for accurate testing of these patients before progressing to surgery. Accurate triage is advisable one day before accessing the hospital for elective procedures. A phone call assessing if the patient present any of high-risk symptoms (fever > 37.5 °, new onset cough, dyspnea, contact with patient infected or high prevalence areas) is mandatory to stratify the risks for the patient, the health care provider and other patients hospitalized

Ai et al. [9], reporting on 1014 patients from the city of Wuhan, revealed that a chest CT demonstrated a higher sensitivity for diagnosis of Covid-19 in comparison with RT-PCR assay from swab samples, with respective rates of 88% (888/1014) and 59% (601/1014). Using RT-PCR as a reference, the sensitivity of chest CT for Covid-19 was 97% (580/601). Interestingly, 60 to 93% of patients had an initial positive chest CT before a positive RT-PCR results, and the mean interval time between the initial negative to positive RT-PCR results was 5.1 ± 1.5 days. These data, combined with the advice of Italian expert's [10], provides strong support and recommendation to combine a CT chest with an RT-PCR assay from swab samples in every patient in Covid-19 pandemic areas who require oncologic surgery, most particularly for esophageal and lung surgery where respiratory complications are well reported.

The second issue is eligibility for elective surgery, and we propose that patients should be stratified according to tumor and patient factors (Figure 1).

3.2.1. Establishing patient's RISK FACTORS:

- Age over 75 [11]
- ECOG PS ≥ 2 or Karnofsky $\leq 60\%$
- Pre-existing comorbidities (cardiovascular disease, previous respiratory condition, end-stage renal disease, moderate-severe liver disease, diabetes, obesity)
- Risk of postoperative complications and the need for ICU unit

Due to high risk of postoperative complications, elective esophagectomy should be delayed when possible, especially in patients with comorbidity of where an extensive lymphadenectomy is advocated. Radical chemoradiotherapy represents a alternative for SCC patients that is supported by international guidelines [1,2]. In patients who have received neoadjuvant chemoradiotherapy, a limited longer period before surgery, as per the NeoRes II trial, is justified [12]. In patients who have an complete clinical response based on CT-PET, bite on bite biopsies of an endoscopically normal esophagus, then a watch and wait policy can be considered at this time, notwithstanding lack of Level I evidence, this particularly applies to esophageal SCC [13].

3.2.2. Establishing cancer PRIORITY:

- Symptoms related to the tumor
- Local compressive symptoms: consider stents or interventional radiology options first
- cTNM: locoregional (I) vs advanced stage (II-III).

Esophageal cancer

Consider endoscopic mucosal resection or endoscopic submucosal dissection (EMR/ESD) , already standard for cT1a disease, for all cT1N0 disease. In patients presenting with T2N0 tumors, with no or few comorbidities, surgery should be proposed; Post-neoadjuvant stage II and III disease should, if possible, continue to be treated surgically but priority can be determined based on likely post neoadjuvant nodal involvement and poorly differentiated histology [14]. Based on the predicted prognosis and the need for extensive

surgical lymphadenectomy, for poorly differentiated tumors and SCC, a switch from neoadjuvant to a definitive chemotherapy or chemoradiation can be considered (figure 1). With respect to operative approach, there is no evidence yet to avoid minimally invasive approaches to reduce infection diffusion, but, even in cases negative, we strongly recommend the use of all the disposable personal protection equipment (PPE) including masks (level 2 or 3 filtering face piece (FFP) depending on the aerosol generating risk level), eye protection, double non-sterile gloves, gowns, gaiters, caps and socks.

4. Systemic anti-cancer treatments

Currently, there is no strong evidence about how esophagogastric specific anti-cancer treatments should be adapted in the Covid-19 emergency setting. The “*Thésaurus National de Cancérologie Digestive (TNCD)*”, have proposed alternative schemes for every digestive cancer, including esophagogastric tumors, based on the consensus of experts. (Figure 2) [15]. Clinicians will also need to consider the level of immunosuppression associated with an individual therapy and the condition itself, and patients' other risk factors. Neoadjuvant therapy that requires clinic visits and clinician-patient contact must also be considered, and potentially be modified or protracted [16].

The American Society of Radiation Oncology (ASTRO) [17] advises that new patient consults and new patient starts may be triaged on a case-by-case basis according to the urgency of the situation following discussion with the MDT. The European Society for Radiotherapy and Oncology (ESTRO) adds that therapies that have been considered standard of care should be reconsidered. ESTRO also gives some guidance about the modification of radiotherapy treatments under a tumor-type basis in their recent publication. In respect of esophagogastric tumours, while gastric tumours should be treated with chemotherapy only, esophageal tumours in the view of ESTRO should be treated by “resection or chemoradiation rather than trimodality therapy” [18].

To apply these recommendations, it would appear that starting or extending chemoradiotherapy for localised esophageal tumours (including cT2N0 stages) should be a valid option to consider for these patients, this is also consistent with the French proposal [15]. If services are disrupted, patients should be prioritized for treatment accordingly, and the NICE guideline's prioritisation system is a useful resource in this scenario [19].

5. Nutritional status

During waiting time for a postponed surgery, in order to maintain or even gain optimal performance status prior to surgery, it is highly recommended to closely monitor nutritional status by usual nutritional scores (for example NRS-2002 or MUST scales). Dietary input through virtual clinics is also recommended. It is also advised to correct anemic condition by normally used methods in your institution.

6. Preoperative rehabilitation

If possible, consider to prepare patient-adjusted rehabilitation programs to do at home, to maintain patients fitness and musculoskeletal tone prior to surgery, limit sarcopenia and its consequences. These programs should be sent virtually or by ordinary post to minimize face-to-face contact.

7. Psychological support

Communicate with patients and support their mental well-being to help alleviate any anxiety and fear they may have about Covid-19. Discuss the risks and benefits of changing treatment regimens or having treatment breaks with patients, their families and care-givers.

Implementation of nontraditional care delivery strategies through information technology platforms and telehealth options can implement managing cancer-related issues.

8. Follow-up

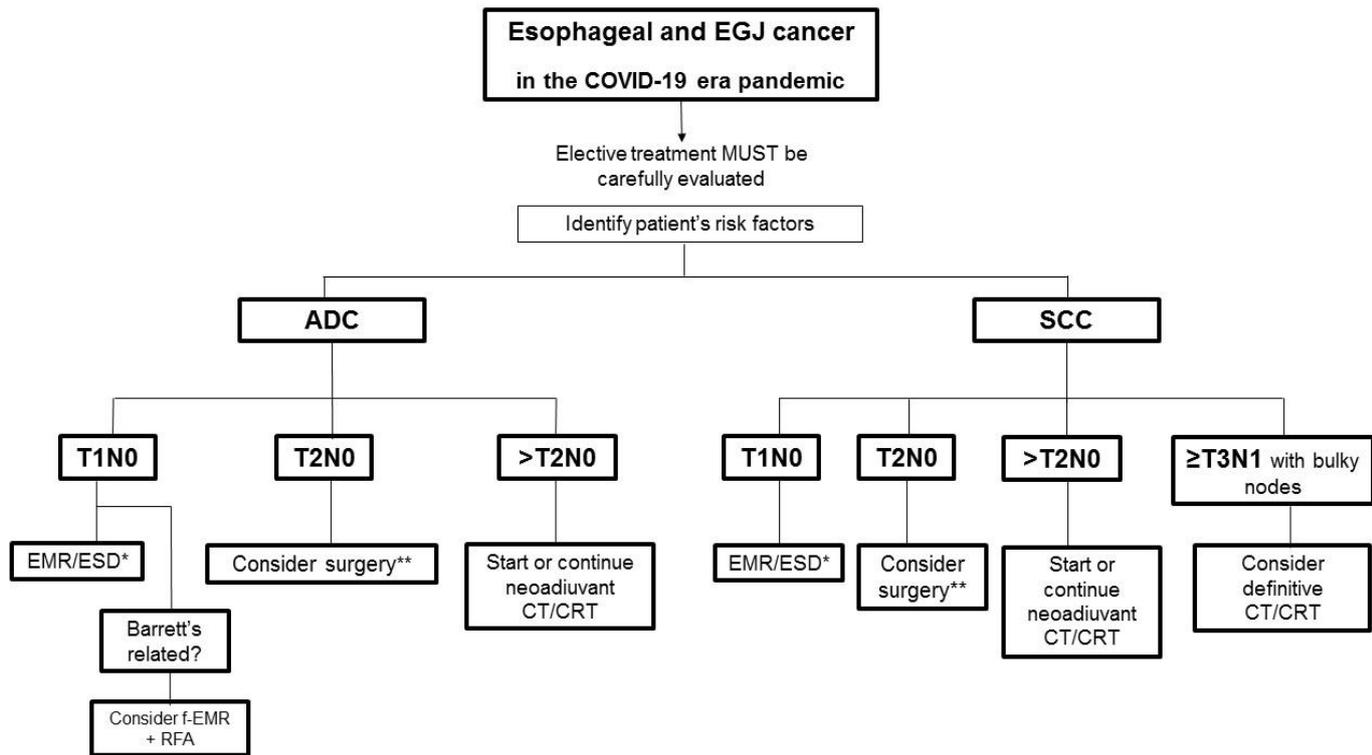
Consider postponing long-term follow-up patients until the crisis has passed, or use preferably telehealth medicine if it cannot be postponed. Consider that CT scanning and other imaging may be limited as radiology departments divert resources towards the coronavirus pandemic. In cases when CT or CRT is indicated by the multidisciplinary team, this must not be delayed and the access of the patient should follow the same route of triaging as for surgery intervention with phone call and oropharyngeal and nasopharyngeal swabs prior to hospitalisation.

9. Conclusions

The sanitary systems were not prepared to face such a pandemic: thousands of people everywhere in the world are infected and need support to fight the respiratory distress. Many people died for this reason. We should take into account our previous daily battle trying to help our patients deal with a particularly difficult cancer, and this battle within a global war on a potentially devastating virus must be maintained as best we can, and

these recommendations, not formal guidelines, are a proposed guide that hopefully will be of value at a time where traditional paradigms are upended.

Figure 1. Proposed flowchart for esophageal and gastroesophageal junction cancer treatment during Covid-19 pandemics.



*If pT1bN0 is confirmed, consider adding CRT adjuvancy and/or closer follow-up and/or elective surgery after the Covid19 emergency has passed, according to MDT decision.

** Consider the patient's personal factors, ASA, nutritional status; if compromised, try to improve with pre-assessment and reconsider the case collectively.

GEJ: gastroesophageal junction; SCC: squamous cell carcinoma; ADC: adenocarcinoma; EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection; f-EMR+RFA: focal endoscopic mucosal resection + radiofrequency ablation; CT: chemotherapy; CRT: chemoradiotherapy.

Figure 2. Alternative anti-cancer treatment scheme proposed by the French Intergroup “Thésaurus National de Cancérologie Digestive (TNCD)” for esophagogastric tumours during Covid-19 crisis (expert’s agreement). [15]

Oncologic disease	Proposals
Localised (GEJ and gastric) tumours: Perioperative chemotherapy	Chemotherapy adjusted to clinic situation: - FLOT if possible, due to the magnitude of the survival benefit, adding a G-CSF [30] - If previous is not possible, consider a dual chemotherapy based on platinum (CapOx in the absence of dysphagia)
Localised oesophagic tumours: Preoperative chemioradiotherapy	- Paclitaxel-carboplatin + radiotherapy preferably - In the event of a complete response, surveillance or delayed surgery [31]
Metastatic disease	First line chemotherapy CapOx +/-trastuzumab (if HER2 positive)

GEJ: gastroesophageal junction; G-CSF: granulocyte colony-stimulating factor; CapOx: capecitabine + oxaliplatin

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