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Lower GI response to the COVID-19 outbreak

Updated 24 April 2020 to reference Rectal Cancer Expert Consensus published by Radiother Oncol, NCCN guidelines and further discussions on the RCR website.

This document was written by Oxford Colorectal Oncologists (Dr R Muirhead, Dr C Jacobs, Dr A Weaver, Prof S Mukerjee, Dr R Owens) with review by Dr Rachel Cooper, Leeds Cancer Centre. The document was based on discussions that took place on the RCR online forum 'Colorectal chemotherapy in light of COVID-19' (RCR member login required) and summarises the similar strategies being drawn up in different centres around the UK.

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Centres are being impacted to different amounts by COVID19 around the UK. There are multiple factors to consider when making management decisions. In terms of capacity of cancer services, including availability of systemic therapies, radiotherapy, radiology, endoscopy and surgery. We must consider the risk of acquiring COVID infection while undergoing interventions; the capacity of a centre to treat COVID; the patient and their risk of mortality from COVID; and the status of the malignancy. The service pressures will change regularly over the coming months. Management decisions for a particular patient must take all of these factors into account and will be different at different timepoints in different hospitals. Clinicians can only use their knowledge and experience to decide what is the right decision for any one patient at a particular point. We would encourage clinicians to discuss difficult cases with fellow clinicians locally and nationally, to reduce the stress and pressure of making these challenging decisions alone.

General principles

- All patients currently on chemotherapy treatment, should be contacted and a decision taken regarding continuing, in view of guidelines below.
- All patients in whom chemotherapy / radiotherapy is continued or started, should be counselled regarding risks and advised about shielding themselves.
- Consultations should be performed by phone or video whenever possible.

Rectal cancer

- ESMO have published expert consensus guidance for rectal cancer treatment in COVID19 pandemic [1]. These are evidence based, so rightly can only offer advice presuming access to surgery remains as before. Our guidance is in keeping with options suggested by them but also considers that due to limited surgical lists, there is a need to go beyond these evidence-based guidelines at present.
- Revised surgical procedures may be appropriate to reduce risk to staff (open versus laproscopic) or reduce risk to patients (ie. Hartmans instead of anterior resection).
- Limit use of total neo-adjuvant therapy (TNT), either before XRT or after XRT unless patient young, fit and biology of tumour necessitates it.

Early / intermediate risk disease

- Consider delaying primary treatment in those very vulnerable or with very early tumours.
- Due to decreasing access to surgery and subsequent ITU; consider SCRT and delayed surgery in selected patients.
- In early stage disease, a single scan at the point of surgery may be appropriate if access to scanning is limited.
- A proportion of these patients will have a complete response therefore organ preservation may become an option.
- The OPERA trial delivering papillon treatment following EBRT remains open in selected centres as it aims to avoid rectal surgery [2].

Locally advanced disease

- SCRT is favoured over LCRT due to reduced visits and reduced use of chemotherapy. In addition, this would prevent compromised radiotherapy treatment if the patient was to test positive during the XRT.
- LCRT still appropriate for young fit patients with significant pelvic wall disease.
- The expert consensus suggests SCRT followed by chemotherapy is an option for selected fit patients with locally advanced tumours (as in the POLISH trial [3]). They suggest the decision to use neoadjuvant chemotherapy will reflect the attitudes to neoadjuvant and adjuvant chemotherapy in each country, the assessment of the risk/benefit ratio, considering the risk factors for COVID19 increased mortality and the capacity and prioritisation of chemotherapy delivery.
- Locally advanced tumours are more likely to have a poor response and as such, it may be appropriate to perform one earlier scan to ensure it is safe to further delay surgery.
- Plan for delayed surgery when it is safe and available.

Adjuvant treatment

- Limit use of adjuvant chemotherapy due to lack of evidence of benefit in this setting [4]. Can be considered in young fit patients who are heavily node positive who have not had neo-adjuvant XRT.

Colon cancer

Neo-adjuvant treatment

- NCCN guidelines [5] advocates the consideration of a course of capecitabine or CAPOX in patients with newly diagnosed tumours that cannot undergo resection, accepting a lack of evidence of improved cancer outcomes [6]. The risk to the patient of receiving chemotherapy, with no evidence of improved cancer, outcome during the pandemic must be weighed up versus the risk of tumour becoming irresectable must be considered.

Adjuvant chemotherapy

Stratify patients according to age and risk/benefit of chemotherapy:

- If benefit of chemo is less than 5% absolute improvement in survival, then do not treat.
- If benefit is between 5 to 10 %, **likely recommend not treating** however merits discussion eg. In young (<60yrs) fit patients who could have capecitabine alone (less bone marrow suppressing and minimal time in hospital).
- If benefit greater than 10% consider treating in young fit patients.
- No patient should receive more than 3 months CAPOX.
- Timing of initiating chemotherapy, up to 12 weeks post op, to depend on local covid prevalence and chemotherapy capacity, which are likely to fluctuate.
- No “adjuvant” chemotherapy post-metastectomy

For example:

- Be cautious offering >70yrs adjuvant therapy
- Consider anyone over 60, particularly with comorbidities, as high risk
- For T4 N0 <70y consider Capecitabine only for 6 months
- Adjuvant oxaliplatin based treatment should be 3 months rather than 6 months.

Metastatic patients

- NCCN guidelines discuss similar strategies to those already undertaken in centres around the UK [5]. These include considering single agent capecitabine rather than CAPOX, limited use of FOLFIRINOX, use of regimens that require less visits to hospital (3 weekly rather than weekly), low threshold for dose reductions or GCSF if it can be delivered at home.
- Treat only people in whom their disease cannot be delayed for 3 months, eg. rapidly growing, systemic symptoms of malignancy, large burden of disease. Delay wherever possible.
- Aim for break after 3 months as per COIN trial [7]
- NHS England have allowed breaks off biological agents at this time, therefore limit maintenance treatment.
- Locoregional treatments for oligometastatic disease should be delayed if biology of disease suggests this is unlikely to be detrimental.
- If patients are proceeding with locoregional treatment, risks and benefits of each treatment in the setting of the pandemic should be considered (eg. SABR may be

preferred to liver resection as it does not require anaesthetic input, is an outpatient treatment with a relatively low toxicity profile).

Anal cancer

- Anal cancer patients should continue to receive standard radical chemoradiotherapy in view of high cure rates and severe morbidity /mortality of uncontrolled disease, provided patient fit.
- PLATO study remains open however trial activity is likely to be curtailed during the pandemic [8].
- Lower threshold to consider hypofractionated treatment as per Hatfield et al. [9] and Charnley et al. [10] for early stage cancer or poor PS patients. (30Gy in 15# used in these publications but 30Gy in 10# would also be appropriate to minimise visits).
- Continue to follow up patients fit for APR if they were to recur in the first 3 years post treatment. Consider delaying FU for those not fit for APR and after 3 years.
- If no elective surgeries are being performed, consider delaying follow up until surgery available.

Exit strategy

This process is continually evolving. While we may be nearing the end of the initial peak and things are currently improving nationally; consideration should be given to the possibility of second peak or resurgence when lockdown is released and the possibility of needing to revert back to some of the principles used over the last few weeks. However, in time, we anticipate clinicians will gradually gain in confidence in reinstituting treatments as COVID becomes less prevalent and the pressures on our services reduce.

This period of altered treatment strategies offers a unique opportunity to study the effects on our patients. We may learn that some aspects of our COVID management are worth considering in future routine practise such as an increased use of SCRT. The CTRad COVID RT Initiative hopes to coordinate this effort with collaboration from a number of national bodies.

References

[1] Marijnen CAM, Peters FP, Rodel C, et al. International expert consensus statement regarding radiotherapy treatment options for rectal cancer during the COVID19 pandemic. In press. DOI: https://doi.org/10.1016/j.radonc.2020.03.039

[2] OPERA trial - https://clinicaltrials.gov/ct2/show/NCT02505750

[3] Bujko K, Wyrwicz L, Rutkowski A, et al. Long-course oxaliplatin-based preoperative chemoradiation versus 5 x 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. Annals of Oncol 2016; 27: 834-842

[4] Carvalho C, Glynne-Jones R. Challenges behind proving efficacy of adjuvant chemotherapy after preoperative chemoradiation for rectal cancer. Lancet Oncol 2017; 18: e354–63. https://doi.org/10.1016/S1470-2045(17)30346-7.

[5] NCCN. Principles for Management of Colorectal Cancer Patients During the COVID-19 Pandemic. April 2020. https://www.nccn.org/covid-19/pdf/Colorectal%20COVID-19.pdf. Accessed 15 April 2020.

[6] Morton D. FOxTROT: An international randomised controlled trial in 1053 patients evaluating neoadjuvant chemotherapy (NAC) for colon cancer. On behalf of the FOxTROT Collaborative Group. Annals of Oncology 2019; 30 (supp 5): v198

[7] Adams RA, Meade AM, Seymour MT et al. Intermittent versus continuous oxaliplatin and fluoropyrimidine combination chemotherapy for first-line treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet Oncol. 2011 Jul;12(7):642-53

[8] Sebag-Montefiore D, Adams R, Bell S. et al. The development of an umbrella trial (PLATO) to address radiation therapy dose questions in the locoregional management of squamous cell carcinoma of the anus. Int J Radiat Oncol Biol Phys 2016;96(2);E164-E165

[9] Hatfield P, Cooper R, Sebag-Montefiore D. Involved-field, low-dose chemoradiotherapy for early-stage anal carcinoma. Int J Radiation Oncol Biol Phys 2008:70(2):419-424

[10] Charnley N, Choudhury A, Chesser P, et al. Effective treatment of anal cancer in the elderly with low-dose chemoradiotherapy. Br J Cancer 2005:92(7):1221-122