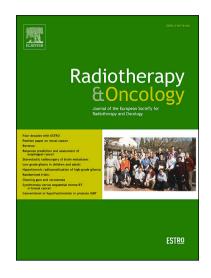# Journal Pre-proofs

Review Article

Recommendations on the use of radiation therapy in managing patients with gastrointestinal malignancies in the era of COVID-19

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Recommendations on the use of radiation therapy in managing patients with gastrointestinal malignancies in the era of COVID-19

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Radiation oncology; gastrointestinal neoplasms; COVID-19; pandemic

Abstract

As of April 6, 2020, there are over 1,200,000 reported cases and 70,000 deaths worldwide due to COVID-19, the disease caused by the SARS-CoV-2 virus, and these numbers rise exponentially by the day.[1] According to the Centers for Disease Control (CDC), the most effective means of minimizing the spread of the virus is through reducing interactions between individuals.[2] We performed a review of the literature, as well as national and international treatment guidelines, seeking data in support of the RADS principle (Remote visits, Avoid radiation, Defer radiation, Shorten radiation)[3] as it applies to gastrointestinal cancers. The purpose of the present work is to guide radiation oncologists managing patients with gastrointestinal cancers during the COVID-19 crisis in order to maintain the safety of our patients, while minimizing the impact of the pandemic on cancer outcomes.

Introduction

As of April 6, 2020, there are over 1,200,000 reported cases and 70,000 deaths worldwide due to COVID-19, the disease caused by the SARS-CoV-2 virus.[1] According to the CDC, the most effective means of minimizing the spread of the virus is through reducing interactions between individuals. Patients with cancer are at particularly high risk of becoming infected with COVID-19[4] and of developing severe complications or dying of the disease.[5] In fact, in one report detailing the incidence and outcomes of COVID-19 infection in a cohort of cancer patients treated at a tertiary cancer center in Wuhan, the rate of death was a staggering 25%.[6]

As clinicians caring for cancer patients during this pandemic, we must carefully balance efforts to minimize patient visits to the hospital, while still adequately treating their malignancies. Not only are we required to change practice in order to minimize the number of patient visits to the clinic to decrease the risk of exposure to coronavirus, but practices may be forced to change due to operating room closures and staff shortages, as employees become ill and are forced to stay home and quarantine. As inpatient wards are becoming less safe for cancer patients due to the increased risk of exposure to the disease, treatment of patients in an outpatient setting is preferred when possible.

During the COVID-19 pandemic, the RADS framework laid out by Zaorsky et al (Remote visits, Avoid radiation, Defer radiation, Shorten radiation) should be followed.[3] Radiation therapy should be deferred or not recommended, e.g. when the evidence for benefit is controversial or the

overall benefit to the patient is estimated to be small. The National Institute for Health and Care Excellence issued a guideline which includes a risk stratification system for patients needing radiation to help in making management decisions.[7] When radiation therapy is indicated, efforts should be made to reduce the number of treatment fractions delivered. Reducing the number of patients receiving radiation therapy, as well as the number of treatments received, is critically important during the COVID-19 pandemic, not only to benefit the patient being treated, but also for a number of other reasons beyond the individual benefit. First, it minimizes exposure and risk of all patients and staff to the virus. Second, radiation therapy, especially when delivered concurrently with chemotherapy, may cause lymphopenia which is likely to persist over the course of therapy, resulting in immunosuppression and thus increased susceptibility to the virus. This can be minimized with shorter treatment courses, or sequential versus concurrent chemo-radiation therapy (CRT). Finally, each time a COVID-19-positive patient is treated, treatment rooms and machines must be decontaminated, resulting in over-utilization of resources, currently in limited supply.

While reduction in treatment may be necessary for patient safety, and due to resource limitations, it is important to follow safe practices and to respect organ at risk constraints. Therefore, recommendations provided below are based on data showing the safety and efficacy of alternative treatment approaches. It is important to keep in mind that practices are likely to have varying constraints in terms of supplies and personnel depending on location, thus the following recommendations may not apply to all clinics equally. Furthermore, we acknowledge that countries and institutional practices may differ in their approach to treatment, as evidenced by

variable recommendations by contributing authors for certain subsites in this manuscript. Thus, there may be variation in practice among institutions.

We performed a review of the literature, in addition to national and international treatment guidelines, seeking data in support of reducing radiation treatment delivery. It should be noted that while data-driven, not all recommendations are based on level 1 data and thus these recommendations are intended to guide clinicians managing patients with gastrointestinal cancers whose resources (specifically the operating rooms) have been heavily strained by the COVID-19 pandemic. The purpose of the present work is to help clinicians maintain the safety of our patients without compromising cancer outcomes, during a time when treatment practices are being forced to change week to week or even day to day. Table 1 summarizes the recommendations laid forth in this document.

Esophageal Cancer

1. Early stage esophageal cancer (adenocarcinoma and SCC):
    a. T1aN0: Endoscopic mucosal resection.
    b. T1bN0: Surgery alone if possible[8; 9]
    c. T2N0: Surgery alone for adenocarcinoma and neoadjuvant CRT for SCC.[10]
2. Locally advanced (T2N+ or T3+/Nany) operable esophageal carcinoma:
    a. Neoadjuvant CRT: Pre-operative CRT is a standard of care and should be given using the shortest fractionation scheme possible. Based on the CROSS trial, 41.4Gy in 23 fractions with concurrent weekly carboplatin/paclitaxel is

preferred.[11] In centers where staffing is particularly limited, and in which minimizing the number of fractions is of critical importance, the Walsh regimen of 40Gy in 15 fractions can be considered.[12] However, concurrent carboplatin/paclitaxel or FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin)[13] is preferred.

b. Induction chemotherapy: To delay the initiation of daily radiotherapy in centers were these facilities may be strained for staff and resources, induction chemotherapy can be considered prior to CRT.[14-17] It should be noted that this was a controversial recommendation, not supported by all authors, based on data from the CALGB 80803 trial, which has only been published in abstract form. CALGB 80803 demonstrated feasibility and promising outcomes for patients undergoing PET-directed therapy for esophageal adenocarcinoma with treatment based on response after 6 weeks of induction FOLFOX or carboplatin and paclitaxel.[18].

c. Surgery: Patients should undergo re-staging scans and be referred for surgery 6-8 weeks after completion of CRT in centers where surgery can still be performed. In centers where surgical procedures have been discontinued for the forseeable future due to the COVID-19 crisis, management should follow that of inoperable esophageal cancer (see below). If there has been a complete clinical response to neoadjuvant treatment, consider close follow-up with surgery reserved for salvage. For patients with squamous cell histology, consider CRT alone, without surgery, based on the 49% pathological complete response rate in the CROSS trial.[11]

3. Inoperable esophageal cancer:

a. Definitive CRT: For inoperable patients, the maximum dose of radiation should not exceed 50Gy in 25 fractions, as higher doses are ineffective and may even be detrimental.[19; 20] Weekly carboplatin/paclitaxel is the preferred concurrent chemotherapy regimen due to only once weekly administration. Concurrent FOLFOX is another good option due to administration every 2 weeks.[13] For centers where radiation facilities are particularly strained, 40Gy in 15 fractions can be considered. This should be followed by 2 cycles of chemotherapy (with fluorouracil and cisplatin) as per RTOG 85-01.[21; 22]

4. Definitive RT: Patients who are not suitable for chemotherapy can receive RT with a hypofractionated regimen of either 50Gy in either 16 or 20 fractions.[23]   It should be noted that this recommendation was somewhat controversial among authors due to concerns over the potential for increased late toxicity.

5. Advanced disease:

a. Palliative therapy: For patients with advanced disease who have symptoms related to their primary esophageal lesion, a limited course of radiation therapy can be offered. Radiation is preferred over either an esophageal stent or percutaneous endoscopic gastrostomy (PEG) tube placement in order to avoid consumption of limited operative supplies and aerosolization of the virus secondary to intubation. While 30Gy in 10 fractions is a common palliative regimen, shorter courses such as 6-8Gy in a single fraction for pain or bleeding, or 20Gy in 5 fractions for dypshagia, can be used to minimize patient visits to the clinic.[24; 25]

Gastric Cancer

1. Locally advanced (TanyNanyM0) patients:

    a. Peri-operative chemotherapy: For patients with newly diagnosed non-metastatic gastric cancer, treatment with chemotherapy using the FLOT regimen (fluorouracil, leucovorin, oxaliplatin, docetaxel), should be offered to patients regardless of stage.[26]

    b. Neoadjuvant CRT: Preoperative CRT should not be used given the lack of data showing benefit over chemotherapy alone.[27; 28]

    c. Adjuvant therapy: Postoperative radiation therapy should not be routinely administered to patients with gastric cancer due to lack of data demonstrating a benefit.[29; 30] Ten percent of patients in the CRITICS trial, which failed to show a benefit to postoperative CRT, had an R1 resection;[29] thus it is unclear if adjuvant CRT should be offered to patients even in the setting of microscopically positive surgical margins. In all patients who did not receive neoadjuvant chemotherapy, adjuvant chemotherapy should be administered. The role of adjuvant CRT can be considered in cases with very high risk features (e.g. lymphovascular space invasion, node positive, high grade histology, positive margin) after 3-4 months of chemotherapy, taking into consideration the state of the crisis.

    d. Palliation: Radiation therapy should be strictly reserved for palliation of symptoms in patients with gastric cancer at the present time. When choosing a palliative regimen, for bleeding for example, 6 or 8 Gy in one fraction, with an anti-emetic, may be used.[31; 32]

Hepatocellular carinoma (HCC)

1. Early stage HCC:

    a. Orthotopic liver transplanation (OLT): OLT provides the highest chance of cure for HCC patients who meet transplant eligibility criteria and who receive a donor liver. During COVID-19, live donor transplantation is likely to be put on hold, and there may be delays or transient suspension of all transplants. Thus, there is an increased role for 'bridging therapies,'designed to maintain the HCC within eligibility criteria for transplant, possibly for longer times than pre COVID-19. Radiofrequency ablation (RFA), transarterial chemo-embolization (TACE), yittrium-90 (Y90), and stereotactic body radiation therapy (SBRT) may be used to bridge HCCs that are at risk of growing to a stage where the patient would be delisted.

    b. Surgery: Resection is a curative treatment for patients with early stage tumors (single, no vascular invasion or extraheaptic spread). There is no role for neoadjuvant therapy; however during COVID-19, if resection is not possible, alternative therapies (as suggested below) may be used instead of resection; and resection may be avoided or delayed to the time of progression.

    c. Locoregional therapies:

        1. RFA is most effective for smaller tumors (e.g. < 4cm) whenever technically feasible.

        2. TACE or Y90 are suitable for most early stage HCCs, however, these may not be available at centers restricting procedures due to COVID-19, increasing the number of patients referred for SBRT.

3. SBRT is an alternative ablative therapy that may be used, especially if inpatient and invasive procedures have been suspended. SBRT may be delivered in 1-5 fractions; 3-5 fractions are preferred for central HCCs near the biliary tree (especially if a transplant is planned). Please see Table 1 for dosing schema. Non-invasive procedures for prediction and mitigation of tumor motion (use of 4DCT, abdominal compression, daily imaging, and surrogate markers such as biliary stents or lipiodol from previous TACE) are preferred to use of fiducials given that fiducial placement is risky at this time

2. Following resection: There is no proven role for adjuvant therapy.

3. Intermediate stage HCC:

a. TACE or Y90: The current treatment paradigm for multifocal HCC is TACE or Y90.

b. SBRT: SBRT may be proposed as an alternative option, particularly after incomplete response to prior TACE.[33] .

4. Locally advanced HCC, with vascular invasion:

a. Systemic therapy: Treatment with molecularly targeted therapy (e.g sorafenib or lenvatinib) should be used during COVID-19 in eligible patients.

b. Local therapy: Radiation therapy with TACE was shown to improve survival versus TACE alone in HCC patients with vascular invasion,[34] and SBRT is being studied in other randomized trials (eg. RTOG1112). For patients who continue to have HCC confined to the liver following systemic therapy, or for those who are not eligble for systemic therapy, SBRT may be considered, if available.

c. Best supportive care: For patients with a poor prognosis, e.g. due to massive HCC or declining liver function, best supportive care, rather than active intervention, should be offered. For tumor-related pain, a single fraction of 6-8Gy can be considered.

Cholangiocarcinoma

1. Operable cholangiocarcinoma:

   a. Neoadjuvant therapy: Neoadjuvant chemotherapy (preferably with capecitabine as this can be taken at home) may be considered for patients with operable cholangiocarcinoma in order to delay surgery, extrapolating from data showing benefit to adjuvant therapy.

2. Following resection:

   a. Negative margins: For patients who have had surgery, adjuvant therapy with oral capecitabine is recommended, as per BilCap, as it can be taken at home.[35] Although radiation therapy has been suggested to have a benefit following systemic therapy, due to the lack of level 1 data, radiation therapy should not be used in the adjuvant setting during COVID-19.

   b. Positive margins: For positive surgical margins or node positive disease, a survival benefit to adjuvant radiation after chemotherapy has been suggested;[36] however, given the lack of level 1 data, adjuvant radiation therapy should be deferred during COVID-19.

3. Inoperable cholangiocarcinoma:

   a. Chemotherapy: Chemotherapy (gemcitabine and cisplatin) is recommended as standard of care as the first line of therapy.

b. Radiation therapy: For patients with localized, node negative cholangiocarinoma following systemic therapy, curative intent radiation therapy may be offerred. Concurrent CRT is not recommended.[37; 38] While 15-fractions has been favored over SBRT for intrahepatic cholangiocarcinoma where there is concern over biliary stricture,[39] during COVID-19, SBRT is an acceptable alternative. 3-5 fractions should be consdered for central lesions, and 1-3 fractions for peripheral lesions (please refer to Table 1 for recommended doses).[40] Appropriate biliary stenting should be used prior to all radiation therapy, when available. For centers with particularly strained radiation resources, radiotherapy may be reserved for isolated local progression. Similarly when cure is not possible (multifocal cholangiocarcinoma or node positive cancer), radiation therapy should be deferred until progression, and only if the cancer remains localized.

Pancreas

1. Resectable/borderline resectable pancreatic cancer:

a. Neoadjuvant chemotherapy: In order to delay surgery and the associated inpatient hospital stay or in centers where surgery has been suspended, neoadjuvant therapy can be considered.[41-43]

b. Neoadjuvant radiation therapy: For cases that remain borderline resectable even after a complete course of six months of neoadjuvant chemotherapy, SBRT in 5 fractions (of 30-33Gy) can be considered.[44] For centers without SBRT capability, 25Gy in 5 fractions, or 30Gy in 10 fractions with concurrent gemcitabine, can be used.[45] While SBRT is not

standard in the management of borderline pancreatic cancers, it may be considered as an alternative to continuing chemotherapy until the patient is able to safely undergo surgery in order to reduce the risk of ongoing chemotherapy and its related toxicity. Further, radiation in this context can allow for local disease control until the tumor can be resected. As with SBRT for other gastrointestinal sites, we recommend use of non-invasive procedures for tumor localization and tracking at this time (4DCT, abdominal compression, biliary stents as surrogate markers) for centers that typically use fiducials for localization.

2. Unresectable/locally advanced:

a. Chemotherapy: Patients with unresectable pancreatic cancer should be treated with up to six months of chemotherapy alone with FOLFIRINOX, for medically fit patients, or gemcitabine and nab-paclitaxel for those with relatively poorer performance who are still candidates for combination chemotherapy.[27; 46; 47]

b. Radiation therapy: The role of radiation therapy in patients with unresectable pancreatic cancer was somewhat controversial among the authors of this manuscript due to lack of survival benefit.[48] If there is stability or improvement of local disease after four to six months of systemic treatment, in the absence of distant metastases, centers with SBRT capability may consider offering radiation.[49; 50]. Patients with local progression after chemotherapy are likely to be incurable and thus the role of radiotherapy in these patients is unclear. A single fraction of 8-10Gy may be considered for palliation of symptoms or to prevent future symptoms in patients with local progression.[51]

3. Following resection:

a. Negative margins: There is no role for the routine use of adjuvant radiation therapy at this time, given the lack of high-quality prospective data to support its use.

b. Positive margins: Adjuvant chemotherapy should be administered to complete a full course of six months of chemotherapy. If neoadjuvant chemotherapy was given prior to surgery, additional adjuvant chemotherapy should not exceed the total of six months. During COVID-19, radiation therapy should be omitted due to the lack of level 1 data demonstrating a benefit.

4. Please consider UK Guidelines for management of pancreatic cancer during the COVID-19 pandemic for additional information: https://www.rcr.ac.uk/sites/default/files/pancreatic-cancer-treatment-covid19.pdf

Rectal

1. Early stage rectal cancer:

a. TME (total mesorectal excision) alone

2. Locally advanced (T2N+ or T3-4/Nany) operable rectal patients:

a. Neoadjuvant radiation: In keeping with the recent expert consensus statement on the management of rectal cancer during the COVID-19 epidemic,[52] either long-course CRT or short-course radiation therapy (5Gy x 5 fractions) with or without neoadjuvant chemotherapy can be offered. However, short-course therapy with delay to surgery is preferred.[53]

b. Total neoadjuvant therapy: In cases where surgery cannot be performed due to the COVID-19 pandemic, total neoadjuvant therapy with chemotherapy delivered after either

long-course or short-course radiation should be delivered given existing data showing the

safety and efficacy of this approach, which is also in keeping with guidelines.[27; 54-56]

c. Surgery: Consider delaying surgery to 12 weeks, with re-assessment at 8 weeks.[53; 57; 58]

3. Following surgery for clinical Stage I disease:

a. Adjuvant therapy: For patients with clinical stage I disease who underwent upfront

resection and were upstaged at the time of surgery, adjuvant chemotherapy should be

delivered. The role of CRT should be carefully considered on an individual patient basis

weighing risks and benefits. For a low risk of local failure, radiation therapy may be

deferred. If indicated, long-course CRT is preferred.

4. Inoperable:

a. Definitive CRT: For patients who are inoperable due to medical co-morbidities, the

first line of therapy should be chemotherapy. For those who continue to have local cancer

following chemotherapy, definitive radiation therapy may be considered. Radiation alone

(e.g, 52 Gy in 20 fractions or 25Gy in 5 fractions) is recommended over long-course CRT

at the present time.[59]

Anal

1. Local or locally advanced (TanyNanyM0):

a. Definitive CRT: Patients with anal cancer can be cured with the combination of

chemotherapy and radiation and therefore deviations from the standard treatment

approach (capecitabine or 5-FU plus mitomycin-C plus radiation therapy) are not

indicated, even during this global pandemic.[27] Radiation therapy is recommended to be

delivered utilizing a simultaneous integrated boost (SIB) approach in 28-30 fractions as

per RTOG 0529.[60] Patients with T1N0 can be treated with lower dose of radiation such as 40-50Gy/20-25 fractions, or an even lower dose using an approach similar to the Nigro protocol (i.e. 30Gy/10 fractions) if limited by resources/staff. Patients who are not candidates to receive concurrent chemotherapy (due to comorbidities or poor performance status), can be treated with a hypofractionated regimen of 36-40Gy in 20 fractions to the elective volume with an SIB to 50Gy to the primary tumor.[61; 62]

Oligo-metastases from colorectal cancer

1. Oligo liver metastases from colorectal cancer:

   a. Multi-disciplinary care: The timing of resection of the primary tumor, resection of metastases, systemic therapy and radiation therapy requires multi-disciplinary discussion and individual decision making.

   b. Chemotherapy: Consider delivering additional cycles of chemotherapy in order to delay surgery in facilities where surgeries are note being performed

   c. Local therapies: For patients with potentially curable liver metasetases from colorectal carcinoma, local liver directed therapy should be considered for patients who are unble to undergo resection.

   d. SBRT: If used, SBRT should be delivered in as few fractions as possible. Consider a single fraction of 16-30Gy for small, non-central lesions[63] and a more fractionated approach (48-60Gy in 3-5 fractions) for lesions near the biliary tree.[8; 37; 64; 65]

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Highlights

- Cancer patients are at high risk of dying from COVID-19

- Treatment practices are being forced to change rapidly due to resource and staff shortages

- Social distancing means minimizing patient-staff interactions

- Data-driven recommendations are needed to guide clinicians managing cancer patients

- Goal is to minimize impact of the pandemic on cancer outcomes

Table 1: Summary of Best Practices in managing GI malignancies with radiotherapy in the Time of COVID-19

Disease site	Clinical scenario	Recommended treatment	Notes on radiation
Esophageal	Operable	Concurrent CRT*	41.4 Gy/23 Fx OR 40 Gy/15 Fx with concurrent FOLFOX or carboplatin/paclitaxel
	Inoperable	Definitive CRT*	50 Gy/25 Fx OR 45-50 Gy/15 Fx
	Palliative	RT	20 Gy/5 Fx for dysphagia; 6-8 Gy/1 Fx for bleeding or pain
Gastric	Operable	Peri-op chemotherapy → surgery	No RT
	Resected	Chemotherapy alone	No RT
	Palliative	Palliative RT	6-8 Gy/1 Fx
Liver	Hepatocellular carcinoma	TACE/Y90 or SBRT	30-60 Gy/3-5 Fx
	Liver metastases	Chemotherapy → resection or RFA or SBRT	16-30 Gy/1-3 Fx OR 48-60 Gy/3-5 Fx
Cholangiocarcinoma	Operable	Induction chemotherapy → surgery	No RT
	Inoperable	Induction chemotherapy → RT	67.5 Gy/15 Fx OR 30-60 Gy/3-6 Fx
Pancreas	Resectable	Neoadjuvant chemotherapy → surgery	No RT

	Borderline Resectable	Neoadjuvant chemotherapy → restage; if still BR→RT^	30-33 Gy/5 Fx if SBRT is available OR 25 Gy/5 Fx OR 30Gy/10 Fx with concurrent gemcitabine
	Inoperable	Chemo alone; if good response or stable disease and no metastases → RT	30-40 Gy/5 Fx
Rectal	Locally advanced operable	Induction chemotherapy → RT → surgery	25 Gy/5 Fx
	Inoperable	Induction chemotherapy → RT	52 Gy/20 Fx
Anal	All non-metastatic cases	RT and concurrent chemotherapy	45-60 Gy/25-30 Fx with chemotherapy OR 50 Gy/20 Fx if no chemo

Abbreviations: CRT, chemoradiotherapy; RT, radiation therapy; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; TACE, trans-arterial chemo-embolization; Y-90, yttrium-90; SBRT, stereotactic body radiation therapy; BR, borderline resectable; Gy, gray; Fx, fractions

*Some authors suggest induction chemotherapy with either FOLFOX or carboplatin/paclitaxel in order to delay radiotherapy when radiation staffing may be limited

^Neoadjuvant radiation was not universally recommended in the case of BR pancreatic cancer

Please note, the above fractionation schemes are only recommended if the organ at risk dose-constraints can be achieved.