Radiotherapy management of rectal cancer in the backdrop of the COVID pandemic

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Abstract
Background: COVID-19 outbreak was declared as a pandemic by the World Health Organization in March 2020. Over the last 3 months, the pandemic has challenged the diagnosis and treatment of all cancer, including rectal cancer. Constraints in resources call for a change in the treatment strategy without compromising efficacy.

Recent Findings: Delivery of shorter treatment schedules for radiotherapy offers advantages like short overall treatment time, improved throughput on the machine, improved compliance and reduced risk of transmission of COVID 19. Other strategies include delaying surgery, reducing the intensity of chemotherapy and adoption of organ preservation approach.

Conclusion: The curative treatment of rectal cancer should not be hindered during the COVID pandemic, and modifications in the multi-modality treatment will help achieve quality care.

KEYWORDS
COVID 19, radiotherapy, rectal cancer

1 | INTRODUCTION

COVID 19 pandemic is arguably the most extensive global healthcare emergency of this millennium.1,2 It has rapidly spread across the countries with over 34 205 913 cases and 1 019 605 deaths. Various hospitals have been paralyzed by the enormous needs of COVID 19 patients.3,4 The transmission of COVID in India is increasing with 6 312 584 cases and 98 708 deaths. However, with easing out of public restrictions, more patients will likely be affected. Cancer care during these difficult times is challenging and may lose its priority.5,6 Various aspects of care are put on a back burner.7 There is a danger of high mortality both from COVID and inadequately treated cancer.8-10

There are constraints on resources (particularly supplies and operating room) and hospital staff, which may make delivery of current standard approaches for the treatment of cancer difficult.11 Demands on hospital infrastructure and staff lead to rationing of patient care services. The functioning of operating rooms is affected by short staffing of anesthesia personnel, risk of aerosol generation during surgery and inability to provide adequate postoperative care in intensive care units. The disinfection protocols in the operating room, or linear accelerator suite, impact the number treated per day with reduced staff. There is a shortage or low-quality personal protective equipment for these specialized services. Many frontline medical workers are getting infected, which causes reorganization of other healthcare professionals. Saving most lives receives maximum priority.12 Thus, changes like shorter treatment times and telemedicine patient consults are favored. The pandemic has already transformed significant aspects of cancer care, and experts predict the changes in oncology treatment wrought upon by the epidemic may not be short-lived.5
2 | DISCUSSION

Radiation plays a vital role in the multi-modality treatment of rectal cancer.\textsuperscript{13,14} Rectal cancer patients with intermediate and high-risk factors on preoperative MRI and neoadjuvant radiotherapy are required for down-staging the disease before surgery.\textsuperscript{15} During the COVID pandemic, radiation use for rectal cancer has been classified as medium priority. To maintain continuity of care without compromising outcomes, changes to optimize practice or delivery of multi-modality treatment are needed. “Less is more” is the newfound mantra, and the RADS framework by Zaorsky et al is very appropriate for all settings.\textsuperscript{16,17} The major changes proposed are shortening chemoradiation from 5 weeks to 1 week, delaying surgery from 4-6 weeks to 12 weeks, less intensive chemotherapy and organ preservation approach. These may yield the least chance of side effects while maintaining excellent outcomes and avoid the risk of contracting COVID 19 infection. In this paper, we shall review the evidence for these approaches and their applicability during the COVID pandemic.

2.1 | Adoption of shorter fractionation schedules

There has been a resurgence of short-course radiotherapy (SCRT) in recent years. SCRT is shown to be safe, effective and allows treatment in a short time, thereby reducing patient visits.\textsuperscript{18} Despite similar outcomes to long course RT (LCRT), the adoption of SCRT in routine practice is low with concerns for increased late toxicity and poor down-staging in case of locally advanced cases.\textsuperscript{19} The Swedish rectal cancer study reported late gastrointestinal effects.\textsuperscript{20} However, the portals used for radiotherapy in this study were more extensive than currently used, which spare significant dose spillage to the bowel. During the pandemic, SCRT has various advantages, which make it the preferred treatment schedule. Shorter visits due to the fractionation facilitate physical distancing measures, avoids treatment breaks due to travel restrictions, make it possible to treat more patients with a therapeutic approach on the radiotherapy machine, reduce the chances of contracting the infection (both for patient and physicians) and avoids the need of concurrent chemotherapy (risk of immunosuppression). The role of SCRT in operable rectal cancer and locally advanced/advanced rectal cancer has been proven in randomized control trials. Both the polish trial by Bujko et al and the Australian Trans-Tasman Radiation Oncology Group (TROG) trial compared SCRT with immediate surgery and LCRT with surgery at 4 to 6 weeks in resectable rectal cancer (most in the intermediate-risk group as per ESMO risk stratification). They showed equivalent local recurrence rates, disease-free survival (DFS), overall survival (OS), acute and late toxicity.\textsuperscript{21,22} Down-staging and pathological complete response (pCR) rates were low in SCRT arms; however, no difference was seen in patients requiring APR in distal cancers (<5 cm).\textsuperscript{22,23}

Similarly, in locally advanced and advanced cancers, SCRT with integrated consolidation chemotherapy in waiting period to surgery has the advantage of better down-staging, improved compliance and reduced risk of distant metastases, and studies exploring this approach have shown excellent results. Bujko et al compared SCRT and consolidation chemotherapy (3 cycles FOLFOX 4) with oxaliplatin-based LCRT in 515 cT4 or fixed T3 rectal cancer patients.\textsuperscript{24} The R0 resection rates (primary endpoint), pCR rates, local recurrence and distant metastases were similar in both arms at a median follow-up of 35 months. The OS was higher in SCRT arm (73% vs 65%), and the acute preoperative toxicity was lower in SCRT arm. The updated results of this trial, with a median follow-up of 8 years, show similar 8-year OS of 49% in both arms with no difference in late grade 3+ toxicity between the arms (11% vs 9%).\textsuperscript{25} The major drawbacks of this trial are that MRI was not used for staging (with a possibility of under staging), nonstandard oxaliplatin-based concurrent chemotherapy in the control arm and was not designed based on survival endpoints. These factors are being addressed in the RAPIDO trial, comparing SCRT followed by chemotherapy with LCRT ± adjuvant chemotherapy in locally advanced rectal cancer with DFS as the primary endpoint.\textsuperscript{26} The early results show compliance of over 80% with SCRT + chemotherapy (6 cycles of CAPOX) at the expense of higher grade 3+ toxicity.\textsuperscript{27} The results of RAPIDO in abstract form was presented at ASCO 2020 by Hospers et al, which showed low 3-year disease-related treatment failure (23.7% vs 30.4%; $P = .02$), distant metastasis (19.8% vs 26.6% $P = .004$) and high pathological completed response (27.7% vs 13.8%; $P < .001$) with SCRT and chemotherapy.\textsuperscript{28} The locoregional failure rates (8.7% vs 6.0%; $P = .10$) and quality of life were similar between the two arms. The full manuscript of the RAPIDO trial and results of the STELLAR trial are awaited.\textsuperscript{29} During the COVID pandemic, while the patient awaits surgery after SCRT, consolidation chemotherapy may be added and, to reduce toxicity, dose reductions may be considered.

SCRT is a cost-effective treatment strategy, compared to LCRT, based on an economic modeling study by Raldow et al.\textsuperscript{30} They showed that SCRT was associated with an incremental cost-effectiveness ratio of $133 495 per quality-adjusted life-year. SCRT plus chemotherapy is also a cost-effective approach, as demonstrated by Wang et al.\textsuperscript{31} Although cost-effectiveness is not proven in LMIC, it is logical that 1 week of radiotherapy would reduce the financial burden in terms of stay and reduce exposure to COVID in the hospital setting.

Based on these studies, the adoption of shorter fractionation schedules is strongly recommended by the international expert panel and ESMO.\textsuperscript{32,33} This change is being adopted in major cancer centers, including the United States and Europe, during the pandemic.\textsuperscript{34,35} Rosenblatt et al (IAEA trial with 55% patients from India) and Chakrabarti et al show the feasibility and improved compliance of SCRT in the low middle-income country (LMIC).\textsuperscript{36,37} This change in practice in a resource-constrained setting would benefit the patient greatly during the prolonged pandemic times and beyond.

2.2 | Delayed surgery

The usual practice is to consider surgery within 3 to 7 days or 4 weeks of SCRT and 6 weeks of LCRT. A delay after radiation has benefits in
COVID scenario where scheduling of surgery may be difficult due to resource and staff constraints. The delay will help in down-staging, particularly in cases of distal cancers (< 5 cm from the anal verge), as shown in the Stockholm trial. The Stockholm trial compared SCRT with immediate surgery vs SCRT with delay and found no difference in local recurrence rates, recurrence-free survival and OS between the two arms. The pCR rates were 11.8% and fewer postoperative morbidity in the delayed group. In a real-world scenario, the United Kingdom population-based study, in a cohort of 3469 patients, showed no difference in postoperative outcomes with delayed surgery. In a meta-analysis by Huang et al, there was no difference in OS in LCRT with late surgery, SCRT with immediate surgery and SCRT with delayed surgery. However, the authors also conclude that larger studies are required to come to a more convincing conclusion. In patients who have completed chemoradiation, and awaiting surgery, postponing surgery to 11 weeks can be considered based on GRECCAR 6 trial. There was no difference in 3-year OS, or DFS, however, the complications were higher at 11 weeks vs 6 weeks. Higher postoperative complications seen in GRECCAR trial have not been seen in RAPIDO trial, or trials using total neoadjuvant approach. The response to radiation could be used to tailor the type of surgery (local excision in place of TME) during the pandemic with ongoing triage and rationing of cancer surgeries. GRECCAR 2 trial is a multicentric randomized trial, which compared local excision with TME in 148 down-staged (residual <2 cm) bulky low rectal cancer (good responders to LCRT in T2-T3 disease). Completion of TME was performed in local excision group if pathological stage revealed T2/T3. At a median follow-up of 60 months, there was no difference in local recurrence rates, DFS, OS, distant metastases or cancer-specific mortality. A total of 35% in local excision required TME for completion.

### Postoperative radiotherapy

Few patients who are in early stage, and get operated upfront, may be upstaged after surgery and may need adjuvant chemoradiotherapy. As per ESMO guidelines, adjuvant radiotherapy is indicated in pT4, margin positivity, N2, especially with low tumors and poor-quality surgery. Postoperative radiotherapy has shown in randomized trials and meta-analyses to reduce local recurrence rates significantly. The decision to treat should be carefully weighed and may be deferred in low-risk cases. In case of high risk, LCRT is to be favored.

### Less intensive chemotherapy

Chemotherapy has the risk of myelosuppression, and early reports from China and Italy suggest higher complications from COVID, in patients, after chemotherapy. Thus, changes in the regimens of chemotherapy to minimize myelosuppression should be considered. Intensive regimens can be substituted with lesser ones, and oral drugs may replace intravenous, where feasible, to reduce hospital visits. Avoidance of severe grade 3-4 reactions necessitating emergency room visits can be tried with upfront dose reductions up to 25% and optimal use of growth factors to prevent neutropenia.

The role of chemotherapy in rectal cancer after neoadjuvant chemoradiation in the adjuvant setting is controversial and has not shown survival benefit. The evidence for adjuvant chemotherapy is primarily extrapolated from colon cancer, and the prospective trials are flawed due to low patient numbers. There is a small disease-free survival benefit, especially in nonresponders after neoadjuvant chemoradiation and node-positive patients with no overall survival benefit. There is wide variation in the use of adjuvant chemotherapy worldwide with oncologists from the United States recommending it, and those from Europe negating it. While deciding adjuvant chemotherapy, risk vs benefit should be assessed based on the patient's comorbidities and impact of the pandemic, and the same to be communicated with the patient. For low-risk patients, omitting adjuvant chemotherapy may be considered. In high-risk patients, requiring doublet chemotherapy, initiation of oxaliplatin may be delayed or omitted as it adds very little to single-agent 5FU/Capacitabine. The use of oral capecitabine is to be preferred as it is proven to be equivalent to 5FU and should replace intravenous 5FU. Dosing of capecitabine may be reduced (fixed dosing 1500 mg twice daily 5 days a week or 7 days on and 7 days off) to reduce the risk of severe mucositis and diarrhea.

Following neoadjuvant SCRT, in cases where there is a delay to surgery due to pandemic, chemotherapy may be considered. Studies exploring the total neoadjuvant treatment (TNT) approach have shown significant response rates and are safely tolerated. Although the TNT approach generally uses LCRT, the use of SCRT has demonstrated promising results. These regimens involve the use of doublet chemotherapy, which is FOLFOX based. In addition to the modifications suggested, skipping the bolus 5FU and delaying each cycle by 2 to 3 weeks may help balance toxicity with benefit. The use of telemedicine consults to inform blood reports performed at local should be encouraged to avoid hospital visits.

### Organ preservation approach

Organ preservation approach may be considered in patients with a complete response after neoadjuvant radiotherapy. Studies have shown that wait and watch after complete response has similar outcomes compared to those undergoing surgery. The international wait and watch database of 1009 patients from 15 countries showed that the local regrowth rate is 25% with over 80% occurring within 2 years. The regrowths are limited to bowel wall in 97% and amenable for salvage with a 5-year OS of 85%. Salvage surgery is feasible in 83% of cases with regrowth. Nonoperative management (NOM) may reduce the risk of post-surgery complications and ICU admissions during the COVID pandemic. Although SCRT is criticized for poor down-staging, SCRT with delay or chemotherapy may result in complete responders. Koeter et al evaluated the radiological response rates in 47 elderly patients with comorbidities, treated with SCRT and...
The curative treatment of rectal cancer should not be hindered during the COVID pandemic and is a priority. Modifications in the multimodality treatment will help achieve quality care. These include transition to SCRT in appropriately selected patients, optimally delay in surgery, less intensive chemotherapy and making room for a wait and watch strategy where feasible.

4 | CONCLUSION

The curative treatment of rectal cancer should not be hindered during the COVID-19 pandemic and is a priority. Modifications in the multimodality treatment will help achieve quality care. These include transition to SCRT in appropriately selected patients, optimally delay in surgery, less intensive chemotherapy and making room for a wait and watch strategy where feasible.

CONFLICT OF INTEREST
The authors declare no conflicts of interest.

ETHICAL STATEMENT
Not applicable.

AUTHOR CONTRIBUTIONS
Shirley Lewis: Conceptualization; methodology; supervision; validation; writing-original draft; writing-review and editing. Kaustav Talapatra: Conceptualization; methodology; supervision; validation; visualization; writing-original draft; writing-review and editing.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analysed in this study.

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