Editorial

# Mining the Past to Treat the Present, Ever Mindful of the Future: Low-Dose Radiotherapy and COVID-19 Pneumonia

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In the current issue of *Cancer*, Hess et al. have presented acute toxicity and clinical outcomes from the first 5 patients treated on a clinical trial of low-dose radiotherapy (LD-RT) for hospitalized, oxygen-dependent patients with novel coronavirus disease 2019 (COVID-19) pneumonia.[1]

In this trial, inclusion criteria included a positive COVID-19 nasopharyngeal swab, visible pneumonia on chest radiograph, and current hospitalization as well as either: 1) a decrease in mental status; 2) increased work of breathing; or 3) increased oxygen requirement. LD-RT was administered at a dose of 1.5 Gray (Gy) to the lungs bilaterally and the primary outcome was exacerbation of COVID-19–related symptoms or acute toxicity of ≥grade 4 with efficacy explored as a secondary endpoint. A total of 7 patients were enrolled, 2 of whom were intubated before undergoing LD-RT and thus became ineligible and were not treated, whereas 5 patients were treated with LD-RT. Of these 5 patients, 4 demonstrated clinical recovery graded using a system similar to one used previously, with recovery defined as discharged to home with or without oxygen or hospitalized with no supplemental oxygen.[2] One patient worsened after treatment, ultimately requiring intubation.

## Rationale

One certainly could be forgiven for wondering about the rationale for the study by Hess et al.[1] With a few key exceptions, the use of RT largely is limited to the treatment of cancer in the modern era. However, in the early and mid-20th century, RT was used for such diverse ailments as acne, gastric ulcers, tuberculosis, and pneumonia.[3-8] It is this latter use that is of interest for the current clinical trial.

Beginning as early as 1905, multiple groups of investigators used relatively low doses of RT for the treatment of bacterial and viral pneumonia, reporting on >850 patients.[8] Within these case series, 2 specifically examined the use of LD-RT in patients with viral pneumonia, with 79 patients treated overall.[9,10] Generally, within these series, the study authors believed that treatment with LD-RT was associated with clinical improvement compared with the treatment of the day. Of course, these studies were undertaken in a different era with different standards and generally suffer from a lack of appropriate comparison arms.

Why might LD-RT affect the disease course in patients with viral pneumonia generally or COVID-19 specifically? Acute respiratory distress syndrome (ARDS) is a frequent cause of death in patients with viral pneumonia and COVID-19 is no exception, although its presentation is comparatively unique.[11] ARDS can in many cases - particularly in the case of coronaviruses such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) - be caused by dysregulated and increased local production of multiple proinflammatory cytokines. This leads to fluid accumulation, impaired alveolar function, and, in some cases, systemic inflammatory response syndrome and multiorgan failure.[12-14] The hope is that LD-RT might break this inflammatory cycle, most likely via local immunosuppressive effect.

However, the direct preclinical data for the use of LD-RT within the setting of viral pneumonia lagged behind its clinical use and, even now, are limited. Two studies published in 1946 by the same group of authors, in either a feline or mouse viral pneumonia model, demonstrated, at best, modest signs of efficacy.[15,16] A more recent study, currently in preprint, has suggested that LD-RT may reduce the production of proinflammatory cytokines such as interferon-γ and interleukin 6 (IL-6) and increase the production of anti-inflammatory IL-10 in both human macrophages and murine lung models.[17] In the same study, consolidation in the mouse lung after administration of lipopolysaccharide was reduced with the use of LD-RT, while IL-10 was increased.

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## Current Trials

These clinical and preclinical observations have led to multiple clinical trials of LD-RT both in the United States and worldwide for the treatment of COVID-19. As of this writing, 9 trials addressing this question are listed as recruiting on the ClinicalTrials.gov website, with 4 being performed in the United States, including the study by Hess et al. in this issue of *Cancer*.[1] Indeed, the results of a separate trial recently were published by Ameri et al. using LD-RT at a dose of 0.5 Gy, with similar findings reported.[18] Specifically, clinical recovery was reported in 3 of 4 patients, with 1 patient dying of COVID-19.

## Controversy

The concept of LD-RT has been discussed extensively among radiation oncologists, and indeed has generated a not insignificant amount of controversy within the field, with several editorials generally supporting[19-23] or critical[24-27] of the concept, whereas others propose a via media.[28] Nor has the discussion of this topic been limited to published articles, with multiple threads on social media, particularly Twitter, allowing for significant dialogue between the most interested parties.

The concept of LD-RT for the management of patients with COVID-19 has been polarizing, with several concerns raised within the community. These concerns are centered on 2 broad and interrelated issues: 1) the lack of underlying supporting data for LD-RT; and 2) the risk-benefit ratio of these trials both for patients as well as treating staff.

## Supporting Data

The supporting data for LD-RT trials in patients with COVID-19, as well as their significant flaws, were discussed earlier in the section regarding the rationale for the study by Hess et al.[1] These data largely are quite old and, at least the clinical data, are flawed in relationship to how trials or retrospective reviews are conducted today. The relative merit, or lack thereof, of these studies has been discussed extensively elsewhere.[19-27] Generally, the most I can take away from these reports is that the treating physicians, who had experience in treating similar patients under conditions that no longer exist, believed that the treatment was beneficial in many cases. This obviously has the potential to be colored by huge amounts of bias and certainly is less convincing than cleaner data generated in the modern era. However, I do not believe that these data can be discounted altogether.

Moreover, the clinical data for LD-RT as an immunomodulatory therapy for benign disease are not limited to these case series or to a bygone era. The treatment of inflammatory joint disease with LD-RT is current clinical practice in Germany, with at least some studies indicating a substantial benefit in regard to pain control.[29] Indeed, in Germany, close to 38,000 patients were treated with RT for benign indications annually in the early 2000s, rising to >50,000 since that time, a significant percentage of which was for inflammatory conditions.[30,31] The obvious caveat here is that this certainly is not whole-lung RT for ARDS but does at least provide clinical support for the anti-inflammatory hypothesis in addition to the significantly flawed pneumonia data.

With regard to the paucity of direct preclinical data for the treatment of viral pneumonia or ARDS with LD-RT, there is little to say other than what is available is interesting but not necessarily convincing. There are of course related but indirect studies that hint at a variety of potential mechanisms by which LD-RT may be beneficial in patients with COVID-19,[32] although additional data are needed to both explore the potential mechanism as well as optimize therapeutic timing and dose.

## Risks

The second, and to my mind more pressing, concern is the risk to the patient from the use of LD-RT within this setting. One question, evaluated in the current study by Hess et al,[1] is the risk of RT worsening acute symptomatology. This was not apparent in at least 4 of the 5 patients treated by Hess et al and is encouraging, as were the similar findings in the results reported by Ameri et al.[1,18] This does not completely rule out worsening of acute symptoms by LD-RT in a subset of patients, but does provide a degree of comfort as these and similar trials continue to accrue.

Unfortunately, long-term toxicity, largely a question of secondary malignancy, is a concern that cannot be addressed within the time frame of the trial by Hess et al,[1] or indeed most trials of RT. With the doses used in these trials, as well as the ages of the patients enrolled (eg, a median age of 90 years in the study by Hess et al[1]), the generally estimated risk of secondary malignancy should be low. A recent editorial by Kirsch et al proposed an increased risk of up to nearly 6% for lung and breast cancer after 1 Gy of RT in women aged 25 years based on exposure to nontherapeutic radiation.[24] However, on average, the estimated risk of all secondary malignancies in this model generally ranges from 1% to 2% in patients aged ≥65 years.[24] Moreover, epidemiologic data from patients treated therapeutically with LD-RT for benign disease

have suggested overall estimates of secondary malignancy in the areas of concern of 1% to 3%.[33] For example, these latter data have proposed an approximately 1% risk of lung cancer after treatment with LD-RT (albeit to only a portion of the lung) and a risk of breast cancer of between 0% to 3% in 1 breast among women aged >45 years, with the percentage increasing significantly as the age of the patient decreased.[33] Although the exact risk of secondary malignancy in this patient population may not be completely knowable, particularly because it is likely to be affected by a variety of additional risk factors such as smoking, ultimately the risk is likely low in older patients and must be balanced against the risk of death from COVID-19 in a given population treated on trial.

Generally, the prognosis of patients diagnosed with COVID-19 is related to several factors, including age at presentation, race, sex, medical comorbidities (such as diabetes, hypertension, and heart and kidney disease), obesity, and immunosuppressive conditions.[34-36] Although death because of COVID-19 varies somewhat between study and geographic location, in 1 large study from New York City, mortality in hospitalized patients aged 60 to 69 years was 15%, which nearly doubled with each increasing decade to as high as 52% for patients aged >80 years.[36] However, more precise methods of predicting outcomes after a COVID-19 diagnosis currently are under development.[37] Although these models may not be robust enough to select patients for clinical trial, my hope is that they will become so soon.

In addition, the question of informed consent for LD-RT trials must indeed be taken very seriously, particularly in the face of a less known clinical benefit, the risks of LD-RT, and the clinical acuity of COVID-19 potentially requiring a rapid decision. In the current study, 3 of the 5 patients treated had some element of dementia or a cognitive deficit. This will be an issue in any clinical trial performed among older individuals and safeguards should be in place to ensure the appropriateness of consent. However, the wholesale exclusion of patients with cognitive issues does these patients a disservice in addition to limiting the "real-world" applicability of the outcome. Methods exist to both safeguard potentially vulnerable patient populations such as these as well as ethically include them on clinical trials.[38]

Finally, the question of risk to treating staff must be addressed. A recent prospective study demonstrated that the risk to health care workers of developing COVID-19 is significantly greater than that of the general population, with a hazard ratio of 11.61.[39] This risk depended on several factors such as country of residence, ethnicity, and access to personal protective equipment. Unfortunately, although access to adequate personal protective equipment was found to decrease rates of infection, this did not eliminate the greater risk observed among health care workers.

Most facilities, including our own, have generated protocols for treating patients with known or suspected COVID-19.[40] Although not perfect, these protocols attempt to maximize the safety of staff as well as patients, while still allowing necessary oncologic therapy to continue. Treatment with LD-RT on a clinical trial is a distinct issue, in the sense that RT is a novel modality and each patient treated will be, by definition, an infection risk. In this scenario, I would advocate the imperfect solution of close adherence to all established safety protocols as well as shared decision making with all the treating staff, remaining cognizant of significant power imbalances that can exist between treating physicians and the remaining treatment team.

### Alternatives

The question remains as to whether LD-RT has a future in the management of patients with COVID-19 compared to other available treatments.

Despite high hopes for the medical management of this disease, agents tested thus far in randomized trials either have been negative, as in the case of hydroxychloroquine and IL-6–targeted therapy[41-43] or, if positive, not necessarily living up to expectations. For example, in the phase 3 trial of remdesivir, the 14-day mortality rate was 7.1% in the treated group versus 11.9% in the control arm, with effects confined to those patients with less acute illness. The lone standout to date is the inexpensive steroid dexamethasone, which markedly reduced the incidence of death in intubated patients from 41.4% to 29.3%, with a more modest, although significant, effect on mortality observed among patients receiving supplemental oxygen only (23.2% vs 26.2%).[44]

Currently, there is much hope for convalescent plasma as an efficacious therapy for patients with COVID-19, and an emergency use authorization (EUA) is now in place for this therapy in the US. A very large patient series has been published in pre-print form showing potential benefits of this therapy.[45] Conversely, a recent randomized trial demonstrated no significant benefit to this therapy, with the rather large caveats that the trial was closed early, did not enroll a sufficient number of patients to meet its primary endpoint and that the data generated generally were favorable to the intervention.[46]

Regardless, at this point, it is imperative that we continue to consider additional treatments for patients with severe disease. Although my hopes rest primarily

on the relatively rapid identification and deployment of a vaccine as opposed to specific medical management, it is likely that the need for improved disease management will remain pertinent, at least in the near term. Whether this could conceivably include LD-RT remains to be seen.

### Conclusions

Ultimately, trials of LD-RT for patients with COVID-19 will continue. Understanding there are a multiplicity of conflicting takes on the concept, all I can do by way of conclusion is to state what I would do if this trial was open at my institution (which it is not at present). I certainly would be hesitant to enroll a young patient in a trial of LD-RT for COVID-19 pneumonia. However, in older patients with medical comorbidities known to increase the risk of mortality, I would be much more comfortable in doing so. In addition, I am hopeful that as prognostic criteria continue to evolve, selection for LD-RT trials as well as others for this dreadful disease will allow for more tailored interventions and improved outcomes.

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