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LETTER TO THE EDITOR

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Radiotherapy clinical trial enrollment during the COVID-19 pandemic

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Introduction

In the United States, the COVID-19 pandemic has caused profound changes in radiation oncology practices, including delays to treatment and reductions in patient volume, staff, and practice revenue. However, its impact on clinical trials remains poorly characterized [1]. The results of clinical trials are essential in supporting therapeutic decisions in radiation oncology, yet approximately 1 in 3 of radiotherapy (RT) clinical trials fail, most commonly due to inadequate accrual [2]. Here, we examine the issues arising from the pandemic, describe the enrollment of three RT trials at a tertiary cancer center, and discuss measures taken to promote trial enrollment in the months following the arrival of COVID-19 in the United States.

Impact on oncology clinical trials

While the first confirmed case of COVID-19 in the United States was recorded as early as January 2020, mounting public and political recognition of the novel coronavirus as a potential catastrophe did not occur until early March. On March 13th, President Trump declared a national state of emergency [3,4]. In the weeks that followed, states and counties issued stay-at-home orders, restricted travel, closed nonessential business, and mandated self-quarantine for people traveling – changes that significantly increased geographic barriers to access of care. Many health care institutions and patients were forced to weigh the urgency of scheduled care against the risk of infection by the novel coronavirus, leading to postponed or canceled appointments. Adding to this was an increased financial burden on individuals seeking care, with nearly 21 million US workers losing jobs through May 2020 and an estimated 41% of these reporting medical insurance tethered to employment [5]. These barriers and disincentives have disproportionately affected cancer patients, who must now carefully consider the competing risks of morbidity and mortality from both cancer and COVID-19 [6–8].

We have previously described our departmental efforts to minimize exposure risk, including an intentional reduction of patient volume. Strategies to accomplish this include planned delays for RT, deferment of RT when appropriate, evidence-based hypofractionation, and redistribution of patients between our main campus and regional locations [9,10]. While a deliberate reduction in new patient volume may be a strong contributor to decreased clinical trial enrollment, patients who arrive for treatment may also be deterred from enrolling in oncology trials due to requirements for more frequent in-person visits for follow-ups, labs, and imaging studies. Indeed, pandemic mitigation efforts interfere with the entire lifecycle of a clinical trial, including enrollment, delivery of and adherence to treatment, and outcome assessment [11]. An analysis of Southwest Oncology Group (SWOG) Cancer Research Network trials showed a considerable decrease in the enrollment of patients in late March, especially in those areas most affected by COVID-19 [12]. Among National Cancer Institute (NCI) trials, patient volume for screening and eventual accrual both fell by over 40% in late March [13]. In March and April alone, over 200 oncology clinical trials were suspended or terminated, for which COVID-19 was cited as the primary reason [14,15].

Trials in radiation oncology have fared similarly. An early report of trials in the United Kingdom testing RT hypofractionation or omission had recruitment in April and May 2020 fall to 17–28% of pre-COVID-19 levels. Accrual to a more complex trial testing prostate + pelvic RT fell even more precipitously to just 4% of pre-COVID-19 levels [16]. More dramatically, many trials worldwide have been suspended or stopped altogether. Our review of trials listed on ClinicalTrials.gov involving patients receiving RT and/or utilizing RT in at least one interventional arm revealed 34 trials that had recruitment status changed to 'suspended' through August 31, 2020. Of these, 31 (91%) were suspended on or after March 13th and 22 (65%) explicitly cite the pandemic as the reason for suspension. An additional 71 trials had recruitment status changed to 'withdrawn' or 'terminated' and while none of these explicitly cite COVID-19 as the reason for study closure, 29 (41%) cite insufficient accrual or financial considerations – reasons which may be implicitly connected to the pandemic [17].

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Analysis of selected RT trials at MD Anderson

We retrospectively examined enrollment data for three large randomized controlled trials initiated by investigators in our department. These included SAPHIRE (NCT02912312), which examines patients with invasive breast cancer treated with hypofractionated vs. conventional regional nodal RT, OPAL II (NCT03077841), which studies patients with early stage breast cancer treated with hypofractionated RT over the course of three weeks vs. one week, and EXTEND (NCT03599765), which evaluates patients with oligometastatic malignancies treated with routine drug therapy + local consolidative therapy vs. routine drug therapy alone [18–20]. Between January 1st and August 31st, 238 patients enrolled in these three trials, of whom 197 (83%) were enrolled at the MD Anderson Main Campus or one of the MD Anderson Houston-Area Locations (HALs), which are community-based practices in the greater Houston area. As shown in Figure 1, dramatic increases in the national infection rate correlate with a relative reduction in trial enrollment of 70% from March to April and 45% from June to July [21]. We reviewed the number of consultation visits to our department to evaluate whether these reductions correlated with patient volume. As shown in Figure 2, the numbers of consultation visits were highest in the months of March and July. However, these were among the months with the fewest patients enrolled in the three trials, suggesting that patient volume does not fully explain accrual to the selected trials.

We compared demographics of patients enrolling before or after March 13th, the date of the national emergency declaration. Though comparisons are limited by sample size, there was no statistically significant difference noted on univariable analysis in the average age (61.8 vs. 61.3 years) or race (16% vs. 23% white) of enrollees before or after this date. Using the Bing Maps Locations application programming interface (Microsoft Corporation, Bellevue, WA), we conducted an analysis of distance from the patient's home zip code to treatment facility zip code. There was no significant difference noted in average distance between home and treatment zip code (164 miles vs. 141 miles), though there was a trend toward a smaller proportion of people traveling more than 700 miles for treatment (9% vs. 3%, $p = 0.07$) after March 13th. In addition, after March 13th there was a significantly lower percentage of Hispanic patients enrolling in these trials (18% vs. 7%, $p = 0.02$) and a significantly greater proportion of patients signing informed consent for trial enrollment *via* a telehealth visit (0% vs. 20%, $p < 0.001$).

Changes to encourage trial enrollment

Recent policy changes have reduced some barriers to participation in trials. In March, the National Cancer Institute (NCI) issued guidance for clinical trial activities affected by the pandemic in an effort to provide increased flexibility. New NCI provisions allow for remote consents, virtual visits, transfer of care to a new clinical trial site, engagement of a local healthcare provider for follow up, and shipment of oral investigational agents directly to patients – none of which were standard practices prior to the current pandemic [22–24]. The Food and Drug Administration (FDA) also published guidance and issued temporary clearance for the use of noninvasive remote devices for monitoring vital signs, though their adoption remains unclear [25]. Perhaps the most important policy changes regarding clinical trials

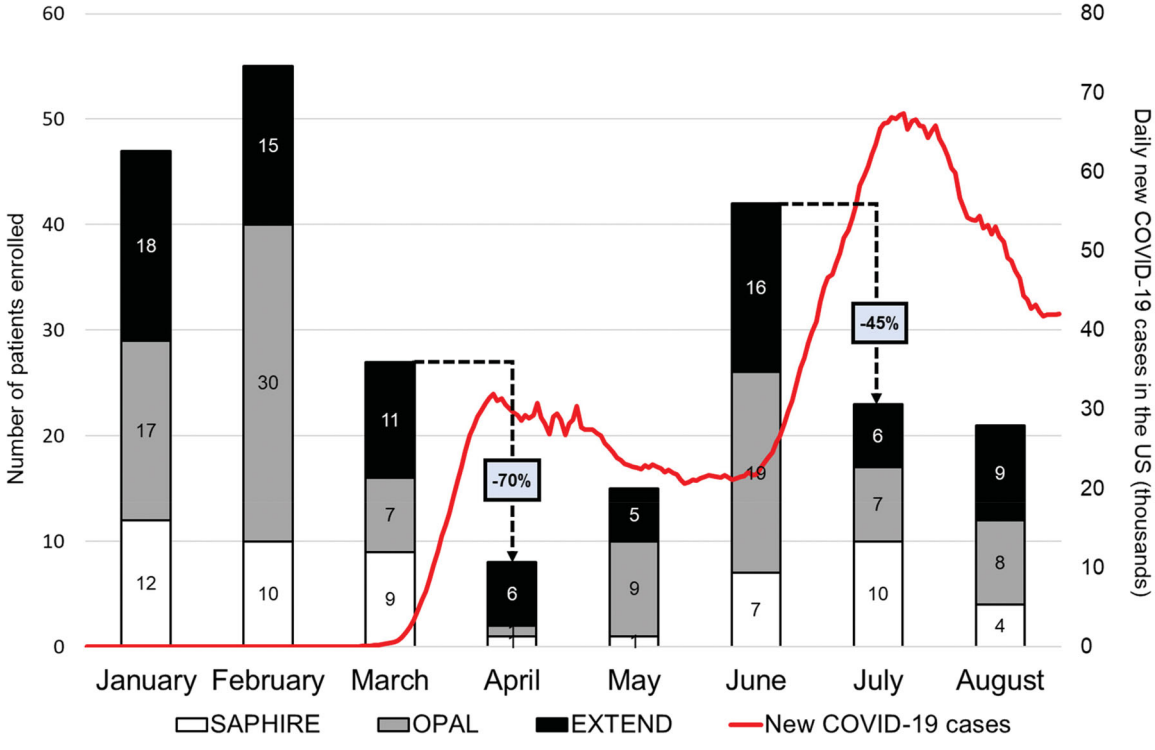

Figure 1. Accrual to three RT trials and new COVID-19 diagnoses in the United States.

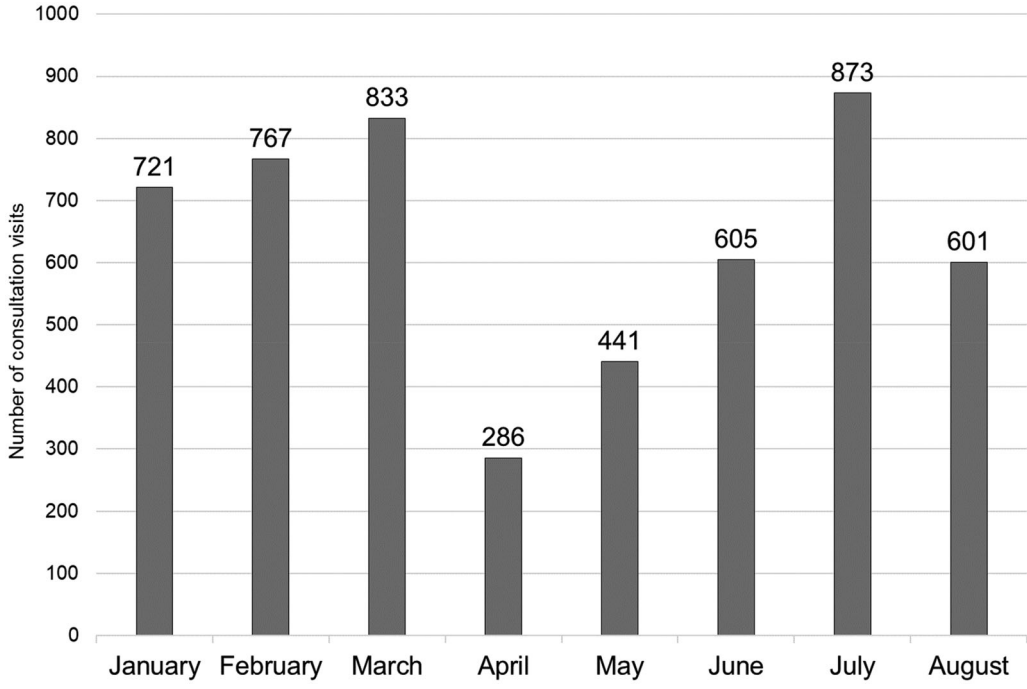

Figure 2. Number of consultation visits seen by the radiation oncology department at MD Anderson Cancer Center.

concern the use of telehealth. The Department of Health and Human Services (HHS) waived several restrictions on telehealth visits for Medicare patients until the conclusion of the COVID-19 public health emergency. As a consequence, telehealth visits and in-person visits are considered equivalent and are paid at the same rate for Medicare beneficiaries. In addition, the waiver removed restrictions limiting telehealth visits to rural patients and halted the use of penalties for use of HIPAA-noncompliant technologies (e.g., Zoom, Skype, and FaceTime) to provide telehealth services. While temporary, these changes substantially reduced the perceived liability risk and barriers to entry for providers seeking to conduct telehealth visits and allowed patients to continue cancer care [26,27]. With the evolution in payment and privacy policies precipitated by the pandemic, the investigators for the three trials reviewed in this study have embraced telemedicine as a conduit to enrollment. In the trials reviewed, 20% of patients enrolled after March 13th did so *via* a telehealth visit allowing for efficient randomization and rapid scheduling of simulation and treatment.

Future considerations for RT trials

Financial and logistical issues are the most commonly cited barriers to trial enrollment and these hurdles have been exacerbated by the COVID-19 pandemic [28]. In addition to the use of telemedicine, there has been a strong movement toward evidence-based hypofractionation to help alleviate the financial toxicity of RT [29]. When designing trials in the COVID-19 era, investigators must consider that the availability of an abbreviated RT regimen may motivate otherwise unwilling patients to pursue treatment, whether on a trial or not. Careful consideration should be given to including hypofractionation in treatment arms when designing trials.

The American Society of Clinical Oncology recently released recommendations for promoting health equity, one of which is ensuring equitable access to research. The ongoing pandemic serves as a sobering reminder for us to consider distributional justice in trials. Many studies have shown that racial and ethnic minorities are more likely to be infected by the novel coronavirus and to suffer from worse outcomes related to COVID-19 [30–32]. Unfortunately, these same groups have also been disproportionately affected by loss of insurance coverage secondary to unemployment, disruptions to access in health services, and worse survival for cancers regardless of stage at diagnosis. In our analysis of three RT trials at MD Anderson, there was a significant decrease in the proportion of Hispanic patients enrolling after March 13th, suggesting that government and institutional measures to encourage enrollment may not have done so equitably. Further study into policies, systems, environments, and practices that improve equitable participation in radiation oncology trials is sorely needed [33].

The COVID-19 pandemic has forced radiation oncologists to think of creative solutions to impossible problems but data – not creativity alone – will help us to understand how to best serve our patients. Well-designed clinical trials produce the highest level of evidence to corroborate our decisions moving forward and we need to adapt to promote their success.

Disclosure statement

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Affairs (to MD Anderson). Dr. Tang reports consulting fees from Reflexion Medical, Inc. Dr. Yeboa reports grant funding from the Brockman Foundation Medical Research Grant Program. Dr. Koong reports holding shares of Aravive, Inc. All reported conflicts are outside the submitted work.

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References

[1] Wakefield DV, Sanders T, Wilson E, et al. Initial impact and operational responses to the COVID-19 pandemic by American Radiation Oncology practices. Int J Radiat Oncol Biol Phys. 2020; 108(2):356–361.
[2] Nguyen TK, Nguyen EK, Warner A, et al. Failed randomized clinical trials in radiation oncology: what can we learn? Int J Radiat Oncol Biol Phys. 2018;101(5):1018–1024.
[3] Taylor DB. A timeline of the coronavirus pandemic. In: D. B. Taylor, editor. Book a timeline of the coronavirus pandemic. New York, NY: The New York Times; 2020. Available from: https://www.nytimes.com/article/coronavirus-timeline.html
[4] Trump DJ. Proclamation on declaring a national emergency concerning the novel coronavirus disease (COVID-19) Outbreak; 2020. Available from: https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/
[5] Collins SRG, Munira Z, Aboulafia, Gabriella N. U.S. Health Insurance coverage in 2020: a looming crisis in affordability: findings from the commonwealth fund biennial health insurance survey; 2020. Available from: https://www.commonwealthfund.org/publications/issue-briefs/2020/aug/looming-crisis-health-coverage-2020-biennial
[6] Papautsky EL, Hamlish T. Patient-reported treatment delays in breast cancer care during the COVID-19 pandemic. Breast Cancer Res Treat. 2020;184(1):249–254.
[7] Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020; 21(3):335–337.
[8] Printz C. When a global pandemic complicates cancer care: although oncologists and their patients are accustomed to fighting tough battles against a lethal disease, Coronavirus Disease 2019 (COVID-19) has posed an unprecedented challenge. Cancer. 2020;126(14):3171–3173.
[9] Noticewala SS, Koong AC, Bloom ES, et al. Radiation oncology strategies to flatten the curve during the coronavirus disease 2019 (COVID-19) pandemic: experience from a large tertiary cancer center. Adv Radiat Oncol. 2020;5(4):567–572.
[10] Hoffman KE. Wait and hurry up: radiation therapy for prostate cancer during the COVID-19 pandemic. Int J Radiat Oncol Biol Phys. 2020;108(2):340.
[11] McDermott MM, Newman AB. Preserving clinical trial integrity during the coronavirus pandemic. JAMA. 2020;323(21):2135–2136.
[12] Unger JM, Blanke CD, LeBlanc M, et al. Association of the coronavirus disease 2019 (COVID-19) outbreak with enrollment in cancer clinical trials. JAMA Netw Open. 2020;3(6):e2010651.
[13] Doroshow JH. COVID-19 and cancer clinical trials: 1st virtual joint meeting of NCI board of scientific advisors & national cancer advisory board; 2020. Available from: https://deainfo.nci.nih.gov/advisory/joint/0420/Doroshow.pdf
[14] COVID-19 and clinical trials. Cancer Research Institute; 2020. Available from: https://www.cancerresearch.org/scientists/immuno-oncology-landscape/covid-19-oncology-clinical-trials
[15] Upadhaya SY, Xin J, Oliva C, et al. Impact of COVID-19 on oncology clinical trials. Nat Rev Drug Discov. 2020;19(6):376–377.
[16] Hall E, Lewis R, Snowdon C. Life after COVID-19 for cancer clinical trials. Int J Radiat Oncol Biol Phys. 2020;108(2):486–488.
[17] Medicine UNLo. ClinicalTrials.gov. US National Library of Medicine. [cited 2020 Sep 1]. Available from: https://clinicaltrials.gov/
[18] Hypofractionated vs. conventional regional nodal radiation therapy for patients with invasive breast cancer; 2017. Available from: https://ClinicalTrials.gov/show/NCT02912312.
[19] Hypofractionated partial breast irradiation in treating patients with early stage breast cancer. Available from: https://ClinicalTrials.gov/show/NCT03077841.
[20] Systemic therapy with or without local consolidative therapy in treating patients with oligometastatic solid tumor; 2018. Available from: https://ClinicalTrials.gov/show/NCT03599765.
[21] Roser MR H., Ortiz-Ospina E, Hasell J. Coronavirus Pandemic (COVID-19); 2020.
[22] Interim guidance for patients on clinical trials supported by the NCI cancer therapy evaluation program and the NCI Community Oncology Research Program (NCORP). National Cancer Institute; 2020. Available from: https://ctep.cancer.gov/content/docs/Memorandum_on_Interim_Guidance_for_Clinical_Trial_Activities_Affected_by_the_Novel_Coronavirus-3-13-2020.pdf
[23] FDA guidance on conduct of clinical trials of medical products during COVID-19 public health emergency: guidance for industry, investigators, and institutional review boards. U.S. Department of Health and Human Services Food and Drug Administration; 2020 [cited 2020 Sep 27]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency
[24] van Dorn A. COVID-19 and readjusting clinical trials. The Lancet. 2020;396(10250):523–524.
[25] Enforcement policy for non-invasive remote monitoring devices used to support patient monitoring during the coronavirus disease 2019 (COVID-19) public health emergency (Revised); 2020. pp. 1–12.
[26] Maroongroge S, Smith B, Bloom ES, et al. Telemedicine for radiation oncology in a post-COVID world. Int J Radiat Oncol Biol Phys. 2020;108(2):407–410.
[27] Plana DA, Sinha A, Michael S. Re-envisioning clinical trials during The COVID-19 pandemic. Health Affairs Blog; 2020. Available from: https://www.healthaffairs.org/do/10.1377/hblog20200702.963588/full/
[28] Nipp RD, Hong K, Paskett ED. Overcoming barriers to clinical trial enrollment. Am Soc Clin Oncol Educ Book. 2019;39:105–114.
[29] Thomson DJ, Yom SS, Saeed H, et al. Radiation fractionation schedules published during the COVID-19 pandemic: a systematic review of the quality of evidence and recommendations for future development. Int J Radiat Oncol Biol Phys. 2020;108(2): 379–389.
[30] Webb Hooper M, Nápoles AM, Pérez-Stable EJ. COVID-19 and racial/ethnic disparities. JAMA. 2020;323(24):2466–2467.
[31] Yancy CW. COVID-19 and African Americans. JAMA. 2020;323(19): 1891–1892.
[32] Selden TM, Berdahl TA. COVID-19 and racial/ethnic disparities in health risk, employment, and household composition. Health Aff (Millwood). 2020;39:1624–1632.
[33] Patel MI, Lopez AM, Blackstock W, et al. Cancer disparities and health equity: a policy statement from the American Society of Clinical Oncology. J Clin Oncol. 2020;38:3439–3448.