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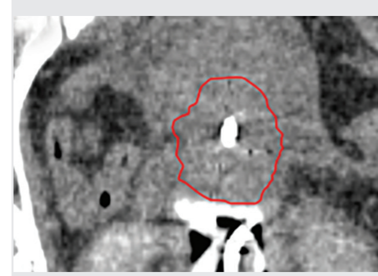
SA-CME CREDIT

Management of Head and Neck Cancer Patients During the Epidemic of Covid-19 in Wuhan
Q Wu, X Yang, F Wu, Y Zhong, Zhongnan Hospital of Wuhan University

Leading a Radiation Medicine Department from the Epicenter of the COVID-19 Pandemic in the United States
D Koffler, S Teckie, L Potters, Zucker School of Medicine, Hofstra/Northwell

Precious Moments: Lessons Learned During COVID-19
B Movsas, Henry Ford Cancer Institute



Radiation Oncology Case
Brachytherapy for Cervical Cancer in an Asymptomatic Patient with Confirmed COVID-19 Diagnosis

APPLIED RADIATION ONCOLOGY™

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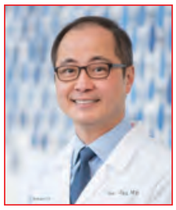

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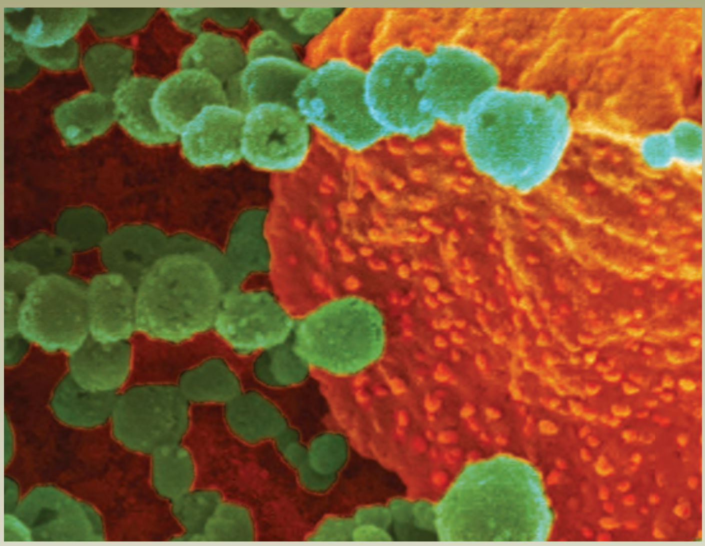

FOCUS: COVID-19

DEPARTMENTS

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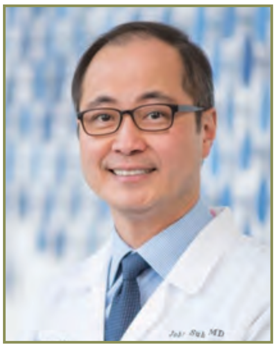
EDITORIAL

Care During a Pandemic: Managing Radiation Treatment Amid COVID-19



John Suh, MD, FASTRO, FACR
Editor-in-Chief

The impact of COVID-19 around the world has left a catastrophic and unimaginable toll on global economies, health care systems and, most regrettably, lives. Many in the health care field have witnessed this devastation firsthand, with a tremendous strain on resources compounding the problem. The effect on cancer care has been particularly dire especially when factoring in potential consequences of delaying medical treatments.

In this month's issue, which focuses on COVID-19, authors from Wuhan, New York and other areas discuss their experiences and strategies of providing radiation treatments during an uncertain time, which has brought much emotional distress and fear. The review article, *Leading a Radiation Medicine Department from the Epicenter of the COVID-19 Pandemic in the United States*, describes techniques for resource allocation, including ways to prioritize patients for treatment initiation, maximize telemedicine, and design hospital avoidance strategies at Northwell Health. The authors also describe implementation of evidence-based hypofractionation guidelines and strict personal protective equipment regulations.

A second review, *Management of Head and Neck (HN) Cancer Patients During the Epidemic of COVID-19 in Wuhan,* details strategies for balancing the risks of contracting COVID-19 with the benefits of radiation therapy for head and neck cancer, a common malignancy in China. The authors also discuss their specific approach for diagnosis and treatment during the outbreak, reflecting on issues such as ward management, epidemic surveillance, radiation and chemotherapy management, nutrition education, psychological interventions, and follow-up care.

Both reviews, which offer SA-CME credit, provide excellent accounts of treatment management strategies from hospitals located in the epicenters for COVID-19.

The two case reports, *Radiation Therapy Continuation for a Patient Diagnosed with COVID-19 in a High-volume Radiation Oncology Practice* and *Brachytherapy for Cervical Cancer in an Asymptomatic Patient with Confirmed COVID-19 Diagnosis,* further underscore a critical theme during an infectious pandemic: the need for uniform policies and procedures to ensure staff and patient safety while optimizing care.

Finally, we are pleased to feature a Resident Voice column and guest editorial on COVID-19. The former, titled *The Impact of COVID-19 on Radiation Oncology Department Workflow in the United States*, discusses hypofractionation, physician recruitment to frontline treatment, and paradigm-changers such as telemedicine's expanding role. The latter article, *Precious Moments: Lessons Learned During COVID-19*, shares how guidance, new safety measures, virtual consults and follow-ups, daily huddles and numerous concerted efforts helped a large Detroit institution mount a courageous battle in a time of crisis. Moreover, it describes Dr. Ben Movsas' poignant personal experience of overcoming the virus, grappling with vulnerability and questions of fate, like so many of our cancer patients.

As communities continue to reopen, what happens next remains uncertain, but through kindness, empathy and understanding, we will get through this pandemic together. Your commitment, courage and humility are inspiring. Thank you for your extra efforts to ensure cancer patients receive timely radiation treatments during the pandemic.

Dr. Suh *is the editor-in-chief of* Applied Radiation Oncology, *and professor and chairman, Department of Radiation Oncology at the Taussig Cancer Institute, Rose Ella Burkhardt Brain Tumor and Neuro-oncology Center, Cleveland Clinic, Cleveland, OH.*

FROM THE PUBLISHER

Kieran N. Anderson

Where I Stand

Over the last few months, mostly as a result of the global COVID-19 pandemic, I've had a bit more time to reflect on what is important to me as it relates to my life, my family, my businesses, and what I can do for those who may be less fortunate than me. In truth, I consider myself pretty lucky, as the son of two smart and amazingly caring immigrants from Ireland and Jamaica who taught me early on that in this country of ours, you can be anything you want if you work hard and do the right thing. To some degree, they were right as it relates to our family's pursuits.

However, this is not so true for many of our fellow African American citizens. Many are stuck in generational poverty as a result of unfair housing laws and limited access to quality education and employment opportunities, not to mention a criminal justice system whose laws and procedures have worked against this community — a community with the same unalienable rights and freedoms as any other [white] citizens, under the Constitution.

These systemic acts of racism are clear to me, especially as the son of a black man. I stand in solidarity with those who reject racism at all levels, and support the "Black Lives Matter" movement and citizens of all races and creeds who have taken to the streets across the globe to protest the cruel and deplorable deaths of George Floyd, Breonna Taylor, Ahmaud Arbery, and so many others whose names must never be forgotten.

These senseless deaths are just as tragic as the reduced access to quality health care that plagues impoverished communities, where in many urban and rural settings the local community hospitals have been closing or are significantly underfunded.[1] These disparities are also blatantly evident in the disproportionate number of African Americans affected by COVID-19 for numerous reasons, many of which are at the root of racism in this country.

The mission of Anderson Publishing and our respective publications is to educate health care professionals in all aspects of medical imaging and radiation oncology. We stand with the many medical societies that have denounced the ongoing injustices that deeply impact the African American community. We pledge continued advocacy for diversity, inclusion, and equitable access to health care. And we share the sentiments of the American Medical Association, who in their recent statement said that "racism in its systemic, structural, institutional, and interpersonal form is an urgent threat to public health, the advancement of health equity, and a barrier to excellence in the delivery of medical care."[2]

In his sermon in Selma, Alabama, on March 8, 1965, the Reverend Dr. Martin Luther King, Jr. described how "lives begin to end the day we become silent about things that matter." Dr. King was referencing his opposition to "Bloody Sunday," when protesters were beaten by police on the Edmund Pettus Bridge — but his words have particular relevance today. We will not be silent. I, and those who stand with me here at Anderson Publishing, oppose racism and police brutality, unconditionally and in all its forms.

***Kieran N. Anderson** is the Group Publisher, Applied Radiation Oncology, and Vice President, Anderson Publishing, Ltd.*

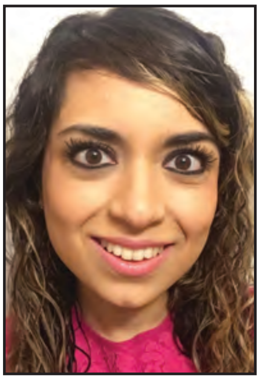
References

1. Coleman-Lochner L, Hill J. Hospital bankruptcies leave sick and injured nowhere to go. Prognosis, Bloomberg. January 9, 2020. Accessed June 15, 2020. https://www.bloomberg.com/news/articles/2020-01-09/hospital-bankruptcies-leave-sick-and-injured-nowhere-to-go
2. AMA Board of Trustees pledges action against racism, police brutality. American Medical Association. June 7, 2020. Accessed June 11, 2020. https://www.ama-assn.org/press-center/ama-statements/ama-board-trustees-pledges-action-against-racism-police-brutality

RESIDENT VOICE

The Impact of COVID-19 on Radiation Oncology Department Workflow in the United States

Amishi Bajaj, MD



Amishi Bajaj, MD

Oncologic care care is situated at a uniquely troubling intersection between the desire to safeguard a vulnerable patient population from COVID-19 while providing necessary treatment in a timely manner so as to not compromise oncologic outcomes. Cancer patients are deemed particularly susceptible based on age, performance status and, frequently, immunosuppression secondary to ongoing systemic therapy, among other sociodemographic and treatment-related factors. With about 50% of cancer patients receiving radiation therapy as part of their management,[1] radiation oncology departments across the country have rapidly implemented appreciable adaptations to workflow while contemplating major questions, including: What is the best way to prevent exposure? What is the optimal timing for delivering radiation therapy? How will changes in clinical decision-making affect the future? While some answers remain elusive, other solutions are effectively addressing concerns.

Extensive efforts are underway to minimize exposure and disease spread. Patients and health care workers are often required to use separate entrances and undergo separate screening. Upon arrival to the radiation oncology department, patients again undergo screening and further triaging,[2] with appointments at spaced intervals when possible to minimize prolonged overlap in the waiting room. For urgent clinical scenarios in which a COVID-positive patient must receive radiation therapy, all equipment is sterilized. Treatment breaks are another issue for newly diagnosed COVID patients, as Centers for Disease Control and Prevention (CDC) guidelines propose a 14-day minimum quarantine,[2] increasing treatment package time and sacrificing confidence in local control. To pre-empt these potential breaks and minimize health care visits even for COVID-negative patients, the American Society for Radiation Oncology's (ASTRO's) COVID-19 recommendations urge using hypofractionated treatment regimens when appropriate.[3]

***Dr. Bajaj** is a PGY2 resident at Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Feinberg School of Medicine, Chicago, IL.*

It is crucial that we ensure patients do not feel socially isolated or abandoned by their health care providers in a time of great uncertainty while they are already struggling to overcome the emotional turmoil inherently associated with a cancer diagnosis.

A paradigm-shifting adaptation to department workflow is the increasing use of telemedicine.[2] This transition has been absolutely instrumental in minimizing exposure for patients and health care workers alike while reducing workforce numbers. All the while, it is crucial that we ensure patients do not feel socially isolated or abandoned by their health care providers in a time of great uncertainty while already struggling to overcome the emotional turmoil inherently associated with a cancer diagnosis.

For now, as radiation oncologists are increasingly called to assist colleagues managing a seemingly endless number of COVID-positive inpatients, there has not yet been explicitly documented evidence of a strain on the radiation oncology workforce to the point of compromising throughput. If further deployment should occur, let us never lose sight of the supreme privilege in practicing the healing arts, whatever that may entail.

As country physician Dr. William Victor Johnson said in *Before the Age of Miracles*, "No one can do better as there is no one else here."[4] Most certainly, we are here to fulfill our duty to patients across the world. Beyond being radiation oncologists, we will always be – first and foremost – physicians.

References

1. Baskar R, Lee KA, Yeo R, Yeoh KW. Cancer and radiation therapy: current advances and future directions. *Int J Med Sci.* 2012;9(3):193-199.
2. Rivera A, Ohri N, Thomas E, Miller R, Knoll MA. The impact of COVID-19 on radiation oncology clinics and cancer patients in the U.S. [published online ahead of print, 2020 Mar 27]. *Adv Radiat Oncol.* 2020.
3. COVID-19 Clinical Guidance. American Society for Radiation Oncology. Accessed April 7, 2020. https://www.astro.org/Daily-Practice/COVID-19-Recommendations-and-Information/Clinical-Guidance.
4. Rourke J. The ideal family physician: W. Victor Johnston oration to the College of Family Physicians of Canada, Convocation, Winnipeg, Man, October 2007. *Can Fam Physician.* 2008;54(1):18-21.

GUEST EDITORIAL

Precious Moments: Lessons Learned During COVID-19

Benjamin Movsas, MD, FASTRO

Before I shared my own personal experience with coronavirus on an ASTRO (American Society for Radiation Oncology) video (www.rtanswers.org/covid), I hesitated, as I never had a severe case and now, thank God, am recovered and back to work. Indeed, our thoughts and prayers go out to all those suffering from the coronavirus and also to family and friends of those who have tragically succumbed to this illness. So why share my relatively limited episode? Mostly to try and spread some hope so we keep in mind that there are also many people who fortunately have more mild cases and even more who get better and recover. I cannot thank everyone enough for the wonderful responses and support I have received in this regard. It means so much to me.

Even though my case was not severe, when you are so tired that you cannot get out of bed, yet your pulse ox is only 94%, it makes you wonder — what happens if my condition worsens? Beyond the need for social distancing, some of the most challenging aspects of coronavirus, despite our medical knowledge, are the many unknowns and the ultimate recognition of our vulnerability as humans.

Like the vast majority of radiation centers, the Henry Ford Cancer Institute (HFCI) Radiation Oncology Department continued to treat patients as clinically indicated during this pandemic, with guidance from our infectious disease colleagues to implement enhanced safety measures and precautions to protect cancer patients and staff. This includes social distancing for patients and staff, appropriate use of masks and personal protective equipment (PPE), as well as additional cleanings of our treatment units and department. Additionally, all Henry Ford patients and employees are screened prior to entering the facility.

Remarkably, during this period, the HFCI's radiation oncology treatment volumes averaged about 90%-plus of baseline. Staff who could work remotely did so (eg, physics and dosimetry staff, among others). We also have significantly increased the use of virtual consults and follow-ups. In addition to many helpful and daily communications/calls at the system level, our department had daily huddles, as well as conference calls several times a week to discuss specific issues related to radiation. The open and regular communications are key in this effort. The dedication and commitment of our entire team to safely treat our cancer patients during this time is truly inspirational.

As I mentioned on the video, this experience has definitely changed me. First, it has made me more grateful. More grateful to my wife and family who helped to care for me. More grateful to my wonderful cancer team here at HFCI who so expertly and safely treat our cancer patients, and, likewise, more grateful to each of you, my dedicated colleagues in radiation oncology who are working so hard to do the right thing for our cancer patients. Let's together all thank our tireless medical teams around the globe who are sacrificing each day to address this ongoing challenge.

Beyond this, I am changed in yet another way. One day I was walking with my wife on a beautiful sunny afternoon. And I was simply overwhelmed by a powerful feeling as I suddenly realized how precious this moment was — just to be able to walk outside, to take a deep breath, and to enjoy this with my wife. These are some of the precious moments in life that I hope to never again take for granted but to always cherish. So, what's next? Well, donating my plasma for one … and applying these lessons learned to my daily life.

***Dr. Movsas** is the chair of the Department of Radiation Oncology, Henry Ford Cancer Institute, MI.*

SA-CME Information

LEADING A RADIATION MEDICINE DEPARTMENT FROM THE EPICENTER OF THE COVID-19 PANDEMIC IN THE UNITED STATES

Description

The acute redeployment of health care resources toward COVID-19 has had an immediate impact across the entire health care continuum and, in particular, to the treatment of cancer. The ability to perform surgery, biopsies, procedures, and to offer other ancillary clinical and supportive services, has been significantly impacted. Much has been done to proactively prepare for COVID-19 and to implement policies. The purpose of this review article is to outline how the department of radiation medicine in an epicenter location has managed the COVID-19 crisis to date.

Learning Objectives

After completing this activity, participants will be able to:

1. Learn and apply the authors' techniques for resource allocation after COVID-19 has had an impact on their healthcare system. Techniques include prioritization of radiation oncology patients for treatment initiation, proactive hospital avoidance strategies, and minimization of in-person visits by using telehealth.
2. Implement evidence-based hypofractionation guidelines and strict guidelines on use of personal protective equipment (PPE) for protection of patients and staff.

Authors

Daniel Koffler, MD, *is a resident,* ***Sewit Teckie, MD,*** *is an associate professor, and* ***Louis Potters, MD, FACR, FASTRO, FABS,*** *is professor and chair of Radiation Medicine at Zucker School of Medicine, Hofstra/Northwell, Hempstead, NY.*

MANAGEMENT OF HEAD AND NECK CANCER PATIENTS DURING THE EPIDEMIC OF COVID-19 IN WUHAN

Description

The rapid spread of the new coronavirus disease (COVID-19) identified toward the end of 2019 significantly impacted everyone in China, and all over the world. Head and neck (HN) cancers are a common malignant tumor type in China, with chemoradiation the standard of care for locally advanced disease. However, the COVID-19 epidemic interrupted the routine diagnosis and treatment of all cancers, including HN cancers, which can progress quickly if treatment is significantly delayed. Cancer patient care at the epicenter of COVID-19 was particularly challenged. Based on the management experience of patients with HN cancer during the outbreak of COVID-19 at a cancer institute in Wuhan, the authors summarize management strategies of patients with HN cancer to provide reference for health care providers facing similar challenges.

Learning Objectives

After completing this activity, participants will be able to:

1. Understand the importance of radiation therapy in head and neck cancer.
2. Make appropriate risk-benefit decisions when determining radiation therapy for COVID19 patients.

Authors

Qiuji Wu, MD, PhD; Xiting Yang, MS; *and* ***Fengyang Wu, MS;*** *are residents, and* ***Yahua Zhong, MD, PhD****, is department chair, all in the Department of Radiation and Medical Oncology, Zhongnan Hospital of Wuhan University, Hubei Key Laboratory of Tumor Biological Behaviors, and Hubei Cancer Clinical Study Center, all in Wuhan, China.*

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SA-CME (see page 9)

Management of Head and Neck Cancer Patients During the Epidemic of COVID-19 in Wuhan

Qiuji Wu, MD, PhD; Xiting Yang, MS; Fengyang Wu, MS; Yahua Zhong, MD, PhD

At the end of December 2019, an outbreak of the 2019 novel coronavirus disease (COVID-19) broke out in Wuhan, China.[1] The virus has been identified as a novel β-coronavirus homologous to severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) viruses.[2] Current research demonstrates that the virus is mainly transmitted through respiratory droplets and direct contact. This virus has also been detected in saliva, feces, urine and other samples and, therefore, other routine methods of transmission cannot be excluded.[3] The entire population is susceptible to this virus, for which the incubation period is relatively long (median incubation time 4 days) and the mortality rate from early retrospective studies in China is high (1.4% to 4.3%).[4,5] On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic. As of April 29, 2020, more than 3,000,000 confirmed cases have been reported in more than 200 countries and regions, resulting in over 207,000 deaths (https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200429-sitrep-100-covid-19.pdf?sfvrsn=bbfbf3d1_2). The epidemic continues to spread rapidly. The world is facing increasing pressure for epidemic prevention and control, and the medical system is already overloaded in many areas.

Soon after the epidemic broke out, strict prevention and control measures were adopted across China. Among them, Hubei, especially Wuhan City, where the epidemic was most severe, implemented unprecedented measures to lock down the city. All traffic in and out of Wuhan was suspended, including flights, trains, buses, boats, and private cars. All communities were strictly isolated and screened for infected patients. To cut the chain of transmission and to isolate all suspected and confirmed cases into confined treatment areas, the government converted a large number of hospitals into infectious disease prevention and treatment sites. Meanwhile, several large designated prevention and treatment hospitals for COVID-19 in Wuhan were quickly built while numerous medical staff were recruited to participate in the epidemic prevention and control work.

Under such circumstances, cancer patients face significant difficulties in disease diagnosis and treatment. First, cancer patients are often immunosuppressed due to the effects of cancer and anti-cancer treatment, and thus are prone to infection with the novel coronavirus. As a result, the prognosis after infection for cancer patients is worse than that of the general population.[6] Second, under the rigid epidemic prevention measures, all cancer patients were also subject to strict restrictions similar to other local residents and were unable to start or continue their prescribed cancer treatment, or enter treatment facilities. Third, during isolation, the psychological pressure of patients increases sharply,[7] along with nutrition and sleep disorders, all of which adversely impact treatment and recovery. Fourth, in order to stop the nosocomial spread of the epidemic, most of the cancer centers and oncology departments in Hubei Province, especially in Wuhan, ceased normal operation. Last but not least, many oncology medical staff were deployed to frontline anti-epidemic work, making it particularly

__Dr. Wu, Ms. Yang,__ and __Mr. Wu__ are residents, and __Dr. Zhong__ is department chair, all in the Department of Radiation and Medical Oncology, Zhongnan Hospital of Wuhan University, Hubei Key Laboratory of Tumor Biological Behaviors, and Hubei Cancer Clinical Study Center, all in Wuhan, China. *We would like to acknowledge staff from the Cleveland Clinic for their review of this article, in particular Ping Xia, PhD, and Anthony Mastroianni, MD, JD, MBA. Funding program: This work was supported by the National Natural Science Foundation Youth Project (grant number: 81803061) and the Foundation of Health Commission of Hubei Province of China (grant number: WJ2019H064). Disclosure: The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.*

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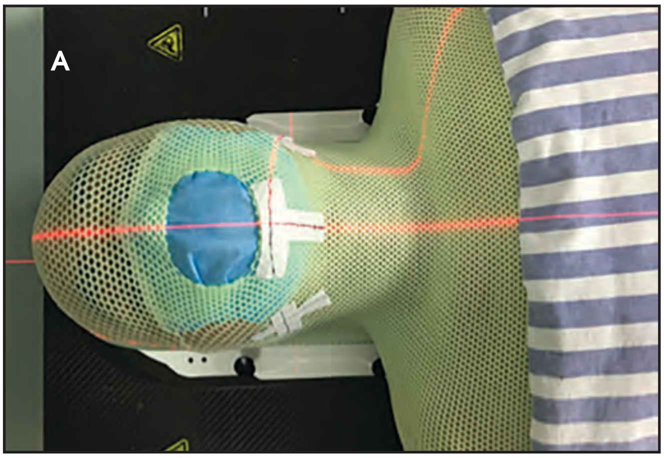

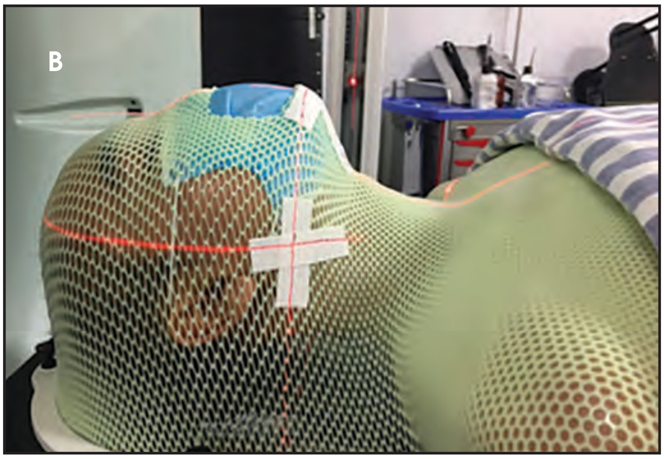

FIGURE 1. *Anterior (A) and lateral (B) view of a patient with nasopharyngeal carcinoma undergoing computed tomography (CT) simulation scanning. The patient was asked to wear a face mask and was immobilized with an individualized thermoplastic mask that allow patients to breathe freely through a cavity in the nose and mouth area.*

difficult for cancer patients to obtain adequate cancer diagnosis and treatment.

Head and neck (HN) cancer is a common malignancy worldwide and is more prevalent in China. Radiation therapy and chemotherapy comprise the cornerstones of HN cancer treatment.[8] For potentially curable tumors, early detection, diagnosis, and early treatment are critical to increase the cure rate and improve patient survival. However, during the COVID-19 epidemic, the diagnosis and treatment of HN cancer patients has been greatly affected. Strategies to maximally prevent viral infections and, at the same time, maintain adequate anti-tumor treatment are outstanding issues under consideration. Since the outbreak of COVID-19, the Cancer Institute of Zhongnan Hospital of Wuhan University has been in the center of the epidemic. We have therefore adopted a specific approach for cancer diagnosis and treatment during this period. This review summarizes diagnosis and treatment strategies for patients with HN cancer during the epidemic at our institute.

Inpatient Management

Management of Wards

In the early stages of the COVID-19 outbreak, given that hospitals are high-risk areas for the spread of disease and that cancer patients might be particularly vulnerable to viral infections, we discharged most cancer patients (who are typically inpatient for concurrent chemoradiation) home from the hospital according to the overall deployment plan of our local hospital. We instructed patients and their families to maintain close contact with our medical staff, with guidance on how to decide when to return to the hospital and continue cancer treatment. Nevertheless, a few patients failed to leave the hospital on time due to city lockdown and transport suspension. Since some were receiving radiation therapy and chemotherapy, we decided to continue with the treatments. Relying on the Law of the People's Republic of China on the Prevention and Treatment of Infectious Diseases and Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia released by the National Health Commission and National Administration of Traditional Chinese Medicine, and the Institutional Guide of Coronavirus Infection Prevention and Control of Zhongnan Hospital of Wuhan University, we temporarily transformed the wards into a clean area, a potentially contaminated area, and a contaminated area. All medical staff including radiation oncologists, medical physicists, radiation therapists, nurses, and environmental services personnel underwent mandatory training on the prevention and control of the novel coronavirus. All personnel were required to strictly implement disinfection and wear personal protective equipment upon entering and leaving contaminated areas to protect the medical staff and prevent iatrogenic infections. For all patients remaining in the hospital, we designated individual rooms for each patient, and asked patients to follow guidelines and restrict their activities in the designated area. Patients with symptoms or suspected of viral infection were isolated and managed in the contaminated area. To reduce the risk of virus transmission, we asked patient family members to avoid unnecessary visits and our full-time nursing staff would distribute meals and take care of other daily activities.

Epidemic Surveillance

To closely monitor the epidemic, we adopted several strategies. First, we performed temperature monitoring twice daily for all medical staff and patients in the hospital. Patients presenting with suspected symptoms, such as fever, fatigue, cough, sputum, shortness of breath, myalgia, diarrhea and other symptoms, were immediately isolated and screened for novel coronavirus infection. These included routine blood tests, liver and kidney function, complete set of respiratory pathogens,

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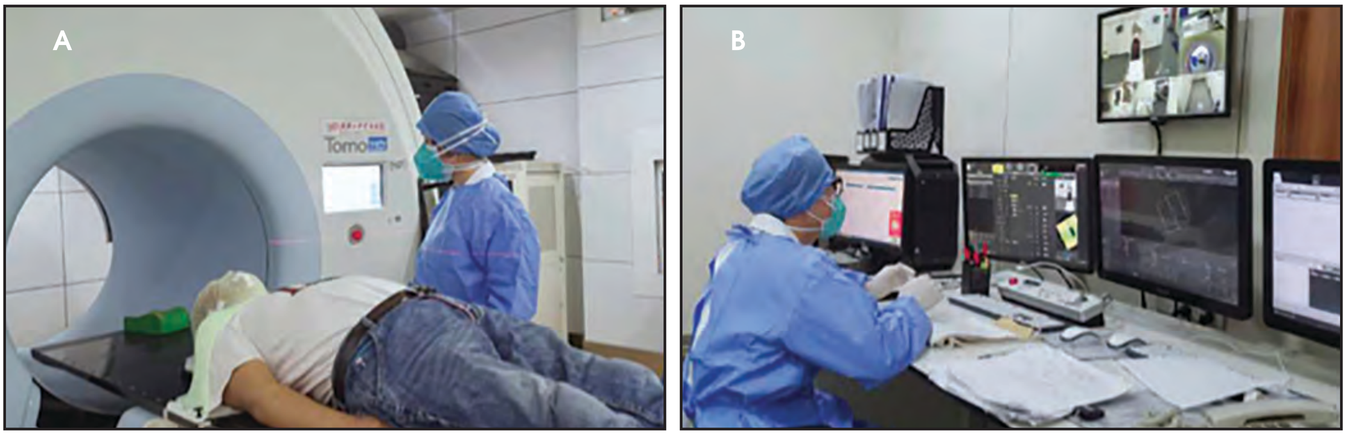

FIGURE 2. *(A, B) Patient and medical staff protection for radiation therapy. Informed consent was obtained from the patient for the anonymous use of these pictures.*

influenza virus testing, procalcitonin (PCT), C-reactive protein (CRP), etc.[9] Chest computed tomography (CT) was obtained in cases of suspected pneumonia. Later, when the detection of nucleic acid and antibodies of the novel coronavirus were available, both tests were performed to determine whether the patient was infected. Clinically suspected patients such as those with typical symptoms and atypical CT images but without positive viral detection were subjected to multidisciplinary consultations with experts from the Department of Infectious Diseases, the Department of Respiratory Medicine, and the Department of Critical Care Medicine. Any confirmed cases were transferred to the Department of Infectious Diseases for isolated treatment of COVID-19 during which period the anti-cancer treatment would be suspended. As of the date of report, there have been no confirmed cases of COVID-19 involving the medical staff nor a new infected case of COVID-19 among patients subsequently treated in our department.

Management of Radiation Therapy

Radiation therapy is a key modality of cancer treatment. Given the unique property of accelerated repopulation of cancer cells after receiving radiation, radiation therapy should not be interrupted for any length of time during the treatment course.[10] Since both infection prevention and cancer treatment greatly affect a patient's survival and quality of life, a panel of experts agreed to maintain radiation therapy for patients requiring radiation treatment as a single modality. We set up temporal adapted treatment protocol and procedures, and reported to the hospital. Before all treatments, patients were fully informed about the risk of potential viral infection, and had to sign a Risk Notification of Novel Coronavirus Infection During Radiation Therapy prior to treatment, which emphasized the importance of the continuity of radiation therapy and the potential risk of infection. Patients were asked to strictly follow the guidance of radiation oncologists and obey the prevention and control measures during their treatment. Individual appointments were strictly implemented for simulation and each radiation therapy treatment, thereby minimizing waiting time. Sterilization and protective measures were applied for each patient at each step of treatment (**Figure 1**). Figure 1 shows a patient wearing a face mask under the conventional immobilization head mask. Patients were also asked to comply with appointment times to avoid crowds and infection. Radiation therapists were equipped with protective clothing, masks, and gloves and disinfectants (hand hygiene) (**Figure 2**) to reduce iatrogenic infections. As of the date of report, our center has collectively treated 48 HN cancer patients, of whom 46 completed radiation therapy, and 2 patients were still undergoing treatment. Among them, 3 patients with nasopharyngeal carcinoma successfully completed definitive concurrent chemoradiation therapy. Patients who completed their treatment were screened for COVID-19. No infections were detected and these patients were discharged. During the epidemic, around 30 patients (about 30%) in the HN Cancer Department had treatment delay (about two-and-a-half months) or interruption. Studies of the effect of radiation therapy delays or interruptions on cancer patients are ongoing.

Management of Chemotherapy

Cisplatin-based chemoradiation therapy is a necessary component of the standard of care for locally advanced HN cancer ineligible for surgery, or as part of adjuvant treatment.[11] High-dose cisplatin can result in frequent severe adverse effects. To further minimize the side effects of concurrent chemoradiation therapy during the epidemic, we used alternative chemotherapy drugs with a lower toxicity profile. For example, studies in nasopharyngeal carcinoma showed that concurrent chemoradiation therapy with nedaplatin showed comparable effects to concurrent chemoradiation therapy with cisplatin, but significantly reduced gastrointestinal toxicity and ototoxicity. However, nedaplatin increases the risk of myelosuppression.[12]

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Therefore, we delivered concurrent chemotherapy with nedaplatin to patients and strengthened supportive care for hematopoetic toxicity. Within 48 hours of chemotherapy completion, pegylated recombinant human granulocyte colony-stimulating factor (PEG-rhG-CSF) was administrated to reduce the risk of myelosuppression caused by chemoradiation. In monitoring myelosuppression, routine blood tests were performed at least twice a week and other supportive treatments such as erythropoietin and thrombopoietin were used in cases of severe anemia and thrombocytopenia, respectively. During the epidemic, patients tolerated the treatments well with no grade III-IV toxicities.

Supportive Treatments

During the outbreak, we also reinforced nutritional support for HN cancer patients. Oral hygiene, and radiodermatitis prevention and treatment were also carried out. Additionally, we offered psychological counseling for patients to mitigate their anxiety, fear and depression. We also encouraged patients to maintain communications with their family through video and telephone calls, and to report any discomfort during their hospital stay.

Outpatient Management

Epidemic Prevention and Education

We encouraged outpatients to remain in close contact with their doctor-in-charge and explained the real-time situations of epidemics and the possible influence on their disease and treatment. We tried to reduce patient anxiety regarding potential treatment delays and interruption. We also explained through telephone and social networks to patients and their families about the prevention and control of the epidemic. First, we advised that they should follow government guidelines, avoid going out and congregating in crowds, take body temperature daily, and report to the community epidemic prevention management agencies when pneumonia-like symptoms arose. Second, we advised that patients should wear masks, ensure frequent hand hygiene, and avoid direct contact with unknown persons. Thirdly, patients were encouraged to exercise regularly, ensure adequate sleep, maintain a positive mood, improve nutrition, etc. Fourth, should the patient or family members develop fever, cough, sputum, chest tightness, dyspnea, diarrhea and other symptoms, they were instructed to immediately report to their epidemic prevention management agency, check for viral infections, and accept isolated observation or treatment in case of confirmed infection, etc.

Medical Treatments

Chemotherapy for outpatients with HN cancer mainly includes induction chemotherapy, maintenance treatment for patients whose radiation therapy course was interrupted, and salvage chemotherapy for patients with relapsed or metastatic cancers. Due to the duration of traffic restrictions and personnel isolation during the epidemic, most patients could not undergo regular chemotherapy, and some patients who required radiation therapy could not start or complete ongoing radiation therapy. To ensure the continuity of cancer treatment and to prevent cancer progression, we recommended oral chemotherapy drugs under the guidance of medical oncologists to control tumor growth while reducing the incidence of viral infections during recurrent visits to the hospitals. Additionally, we also educated patients to be aware of potential adverse effects and how to manage these adverse effects.

For example, oral fluorouracil derivatives showed anti-cancer effect in nasopharyngeal carcinoma, and were well tolerated; most adverse effects were easily managed. Oral capecitabine showed good effects as neoadjuvant chemotherapy in locally advanced nasopharyngeal carcinoma, as single-agent chemotherapy in relapsed or metastatic nasopharyngeal carcinoma, and was superior as maintenance treatment vs observation in metastatic nasopharyngeal carcinoma.[13-15] S-1 is another derivative of oral fluorouracil that also showed anti-cancer effect as concurrent chemoradiation therapy, or as salvage chemotherapy for relapsed or metastatic nasopharyngeal carcinoma.[16-18] Common adverse effects of oral fluorouracil derivatives included fatigue, hand and foot syndrome, myelosuppression, nausea, vomiting, diarrhea, oral mucositis, and skin pigmentation. We required that doctors-in-charge maintain close contact with patients undergoing oral chemotherapy via phone or social network, and promptly guide patients to deal with possible side effects. When adverse effects occurred during treatment, the patients were asked to report to their doctor-in-charge who would evaluate the degree of the adverse effect and then guide symptomatic treatment. Treatments were discontinued in cases of severe adverse effects. For some patients with advanced HN cancers, appropriate nutritional support and analgesic treatment were recommended to their community doctors during the epidemic.

Catheter Maintenance

Some patients left the hospital with central venous catheters, mostly peripherally inserted central catheters (PICC). According to PICC nursing routines, patients were required to perform PICC maintenance at least once a week to reduce the occurrence of catheter-related complications such as catheter blockages, infections, and catheter-associated thrombi.[19] Our institute maintained PICC clinics for patients in Wuhan who needed PICC maintenance. Individual appointments, screens for viral infection, adequate staffing, and patient protection measures were in place for the scheduled PICC maintenance. For patients residing outside Wuhan who

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found it difficult to come for scheduled PICC maintenance, considering that PICC might not be used for a long period, we recommended that PICC be removed at the nearest medical site.

Nutrition Education

During radiation therapy and chemotherapy, patients with HN cancer often suffer appetite loss and malnutrition due to adverse reactions including gastrointestinal side effects, xerostomia, and swallowing dysfunction. Therefore, nutrition education and, if necessary, nutrition interventions were addressed during the outbreak. Through communication among attending physicians, patients and their families, it was essential to follow the eating habits and the nutritional status of patients and to guide them to eat more protein-rich, digestible food, and balanced diets. We also encouraged patients to quit smoking and drinking alcohol. Appropriate enteral nutritional products could also be supplemented, according to their nutritional status. In case of malnutrition, regular blood tests and electrolytes analysis guided nutrition support treatment in the nearest medical site.

Psychological Interventions

Great psychological pressures arise in HN cancer patients and their families, which manifest as anxiety, nervousness, irritability, decreased appetite, and poor sleep quality, etc. The main sources of psychological stress for patients were uncertainty of the epidemic, anxiety about the interruption or delay of treatment, and fear of disease progression. In addition, long-term isolation and cancer-associated symptoms also increase the patient's psychological pressure. In response to this situation, the attending physicians encouraged the patient to establish confidence via mutual communications, and make proper arrangements for treatments and management of adverse reactions during the epidemic. For some patients with greater psychological pressure, specific psychological interventions from professional psychologists and psychiatrists were required.

Follow-up Patient Management

Considering the risk of viral infection during recurrent hospital visits, patients under regular follow-up were advised to postpone follow-up visits and avoid returning to the hospital during the epidemic. During this period, patients were encouraged to maintain contact with their attending physicians through telephone or social networks to conduct a specific discussion on the review of their disease and possible discomfort. Tele-health consultations through certain apps on smartphone were also implemented.

Conclusion

At present, the epidemic of COVID-19 in Wuhan and other cities in Hubei Province has been temporarily controlled. Given the urgency of the diagnosis and treatment of malignant tumors, our cancer institute is gradually opening up (January 23, 2020, switch to state of emergency; March 21 open up; April 20 reach to full capacity) in an orderly manner. We hope that in the near future, the epidemic will eventually subside, allowing patients to be treated in a timely manner. We have endured much in the epidemic and also accumulated valuable experience in dealing with various issues. Based on the concept that life is priceless and all patients should be the center of our work, we were able to minimize the losses caused by the epidemic.

References

1. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. *Nature.* 2020;579(7798):265-269.
2. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* 2020;382(8):727-733.
3. To KK, Tsang OT, Chik-Yan Yip C, et al. Consistent detection of 2019 novel coronavirus in saliva. *Clin Infect Dis.* 2020; ciaa149.
4. Guan W-j, Ni Z-y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* 2020;382:1708-1720.
5. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *J Amer Med Assoc.* 2020;323(11):1061-1069.
6. 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.
7. Xiang YT, Yang Y, Li W, et al. Timely mental health care for the 2019 novel coronavirus outbreak is urgently needed. *Lancet Psychiat.* 2020;7(3):228-229.
8. Strojan P, Vermorken JB, Beitler JJ, et al. Cumulative cisplatin dose in concurrent chemoradiotherapy for HN cancer: a systematic review. *Head Neck.* 2016;38Suppl1: E2151-2158.
9. National Health Commission of China. New coronavirus pneumonia prevention and control program (4th ed). Jan 22, 2020. Accessed February 4, 2020, in Chinese. http://www. gov.cn/zhengce/zhengceku/2020-01/28/5472673/ les/0f96c10cc09d4d 36a6f9a9f0b42d972b.pdf
10. Yang J, Yue JB, Liu J, Yu JM. Repopulation of tumor cells during fractionated radiotherapy and detection methods (review). *Oncol Lett.* 2014;7(6):1755-1760.
11. Chow LQM. Head and neck cancer. *N Engl J Med.* 2020;382(1):60-72.
12. Tang LQ, Chen DP, Guo L, et al. Concurrent chemoradiotherapy with nedaplatin versus cisplatin in stage II-IVB nasopharyngeal carcinoma: an open-label, non-inferiority, randomised phase 3 trial. *Lancet Oncol.* 2018;19(4):461-473.
13. Sun XS, Liu SL, Liang YJ, et al. The role of capecitabine as maintenance therapy in de novo metastatic nasopharyngeal carcinoma: a propensity score matching study. *Cancer Commun (Lond).* 2020;40(1):32-42.
14. Chua D, Wei WI, Sham JS, Au GK. Capecitabine monotherapy for recurrent and metastatic nasopharyngeal cancer. *Jpn J Clin Oncol.* 2008;38(4):244-249.
15. Dada R, El Sayed M, Zekri J. Neoadjuvant chemotherapy with capecitabine plus cisplatin in patients with locally advanced nasopharyngeal cancer: case series study. *J Glob Oncol.* 2017;3(5):455-458.
16. Zhang S, Zhou L, Huang X, Lin S. A retrospective study of concurrent chemoradiotherapy plus S-1 adjuvant chemotherapy on curative effect for treatment of patients with N3 stage nasopharyngeal carcinoma. *Cancer Manag Res.* 2018;10:1705-1711.
17. Zong J, Xu H, Chen B, et al. Maintenance chemotherapy using S-1 following definitive chemoradiotherapy in patients with N3 nasopharyngeal carcinoma. *Radiat Oncol.* 2019,14(1):182.
18. Peng PJ, Cheng H, Ou XQ, et al. Safety and efficacy of S-1 chemotherapy in recurrent and metastatic nasopharyngeal carcinoma patients after failure of platinum-based chemotherapy: multi-institutional retrospective analysis. *Drug Des Devel Ther.* 2014;8:1083-1087.
19. Schiffer CA, Mangu PB, Wade JC, et al. Central venous catheter care for the patient with cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* 2013;31(10):1357-1370.

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Leading a Radiation Medicine Department from the Epicenter of the COVID-19 Pandemic in the United States

Daniel Koffler, MD; Sewit Teckie, MD; Louis Potters, MD, FACR, FASTRO, FABS

SARS-CoV-2, or the novel coronavirus, has spread rapidly throughout the world in the early months of 2020, with 2,432,092 confirmed cases worldwide of COVID-19, the disease caused by SARS-CoV-2, and 166,794 deaths as of April 20, 2020.[1] The consequent strain on medical resources has been immense. The US overtook China on March 27, 2020, to have the highest number of confirmed cases and on April 17, 2020, the resource utilization estimated national shortage of hospital beds was 5,403, and intensive care unit (ICU) beds was 8,854.[1,2] In New York State, with by far the highest COVID-19 burden in the US, those figures were 7,237 hospital beds and 6,175 ICU beds, respectively, on April 9, 2020, the date of peak statewide resource utilization.[2] This crisis will likely be the defining event of our generation similar to the world wars in the early and mid-1900s, and how it unfolds over the ensuing months to years remains unclear, with an economic and health impact worldwide yet to be fully recognized.[3] The acute redeployment of health care resources toward COVID-19 has had an immediate impact across the entire health care continuum and, in particular, to the treatment of cancer. The broader macro-impact on health outcomes from heart disease to cancer is not likely to be known for months and years to come.

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Early Impact of COVID-19 on New York, Northwell Health, and Oncology Population

On March 11, 2020, when COVID-19 was officially declared a pandemic by the World Health Organization, there were 56 confirmed cases of COVID-19 in New York State. Shortly after on March 22, New York State closed non-essential businesses and issued a stay-at-home order. As of this writing, there have been 232,782 cases within the Northwell Health geographic area of New York and its suburbs, with 14,137 deaths.[4] Since the second week of March 2020, the entire focus of our health system, with 23 hospitals and more than 72,000 employees, has been to stand up more than 1,200 additional inpatient beds and to rebuild and configure spaces in our current buildings for inpatient and ICU care. Auditoriums have been ripped apart. Endoscopy, post-anesthesia care units (PACUs), step-down units and more have been converted into ICUs. Beginning the last week of March, operating rooms (OR) were closed for elective cases except for medical emergencies, with an OR volume normally exceeding 1,000 cases per day reduced to about 80 or less. The ICUs quickly reached capacity with a continued census of more than 800 patients on a ventilator. The burden on the Northwell system (**Figure 1**) is approximately in line with statewide case and mortality trends (**Figure 2**).[4] It appears that we have hit the peak on hospitalizations with, as of this writing, 3 days of a positive trend where discharges marginally outnumber admissions. Still, the long lengths of stay associated with COVID-19 will require continued redeployment of physicians, nurses, technologists and others to help cover the volume of illness.

The impact on cancer services has been dramatic. The ability to perform surgery, biopsies, and procedures, and offer other ancillary clinical and supportive services has been significantly impacted. We have taken numerous proactive steps to prepare for COVID-19

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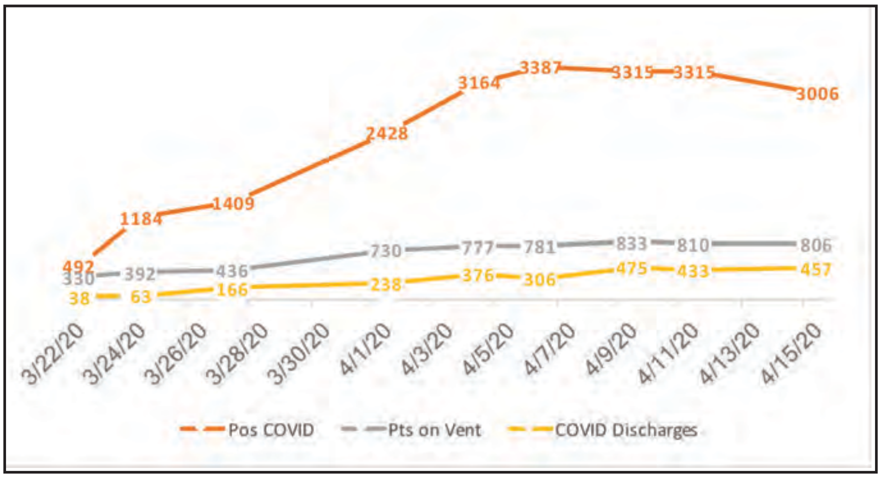

FIGURE 1. Impact of COVID-19 at Northwell Health – hospitalized patients: 3/22/2020-4/15/2020

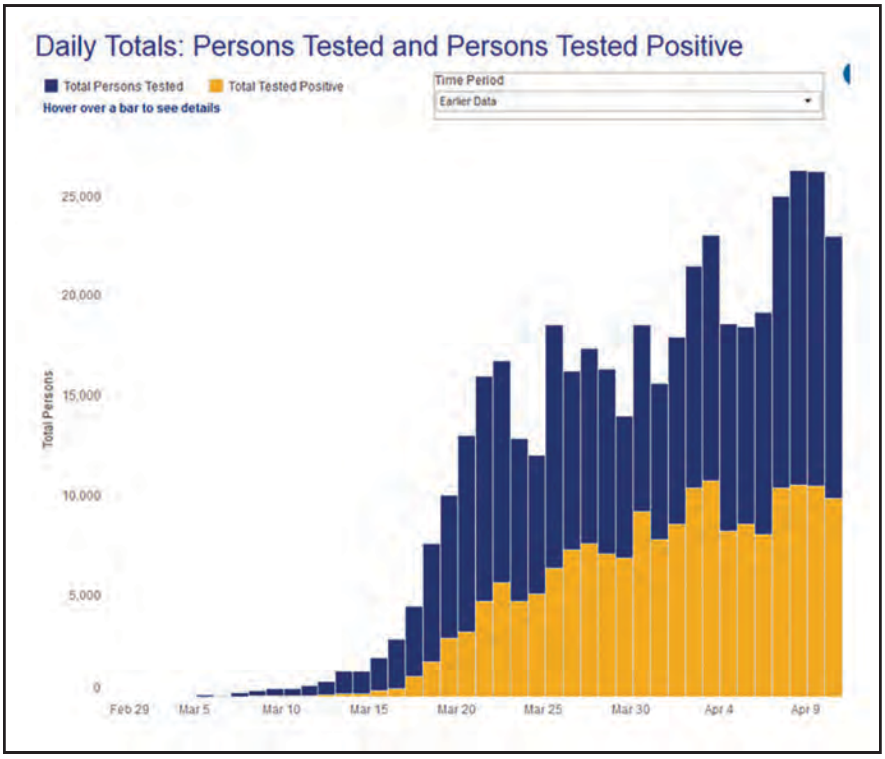

FIGURE 2. New York State COVID-19 incidence trends 2/29/2020-4/10/2020

Table 1. Principles of Department During COVID-19, as Outlined in March 15 Department Email
Our Priorities During COVID-19 Are the Following:
1. Protect the health of staff
2. Protect the health of our patients
3. Ensure continuation of care for active patients receiving radiation therapy
4. Maintain access to patients requiring radiation therapy services
5. Provide an appropriate standard of care to infected patients only if priorities 1-3 can be met

and implement policies over the past 7 weeks (as of this writing). The purpose of this review article is to outline how the department of radiation medicine has managed the COVID-19 crisis to date.

Impact on Our Radiation Medicine Department

The public health crisis sketched above has had a major downstream impact on medical services not immediately related to its mitigation, including our Radiation Medicine Department. The Department of Radiation Medicine of the Northwell Health Cancer Institute comprises 9 radiation oncology clinics across 6 of the 9 downstate New York counties and provides cancer care to patients throughout this regional area. In the immediate prelude to the pandemic, the department's daily census on average consisted of 270 patients receiving external-beam radiation, 6 to 10 receiving stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT), 2 receiving Gamma Knife (Elekta), 20 simulations, 18 new-starts, as well as various brachytherapy procedures, and other patient evaluation and management (E/M) visits. As early as the week of March 9, it was becoming apparent that New York would be significantly affected by COVID-19. This "quiet before the storm" was worsened by constant news reports, which distracted from our day-to-day operations. Nevertheless, we had time to plan without fully recognizing the impact within the department and overall.

On March 15, an email was sent to our physicians and administrators outlining the over-riding principles (**Table 1**) and action items needed for safe operations. These principles have served without compromise since.

We also determined that follow-up visits should be curtailed and converted initially to a phone call while telehealth services were being implemented. Additionally, we asked physicians to catalog cases into critical and noncritical categories in case of staffing issues, and to

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Table 2. Prioritization of Radiation Treatment Start Date Based on Treatment Urgency

Priority	Description	Example Cases
Priority I	Cases where a delay of treatment may result in a loss of life, progression of disease or a permanent loss of neurological or other function. These patients are to be assessed and managed accordingly.	1. Oncologic emergencies 2. Advanced head and neck 3. Advanced gastrointestinal 4. Advanced gynecologic 5. Advanced lung
Priority II	Cases that may be delayed for up to 4 weeks, and delay in treatment is unlikely to result in a loss of life or negatively impact a patient's prognosis. If a patient's treatment is deferred, waiting lists should be created for priority II patients requiring treatment. These waiting lists will be reviewed at least weekly depending on the overall situation and the availability of treatment slots.	1. Early stage head and neck 2. Early stage lung 3. Lymphoma 4. Brain stereotactic radiosurgery of benign diseases
Priority III	Cases that may be delayed for 30 days or more, where such delay in radiation treatment is unlikely to result in a loss of life or negatively impact a patient's prognosis. If a patient's treatment is deferred, waiting lists should be created for priority III patients requiring treatment. These waiting lists will be reviewed for pending treatment accordingly and the patients contacted with follow-up as needed.	1. Early stage prostate 2. Early stage breast 3. Prostate on androgen deprivation

Table 3. Prioritization Assignment of All Pending Patients (total n = 253) as of March 20, 2020

Priority	N	%
I	150	59%
II	68	27%
III	35	14%

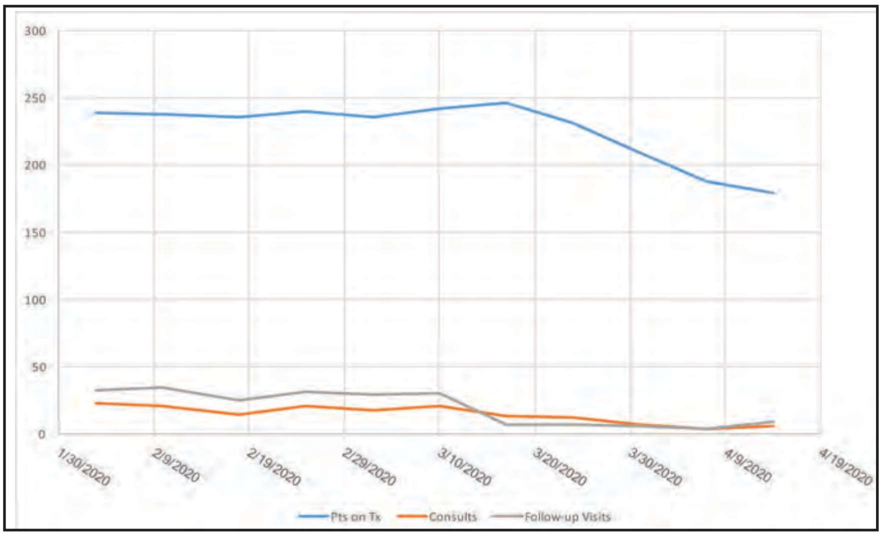

FIGURE 3. *Average daily patient load in radiation medicine (not including one community site) during COVID-19*

start anticipating cancelled procedures and surgeries.

While we never had an issue obtaining personal protective equipment (PPE) at Northwell, PPE policies evolved during this early phase of the crisis, creating some staff concern and anxiety. Also evolving at this time was the management of staff exposures and patient screening. We started to deploy work-from-home (WFH) orders for some back-office staff, including those performing treatment planning, to reduce personnel volume and thereby lower exposure risk.

Additionally, on March 17, we issued a policy for our residency program to protect residents and minimize their exposure without compromising training. The policy stated that residents would immediately do the following: WFH on their attendings' academic days and other days when no clinic or hospital visits were scheduled for their respective services; don context-appropriate PPE for all patient encounters; perform contouring, plan review, clinical note writing, and other such work remotely to the extent feasible; and participate in didactic sessions and tumor boards via video chat and/or teleconference. On April 1, we also implemented weekly teleconference check-ins between the residents and program director regarding operational concerns and resident well-being.

Prioritizing Patients for Radiation Start

By March 19 a more detailed outline was developed to prioritize patient treatment urgency into three categories (**Table 2**). At that time, we had 253 patients in the queue between consultation and treatment start. A department-wide video conference was convened on the

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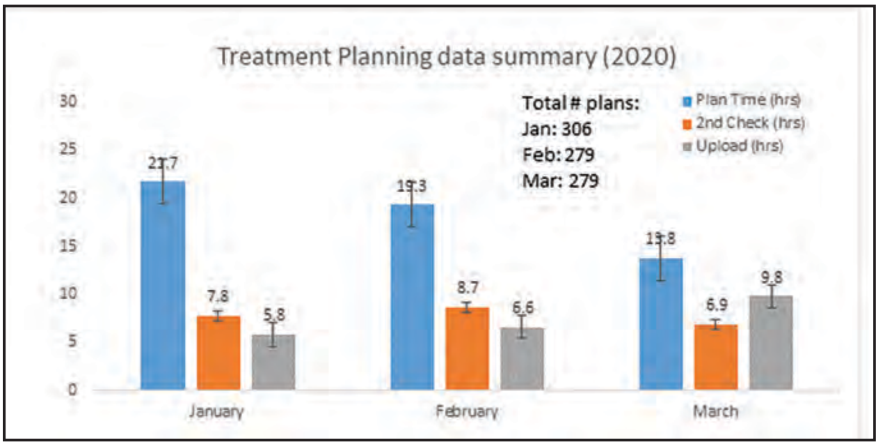

FIGURE 4. Physics monthly planning volumes and average time to completion for three steps: Treatment plan, 2nd check, and plan upload (in hours); January through March 2020.

FIGURE 5. Staff dressed in appropriate personal protective equipment (PPE) while treating our first SARS-CoV-2 positive patient.

Table 4. Lessons Learned for Managing a Radiation Medicine Department Through the Crisis Phase of COVID-19

1. Decrease treatment volume
- Facilitate spacing of patients during the day, decreasing foot traffic through the department.
- Assign radiation therapist rotations that decrease team size on the linear accelerator.

2. Have a back-up plan ready
- We planned for residents and even attendings to work with a tech to keep treating if needed; this has not yet been necessary.

3. Work from home (WFH)
- We have instituted WFH for secretarial, billing, physics and dosimetry teams
- Plan for extra laptops and remote access, especially for treatment planning off site.

4. Daily huddles
- The staff want to understand the situation and have many questions. Leaders have access to information that the staff does not have. It is vital to share as much with them as possible.

5. Be flexible (and admit to that flexibility)
- Things change rapidly, and we have written more policies in the last 6 weeks than collectively in the past several years.
- Communicate these changes effectively and quickly.
- Be aware of ad-hoc rule making. The staff will feel like they need to be proactive and may institute some ad-hoc changes. Sometimes these are helpful, and sometimes not.

morning of March 20 where each case was presented and assigned a priority (**Table 3**). While it was laudable to delay the start of up to 40% of our patients, it was not clear if or how many of the staff would become sick and if we could continue to offer access to current patients. As a result, our on-treatment patient volume did not decompress for another 2 weeks due to lagging attrition (**Figure 3**). Although we never experienced a reduction in staff, we had developed contingency plans to maintain access and treatment if that had happened.[5] Likewise, our physics department smoothly transitioned to WFH, with shorter planning times and slightly longer plan upload times likely due to virtual private network (VPN) connectivity (**Figure 4**).

Other actions during the week of March 16-20 included starting a daily administrative operations call, creating a new huddle for on-site staff (at appropriate distance), pre-screening patients before entering our waiting room, converting more than 70% of our E/M visits to telehealth, and managing several staff rule-outs and rule-ins for COVID-19 (**Table 4**).

Maintaining a Culture of Safety

It is critical in a crisis to maintain departmental rules and policies regarding patient safety. During the COVID-19 crisis, we have made a purposeful decision not to relax safety rules whatsoever and to not allow workarounds, but rather to assess and view these rules as the foundation of providing safe care. Doing so has created a routine and set

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Table 5. Consensus Guidelines for Intensive Treatment Management to Reduce Hospitalization and Adverse Events*

Disease Site	Pre-treatment	Acute CTCAE[13] to manage	Suggested Interventions
Anal Cancer	Health system resources potentially unavailable: • Home care / wound care services	Dermatitis Desquamation Pain Diarrhea Dehydration Cytopenias	• Twice weekly OTV after 2nd week • Early use of: Silvadene, sitz baths, anti-diarrheal, pain medication/management • CBC monitoring, weekly MedOnc visits (neutropenia/anemia) • Consider treatment break[i]
Rectal Cancer – advanced, low-lying	Consider induction chemotherapy as part of total neoadjuvant therapy to delay start of radiation[ii]	Dermatitis Desquamation Pain Diarrhea	• Twice weekly OTV after 3rd week • Early use of: Silvadene, sitz baths, anti-diarrheal, pain medication/management • CBC monitoring, weekly MedOnc visits
Esophageal Cancer – advanced	Health system resources potentially unavailable: • Nonemergent procedures (eg, esophageal dilation, tent placement, feeding tube placement) Consider perioperative chemotherapy to defer radiation[iii]	Esophagitis Weight loss Cough Dyspnea	Early • Twice weekly OTV after 2nd week • Early use of: PPI twice daily, oral steroids, Carafate, pain medications, dietary evaluation, nutritional supplement shakes Hospital avoidance • IV fluid hydration by MedOnc - If MedOnc unavailable, IV fluid hydration within RadMed department • NG-tube placement (may be difficult, particularly if obstructive symptoms)
Lung Cancer – advanced	Consider induction chemotherapy (particularly for small cell) Consider deferring adjuvant RT start date for consolidative RT or PCI for SCLC, postop N2 NSCLC	Cough Dyspnea Esophagitis Weight loss Cytopenias	• Evaluate for O2 need (nocturnal, ambulatory, at rest) • Twice weekly OTV after 2nd week • Early use of: oral steroids, PPI, Carafate, pain medications, nutritional supplement shakes • Aggressive management of esophagitis: PPI twice daily, gabapentin, dietary evaluation
Head and Neck Cancers	Health system resources potentially unavailable: • Dental evaluation • Feeding tube placement • Speech/swallow evaluation • Home care / wound care services Consider weekly cisplatin dosing for fit candidates (30-40mg/m2) instead of bolus cisplatin. If borderline candidate for systemic therapy, do not use. Consider altered fractionation to compensate for lack of systemic therapy. For elderly patients, consider hypofractionation and no chemotherapy.	Mucositis Odynophagia Dysphagia Dehydration Weight loss Cytopenias	Early • Twice weekly OTV • Review CBC taken by MedOnc weekly • Early use of: pain medication/management, gabapentin, mouth rinses, nutritional supplement shakes, dietary evaluation Hospital avoidance • When dysphagia begins, start IV fluid hydration by MedOnc (otherwise fluid bolus via PEG if available) twice weekly during chemoradiation - If MedOnc unavailable, consider IV fluid hydration within RadMed department • NG-tube placement if weight loss otherwise meeting criteria for PEG placement • Low threshold to stop chemotherapy if patient develops CTCAE ≥ 3 • Consider treatment break for refractory grade 3 symptoms (< 1 week)

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Table 5. (continued)

Disease Site	Pre-treatment	Acute CTCAE[13] to manage	Suggested Interventions
High-grade Glioma	Standard fractionation vs hyopfractionation for elderly/poor performance status vs palliative	Headaches Nausea Vomiting Seizures	Early • Twice weekly OTV after 2nd week • Steroid management, perhaps more anti-epileptic use than normal Hospital avoidance • If progressive neurologic symptoms, consider outpatient MRI, evaluation by neuro-oncology/neurosurgery
Vulvar Cancer	Health system resources potentially unavailable: • Decreased OR availability —> Increased utilization of definitive chemoradiation • Home care / wound care services	Pain Dermatitis Desquamation Diarrhea Dehydration Cytopenias	• Twice weekly OTV after 2nd week • Early use of: Silvadene, sitz bath, pain medication/management, anti-diarrheal • CBC monitoring, urinalysis, weekly MedOnc visits • Consider treatment break (goal < 1 week)

*adapted with permission from reference 5
[i]RTOG 98-11(14) allowed a 10-day break as needed; in RTOG 0529[15], breaks were mostly due to neutropenia.
[ii]Total neoadjuvant therapy approach added to 2015 version of NCCN guidelines as an acceptable option.[16]
[iii]Perioperative chemotherapy is an alternative option to chemoradiation for distal esophagus and EGJ[17,18]

Key: CTCAE = Common Terminology Criteria for Adverse Events; OTV = on-treatment visit; CBC = complete blood count; PPI = proton-pump inhibitor; IV = intravenous; NG = nasogastric; RT = radiation therapy; PCI = prophylactic cranial irradiation; SCLC = small-cell lung cancer; NSCLC = non-small cell lung cancer; PEG = percutaneous endoscopic gastrostomy; MRI = magnetic resonance imaging; OR = operating room

of expectations that have grounded the staff during the uncertainty of a health crisis unfolding around them. Opportunities to explore modifications of these safety rules provide fresh perspectives toward established policies. However, we have refrained from making such changes in the midst of the crisis, and instead have cataloged feedback from faculty and staff for future discussion, when we are past the acute crisis phase.

Management of SARS-CoV-2 Positivity Among Staff and Patients

The department has had several staff members test positive for SARS-CoV-2 virus. This understandably creates anxiety regarding potential exposures. Fortunately, we have seen relatively little cross infection except at one of our locations early in the crisis where several staff tested positive together. When staff were known to have tested positive for the virus, all patients and staff with whom they had come in contact in the 48 hours prior to falling ill were informed of the exposure. We followed CDC guidelines for health care workers (HCWs) stating that asymptomatic HCWs who had been exposed to a known COVID-19 case should continue working while wearing a surgical mask and undergo twice-daily temperature and symptom reporting. We attribute the low departmental infection rate to Northwell's early policy requiring clinical staff to wear surgical masks at all times, high staff awareness about infection prevention, and a policy requiring patients to wear masks. In addition, the health system instituted an early policy prohibiting in-person group meetings including teaching conferences and tumor boards. This allowed staff to limit exposure to each other and reduced the need to travel between our outpatient and inpatient sites for nonpatient-care-related activities. Further, we protected patients and staff by requiring patients to undergo telephone screening 24 hours prior to their appointment.

We continue to treat infected patients with full PPE with an approach involving the use of a rear door, limited exposure time, increased physical distance, appropriate donning and doffing of full PPE, and appropriate vault decontamination (**Figure 5**). The ability to treat a positive patient in their acute phase of COVID-19 and then to have the illness resolve and continue treatment without the need for full PPE and without a break is also very encouraging.

Current Status: Seven Weeks into the Crisis

Our treatment numbers are about 70% of typical volume and it was helpful to arrive here as we initially did not know how staff would be affected. We are calling this our "soft landing." Now that we are in this position, we can better control new patient flow, with many in the queue assigned a priority level of 2. We

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continue to space out treatments to decrease foot traffic in the waiting room. Coupled with telehealth, our distancing measures have proven highly successful.

As the crisis in New York remains critical, the issue now is redeploying staff. We have had staff from all departmental areas redeployed to inpatient or ambulatory care. Specifically, several nurse practitioners and physician assistants worked on inpatient COVID units for 2 to 4 weeks at a time. Physicians were also added to a redeployment list, but to date were not needed to staff COVID units. It is not clear if this will remain a short- or long-term policy but to date we have not faced critical staffing issues.

We have also begun screening all patients who enter our departments for symptoms related to COVID-19 and we have discouraged visitors from accompanying patients unless they are a formal caregiver. If screening indicates concerning symptoms, the patient is isolated, formally evaluated by a clinician, and referred for immediate testing in our ambulatory locations. Specific ambulatory offices throughout our health system have now been converted for exclusive use as testing centers.

Another area we are addressing is hospital avoidance for our patients (**Table 5**). The goal is to keep our active on-treatment patients out of emergency departments and hospitals. Hospitals are no longer a sanctuary site for supportive cancer care, but rather an iatrogenic risk site with limited resources for the cancer patient. We will be doing things differently with regards to pre-, on-, and post-treatment management, and we are hopeful that some of these changes may make a long-term difference.[5]

Recommendations for Crisis Management

The COVID-19 pandemic represents a challenge to medical practice that is unprecedented in living memory. As other authors have noted, oncology patients face a uniquely precarious situation during this crisis: They are likely to be at elevated risk of severe complications of SARS-Cov-2 infection on the basis of age and pathology alone, and are at further heightened risk of exposure as a consequence of the oncologic interventions intended to prolong life and/or improve quality of life. Patients and their providers must negotiate a Morton's fork between foregoing oncologic care and potentially succumbing prematurely to cancer, or pressing forward with that care and risk succumbing to COVID-19 complications.[6,7]

Moving from the individual doctor-and-patient approach to a system-wide view, oncology departments must take stock of where they find themselves in the framework proposed by Schrag et al: in preparatory, acute, or crisis phases of the pandemic.[7] As of this writing, the majority of the US is in a preparatory phase (intact system with a surplus of manpower and equipment) or acute phase (a system under strain with reduced capacity that can still meet its needs by strategic resource allocations). New York and much of the Northeast, Louisiana, and Michigan are in a crisis phase: a system overwhelmed and facing shortages. It is crucial to marshal resources and prepare staff during the preparatory and acute phases to withstand the crisis phase and minimize the impact on care, to lay plans in advance for a transition out of crisis phase, and indeed to lay preparations for the possibility of cycling between these phases given the possibility of subsequent spikes of infection resulting from causes beyond health care systems' control.[3]

The challenge of oncology care during this crisis is further exacerbated by the loss of oncologic surgeries due to the lack of OR resources and the need to preserve hospital space for COVID-19 patients. This impact also includes the limitation or curtailment of brachytherapy procedures leading us to move away from an accepted standard of care in many instances. From a radiation oncology perspective, there has been a push to shorten treatment courses by implementing hypofractionated options to replace protracted conventionally fractionated radiation therapy. While some of these shorter fractionation schedules have evidence-based outcomes, many alternative treatment schedules have not undergone the same breadth of data collection and analysis. In addition, many physicians may find themselves uncomfortable with these regimens and unable to counsel patients appropriately on the expected short- and long-term effects. Examples include adoption of single-fraction regimens in settings ranging from curative-intent thoracic SBRT to palliative radiation therapy in oncologic emergencies, instead of the multifraction approaches that would be favored under ordinary circumstances.[8,9] Likewise, from a medical oncology perspective, re-evaluation of oral over intravenous chemotherapy and keeping patients out of infusion facilities remains circumspect with regard to equivalent or non-inferior outcomes.[7]

Oncology, by its nature, is a multidisciplinary enterprise and oncologic care is optimized by communication and coordination of therapy between its various clinical branches and in collaboration across health systems. It is encouraging, in this context, to see the swift adoption across many practices nationally and internationally of similar policies to limit clinical volumes and treatment times, while maintaining social distancing as well as the morale and health of providers and ancillary staff.[7-12]

Conclusion

It is undeniable that delays in delivering oncologic care secondary to the scarcity of resources and need for strict social distancing will impact patient outcomes. The degree of that impact, and in which settings it is most significant, will be an urgent subject of future study and analysis. We have outlined here our systematic approach to mitigate that impact

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to whatever extent is feasible and safe in the interim. Our mission in this crisis is to continue to provide exemplary oncologic care while contributing to the public health of our community — perhaps the most severely and acutely affected of any in the world – and we are unwavering in our commitment to do so.

References

1. Johns Hopkins Coronavirus Resource Center. Coronavirus COVID-19 Global Cases by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University. Accessed April 18, 2020. https://coronavirus.jhu.edu/us-map
2. Institute for Health Metrics and Evaluation. COVID-19 Projections, Institute for Health Metrics and Evaluation (IHME) at the University of Washington. Accessed April 18, 2020. https://covid19.healthdata.org/
3. Kissler SM, Tedijanto C, Goldstein E, Grad YH, Lipsitch M. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. *Science.* April 14, 2020.
4. New York State Department of Health. NYSDOH COVID-19 Tracker. Accessed April 18, 2020. https://covid19tracker.health.ny.gov/views/NYS-COVID19-Tracker/NYSDOHCOVID-19Tracker-DailyTracker?%3Aembed=yes&%3Atoolbar=no&%3Atabs=n
5. Chen W, Teckie S, Somerstein G, Adair N, Potters L. Guidelines to reduce hospitalization rates for patients receiving curative-intent radiation therapy during the COVID-19 pandemic: report from a multicenter New York area institution. *Adv Rad Onc,* April 2020. https://www.astro.org/ASTRO/media/ASTRO/Daily%20Practice/PDFs/COVID-Chen-et-al(ADRO).pdf
6. Thomson DJ, Palma D, Guckenberger M, et al. Practice recommendations for risk-adapted head and neck cancer radiotherapy during the COVID-19 pandemic: an ASTRO-ESTRO Consensus Statement. *Int J Radiat Oncol Biol Phys.* Apr 14;S0360-3016(20)31034-8. https://doi.org/10.1016/j.ijrobp.2020.04.016
7. Schrag D, Hershman DL, Basch E. Oncology practice during the COVID-19 pandemic. *J Am Med Assoc.* April 13, 2020. https://doi.org/10.1001/jama.2020.6236
8. Wu, Abraham, Rimmer, Andreas, et al. Thoracic radiation therapy during COVID-19: provisional guidelines from a comprehensive cancer center within a pandemic epicenter. *Adv Rad Onc.* April 2020. https://www.astro.org/ASTRO/media/ASTRO/Daily%20Practice/PDFs/COVID-Wu-et-al(ADRO).pdf
9. Yaerramilli D, Xu AJ, Gillespie EF, et al. Palliative radiotherapy for oncologic emergencies in the setting of COVID-19: approaches to balancing risks and benefits. *Adv Rad Onc.* April 8, 2020. https://doi.org/10.1016/j.adro.2020.04.001
10. Noticewala S, Koong A, Bloom EC, et al. Strategies to flatten the curve during the COVID-19 pandemic in radiation oncology: experience from a large tertiary cancer center. *Adv Rad Onc.* April 2020. https://www.astro.org/ASTRO/media/ASTRO/Daily%20Practice/PDFs/COVID-Noticewala-et-al(ADRO).pdf
11. Rathod S, Dubey A, Chowdhury A, Bashir B, Koul R. A call for new 4R's based radiation oncology model in COVID-19 Pandemic. *Adv Rad Onc.* April 2020. https://www.astro.org/ASTRO/media/ASTRO/Daily%20Practice/PDFs/COVID-Rathod-et-al(ADRO).pdf
12. Simcock R, Thomas TV, Christopher E, et al. COVID-19: Global radiation oncology's targeted response for pandemic preparedness. *Clin Transl Radiat Oncol.* 2020 Mar 24;55-68. https://doi.org/10.1016/j.ctro.2020.03.009.
13. Common Terminology Criteria for Adverse Events (CTCAE). 2017:147.
14. Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. *JAMA.* 2008;299(16):1914-1921. doi:10.1001/jama.299.16.1914
15. Mitra D, Hong TS, Horick N, et al. Long-term outcomes and toxicities of a large cohort of anal cancer patients treated with dose-painted IMRT per RTOG 0529. *Adv Rad Onc.* 2017;2(2):110-117. doi:10.1016/j.adro.2017.01.009
16. National Comprehensive Cancer Network. Rectal Cancer (Version 2.2020). Accessed May 8, 2020. https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf
17. National Comprehensive Cancer Network. Esophageal and Esophagogastric Junction Cancers (Version 1.2020). Accessed May 8, 2020. https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf
18. Al-Batran S-E, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet.* 2019;393(10184):1948-1957. doi:10.1016/S0140-6736(18)32557-1

Tiny Yet Mighty: Nanotechnology in Radiation Therapy

Mary Beth Massat

Nanotechnology is the application of extremely small things—a nanometer is one billionth of a meter—used in science, engineering and technology. It involves the ability to view and control individual atoms and molecules and has been used in designing new therapeutics and diagnostics in medicine. As such, interest is mounting to harness nanotechnology's potential to enhance radiation therapy and advance cancer care.

Background

In 2005, the National Cancer Institute (NCI) and the National Institutes of Health (NIH) established the NCI Alliance for Nanotechnology in Cancer program, convening scientists from physical sciences, chemistry and engineering to work at the nanoscale with biologists and clinicians. The program has been led from its inception by Piotr Grodzinski, PhD, initially within the Office of the Director at NCI and currently from Cancer Imaging Program and the Nanodelivery Systems and Devices Branch (NSDB), where Dr. Grodzinski is branch chief.

Although the alliance's early research demonstrations favored diagnostics, the focus has gradually moved to therapeutic projects such as chemotherapy, immunotherapy, gene therapy, and radiation therapy.[1]

Dr. Grodzinski explains that during the early years of NCI's nanotechnology programs, a key goal was to examine therapeutic and diagnostic strategies for nanotechnology and nanoparticles, building off work performed in academia and supported via funding from the National Science Foundation or the Defense Advanced Research Projects Agency (DARPA), an agency within the Department of Defense (DoD).

"We are now seeing a number of different therapeutics being approved by the FDA, many of them based on liposomal formulation, which is an earlier stage of nanoparticle design," Dr. Grodzinski says.

While liposomal delivery is typically used for chemotherapy, nanotechnologies also focus on radiation therapy. "It's not just radiotherapy enhancers, although that's one bolus of them," says Christopher M. Hartshorn, PhD, program director, NCI Nanodelivery Systems and Devices Branch, who works closely with Dr. Grodzinski. "There are combination platforms to deliver both chemo- and radiation therapy, specifically to provide local attenuation of the tumor microenvironment (TME) and make it more radiation sensitive. Then there are local radiation broadcasting effects that either enhance the x-rays themselves or generate photons locally to make it more similar to photodynamic therapy, albeit to deep tissue."

One such company is Nanobiotix, maker of Hensify (NBTXR3), an aqueous suspension of functionalized crystalline hafnium oxide (HfO_2) nanoparticles for intratumoral delivery, which is synchronized with the onset of the patient's standard radiation therapy treatment. While Nanobiotix has received first market approval in Europe for the treatment of soft-tissue sarcomas, clinical trials are also underway in the US, Europe and Asia evaluating NBTXR3 in head and neck squamous cell carcinomas, lung and liver metastases, hepatocellular carcinoma and others. These trials assess applications including NBTXR3 as a single agent activated by radiation therapy, and as a combination agent with biologics, chemotherapy, and immune checkpoint inhibitors.

"Cancer treatment is very multi-modal in many ways so researchers are also looking at combination therapies combining different modalities: radiation, chemotherapy and/or immunotherapy together," adds Dr. Grodzinski. "Radiation can be used to stimulate the effectiveness of immunotherapy. In one of the innovative works, Andrew Wang, MD [associate professor and radiation oncologist at the University of North Carolina at Chapel Hill] used nanoparticles to capture antigens released upon radiation therapy and then trafficked them through the body to stimulate T-cells.

According to Dr. Hartshorn, the NCI has also funded research on nanotechnology-based radiodynamic therapy to increase the efficacy of checkpoint inhibitor immunotherapies. The lead

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investigator, Wenbin Lin, PhD, the James Franck Professor of Chemistry and Radiation & Cellular Oncology at the University of Chicago, uses metal-organic framework nanoparticles, which combine metal nodes with organic binders injected into the tumor prior to radiation therapy. The external radiation interacts with nanoparticles and triggers reactive oxygen compounds toxic to the cancerous cells. Importantly, the design can incorporate an IDO inhibitor—a novel checkpoint inhibitor—as well as be delivered in combination with existing anti-PD-1/PD-L1 treatment strategies. In preclinical studies, these combinations displayed enhanced efficacy and stimulation of a more prolonged immune response than when used separately. Moreover, the response generated from the initial therapeutic perturbation enabled immune response at the tumor site as well as to nearby and, often, distant lesions.[2]

Dr. Lin's company, RiMO Therapeutics, Inc., began a phase 1 clinical trial of RiMO-301 in patients with advanced tumors clinically accessible for injection.[3] While the company's strategy moving forward is likely for head and neck cancers, Dr. Hartshorn adds that preclinical work has focused on breast, colorectal and ovarian cancers.

At Memorial Sloan Kettering Cancer Center, Director of Intraoperative Imaging Michelle Bradbury, MD, PhD, who is also professor of radiology at the Weill Cornell Medical College and co-leader of one of the Centers of Cancer Nanotechnology Excellence funded by the alliance program, and her team are using a type of nanotechnology called C-dots that are one-thousandth the size of a red blood cell. Much of the work in Dr. Bradbury's lab, which is focused on cancer imaging uses a new generation of multimodal (PET-optical) C-dots-bearing peptides, co-developed with Ulrich B. Wiesner, PhD, Spencer T. Olin Professor of Engineering at Cornell University. Drs. Bradbury and Wiesner, along with colleagues, also re-purposed C-dots for use as drug-delivery vehicles to treat cancer. They published the results of a pre-clinical study demonstrating that these silica nanoparticles functionalized with melanoma-targeted peptides induce cell death in starved cancer cells and cancer-bearing mice.[4] Furthermore, they have begun to incorporate alternative labeling approaches to this platform. The goal is to be able to perform β-particle / α-particle radiation therapy using ^{131}I and ^{211}At radionuclides, respectively.

For nearly a decade, Otto Zhou, PhD, led a group at the University of North Carolina at Chapel Hill in developing a carbon-nanotube-based microbeam radiation therapy (MRT) unit that works muck like a synchrotron, a circular particle accelerator, except it delivers radiation over 20 to 30 minutes compared to the fraction of a second in a synchrotron. Using the MRT, Dr. Zhou and co-authors demonstrated how the device applied a higher radiation dose while sparing normal brain tissue in a preclinical study.[5]

Unfortunately, despite promising preclinical studies of nanotechnologies in cancer treatment, moving to human clinical trials and regulatory approval is challenging. As Drs. Grodzinski and Hartshorn note, many of the innovative technologies are still in pre-clinical studies and are slowly transitioning beyond that stage. "A lot of these technologies are being developed by small companies," Dr. Grodzinski says. "Clinical trials are expensive and these smaller companies can likely go to phase 1; however, they often establish partnerships with larger companies to take those trials further."

It's also the particular cancer application area of these novel nanotechnologies that can lead to success in clinical trials and ultimately regulatory clearance, Dr. Grodzinski adds. Using fairly well-established chemotherapeutic agents with nanotechnology carries less risk for a successful translation than using an inorganic, heavy particle for localized radiation as this requires more thorough characterization and, ultimately, more regulatory hurdles for safety.

Liposomal delivery platforms remain in that lower-risk threshold, says Dr. Hartshorn, because there is 40-plus years of in vivo data to support delivery parameters and well-controlled manufacturing as well as accepted safety parameters for their drug "cargo."

"The broader question is whether these technologies will be accepted or not accepted over time by radiation oncologists," Dr. Hartshorn adds. "In many cases with otherwise immunocompromised individuals, cachectic patients, or pediatrics, therapeutic toxicity doesn't allow them to receive standard-of-care dosing of radiotherapy after a certain point or at all. Yet in most cases, nanoparticle strategies enable lower doses to these individuals, although similar efficacy of the higher dose over time, with decreased toxicity. Also, some of the radiation therapy combination platforms are showing modest curative effects in conjunction with immunotherapy. Collectively, these are strengths of these systems when used for radiotherapeutic applications and should, over time, help to establish them in clinical practice."

In a recent paper, Dr. Grodzinski, Dr. Hartshorn and co-authors write that overcoming tumor heterogeneity hurdles relies on an understanding of nano-bio interactions, particle transport to tumor cells and targeting of TME, or premetastatic disease, to enhance treatment response. A similar approach should be utilized in preclinical research, using in vivo imaging to track carrier and drug delivery within heterogeneous tumor tissue and surrounding microenvironment. Further, nanotechnology/nanomedicine research should stay focused in areas where conventional approaches had little to no success and where the advantages

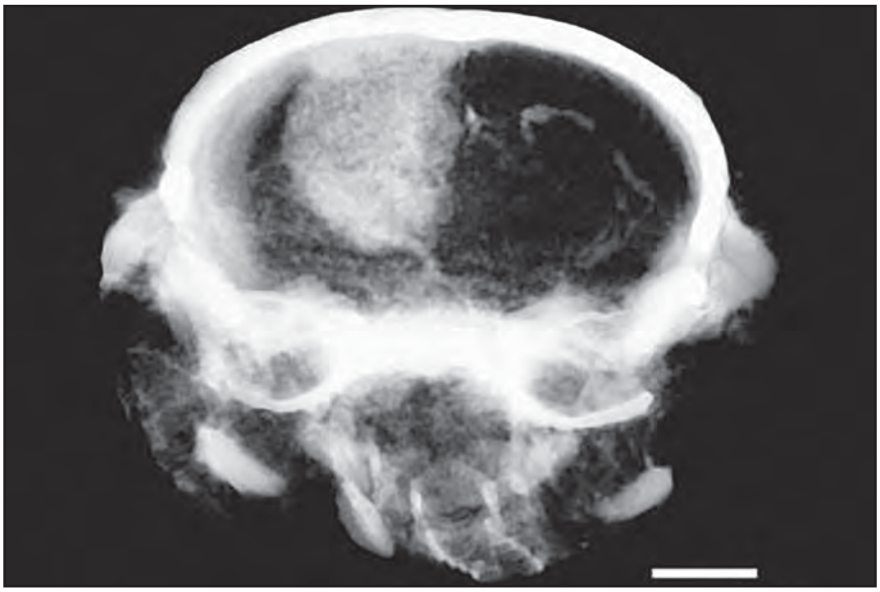

FIGURE 1. MicroCT image of human U87 glioma growing in an athymic nude mouse brain, contrasted after intravenously injected iodine nanoparticles (3.5 g iodine/kg) 3 days after injection. Bar = 2 mm. Taken from Hainfeld JF, Ridwan SM, Stanishevskiy Y, Panchal R, Slatkin DN, Smilowitz HM. Iodine nanoparticles enhance radiotherapy of intracerebral human glioma in mice and increase efficacy of chemotherapy. Sci Rep. 2019;9(1):4505. doi: 10.1038/s41598-019-41174-5. PMID: 30872755. Image courtesy of James Hainfeld, PhD, Nanoprobes.

of nanotechnologies can be effectively used. Rational design methodologies are also essential to bring technology from the bench to the bedside.[6]

Gold Nanoparticles

At Nanoprobes, founder James F. Hainfeld, PhD, has been researching the use of nanoparticles in cancer therapy and other diseases since his days as a senior scientist at Brookhaven National Laboratory in the 1970s. He and Frederic R. Furuya, PhD, developed the Nanogold cluster, comprised of gold compounds with a core of gold atoms and organic groups bound to the surface of gold atoms. Dr. Hainfeld frequently collaborates with Henry M. Smilowitz, PhD, associate professor in the Department of Cell Biology at the University of Connecticut.

Heavy atom nanoparticles made of gold or iodine absorb x-rays. When the radiation is delivered and absorbed by the tissue, the gold/iodine nanoparticles eject electrons, creating free radicals and damaging the tumor DNA. The calculated dose enhancement can be 5 to 8 times the delivered radiation dose and pre-clinical studies have demonstrated up to 10 times the life extension compared to animals that received radiation only.

Drs. Hainfeld and Smilowitz were co-authors of a pre-clinical study using mice where these gold nanoparticles were shown to enhance radiation therapy (x-ray) uptake with a 19:1 tumor to normal brain ratio (**Figure 1**). With the gold nanoparticles, local radiation dose increased by approximately 300 percent and resulted in an average 53 percent tumor-free survival over 1 year compared to 9 percent using radiation alone.[7]

"We focus on brain tumors because cancer drugs are notoriously not effective due to the blood-brain barrier," Dr. Hainfeld explains. "This is an unmet need in cancer."

Although Temozolomide was a breakthrough drug for some brain tumors such as glioblastoma multiforme and anaplastic astrocytoma, there are few options for patients with brain metastases, he adds.

Dr. Hainfeld hopes to initiate human trials soon; in the meantime, he continues to work on refining the particles and delivery. He has learned that high atomic number nanoparticles seem to work best with radiation systems that use kilovolts rather than megavolts—or the older radiation therapy systems. Today's modern linacs use megavoltage x-rays.

"If this nanoparticle method is further developed, then it could bring effective radiation therapy to lower income areas of the world where megavoltage radiation therapy systems are too expensive to acquire," he adds. Dr. Hainfeld is working on segmenting the kilovoltage radiation to avoid the potential for skin burns, a disadvantage of this type of system if the radiation is delivered from only 1 direction.

Although many pharmaceutical companies are focused on small-molecule drugs, Dr. Hainfeld believes nanoparticles are a more versatile platform.

"If you inject or orally take a drug, it goes around the body through the blood and the accumulation in the tumor is not very high," he explains. "Nanoparticles can be made to stay in the blood longer to accumulate in the tumor and not be rapidly excreted. With nanoparticles, we can incorporate multiple components for better targeting and functionality."

First Commercial Radioenhancer

Nanobiotix has embarked on two clinical trials in the US to evaluate the safety and feasibility of Hensify (NBTXR3) in soft-tissue sarcomas. One clinical trial led by Adam Dicker, MD, Thomas Jefferson University Hospital, and Paul Nguyen, MD, Dana-Farber Cancer Institute, involves newly diagnosed patients with unfavorable intermediate risk or high-risk prostate adenocarcinoma.[8] A second trial evaluating the safety, efficacy and tolerability of NBTXR3 activated by radiation therapy in combination with an anti-PD-1 therapy in 3 patient cohorts is ongoing. The first cohort includes patients with locoregional recurrence or relapsed metastatic head and neck squamous cell cancer with the target lesion in a previously irradiated field. In cohorts two and three, patients present with lung or liver metastases from any primary cancer eligible for anti-PD-1 therapy.[9]

The company also announced in early May that a phase 1 trial with NBTXR3 in pancreatic cancer is safe to proceed with The University of Texas MD Anderson Cancer Center per the US FDA.

According to Laurent Levy, PhD, CEO at Nanobiotix, the company has 15 clinical trials in its development plan, including 9 new phase 1/2 trials with MD Anderson treating 6 cancer indications and involving 340 patients.

Key considerations in the development of NBTXR3 were that it fit into the current oncology workflow, can work with any type of radiation therapy system, including proton therapy, and does not change the fundamental processes in radiation therapy.

"The initial question that triggered the work we are doing was, can we use physics to influence a cell from the inside?" says Dr. Levy. "Our product answers that question by improving the dose in the tumor without increasing the dose in surrounding tissue. It is making radiation more efficient, keeping the curative effect while decreasing the side effect (in surrounding healthy tissue)."

Dr. Levy explains the nanoparticle is 15 nanometers and is injected into the patient's tumor the day before treatment using the same pathway used to biopsy the tumor. The particle is designed to absorb the x-rays/radiation—the higher the density of the material, such as hafnium, the higher the x-ray absorption. NBTXR3 remains in the patient's body indefinitely as it is not degraded or excreted from the body and there is no toxicity to the patient. However, in the soft-tissue sarcoma trials, 8 percent of patients had acute immunological response at the time of injection, he adds.

"By adding this one injection of a nanoparticle with hafnium, we can change the outcome for the patient," Dr. Levy says. "We see for most of the head and neck patients it is a sustainable, complete response, with a large proportion of them still alive at 24-month follow-up. Looking at the literature, the median overall survival for this type of patient is around 12 to 13 months."

A Transformational Combination Radiation Therapy

TAE Life Sciences is pursuing a combination biologically targeted radiation therapy through the development of new targeted boron-10 drugs and an accelerator-based neutron system. The company is developing this system, designed to fit in a hospital environment, which overcomes a key limitation: that neutrons for boron neutron capture therapy (BNCT) were historically only available from the core of a nuclear reactor.

BNCT is a combination therapy, comprised of a target drug and radiation, says Bruce Bauer, PhD, CEO of TAE Life Sciences. He explains that the target drug carries boron-10, which has a large cross section to capture neutrons. The drug is delivered intravenously and biologically targets the cancer cell. While it has a short retention within the cancer cell, the drug must achieve a sufficient concentration in the cell, requiring radiation therapy delivery approximately two hours after infusion. The boron-10 then captures the neutrons from the accelerator and begins the process of cytotoxicity.

"When that capture reaction occurs, there's a secondary reaction that takes place that generates a lithium ion and alpha particle," he says. "Most of the damage is done by the alpha particle with a very high linear energy transfer. So, the cytotoxic radiation, which is killing the cell, is generated inside the cell by this capture reaction from the combination of boron and low-energy neutrons." Dr. Bauer adds that the cell death reaction is three times that of a photon and treatments can be delivered in one or two treatment sessions.

Currently, nine BNCT initiatives are underway in Japan, and most recently, BNCT has been approved by the Japanese regulatory bodies and insurers for head and neck cancer treatments. TLS recently announced a dedicated drug development program to improve boron delivery, retention and homogeneous distribution in the cancer cells and their first neutron-beam system is planned to be delivered to a hospital site in China later this year with a goal to start clinical trials in 2021.

References

1. Hartshorn CM, Russell LM, Grodzinski P. National Cancer Institute Alliance for nanotechnology in cancer—catalyzing research and translation toward novel cancer diagnostics and therapeutics. *WIREs Nanomed Nanobiotechnol.* 2019;11(6):e1570. doi:10.1002/wnan.1570

2. Lu K, He C, Guo N, et al. Low-dose x-ray radiotherapy–radiodynamic therapy via nanoscale metal-organic frameworks enhances checkpoint blockade immunotherapy. *Nat Biomed Eng.* 2018;2:600-610. doi:10.1038/s41551-018-0203-4

3. Phase I study of RiMO-301 with radiation in advanced tumors. ClinicalTrials.gov Identifier: NCT03444714. Accessed June 3, 2020. https://clinicaltrials.gov/ct2/show/NCT03444714

4. Kim SE, Zhang L, Ma K, et al. Ultrasmall nanoparticles induce ferroptosis in nutrient-deprived cancer cells and suppress tumour growth. *Nat Nanotechnol.* 2016;11(11):977□985. doi:10.1038/nnano.2016.164

5. Bazyar S, Inscoe CR, Benefield T, et al. Neurocognitive sparing of desktop microbeam irradiation. Radiation Oncology (London, England). 2017 Aug;12(1):127. doi: 10.1186/s13014-017-0864-2

6. Hartshorn CM, Russell LM, Grodzinski P. National Cancer Institute Alliance for Nanotechnology in Cancer—Catalyzing research and translation toward novel cancer diagnostics and therapeutics. *WIREs Nanomed Nanobiotechnol.* 2019;11(6):e1570. doi:10.1002/wnan.1570

7. Hainfeld JF, Smilowitz HM, O'Connor MJ, Dilmanian FA, Slatkin DN. Gold nanoparticle imaging and radiotherapy of brain tumors in mice. *Nanomedicine (Lond).* 2013;8(10):1601□1609. doi:10.2217/nnm.12.165

8. NBTXR3 Nanoparticles and EBRT or EBRT with brachytherapy in the treatment of prostate adenocarcinoma. ClinicalTrials.gov Identifier: NCT02805894. Accessed June 3, 2020. https://clinicaltrials.gov/ct2/show/NCT02805894?term=NBTXR3&cntry=US&draw=2&rank=1

9. NBTXR3 activated by radiotherapy for patients with advanced cancers treated with an anti-PD-1 therapy. ClinicalTrials.gov Identifier: NCT03589339. Accessed June 3, 2020. https://clinicaltrials.gov/ct2/show/NCT03589339?term=NBTXR3&cntry=US&draw=2&rank=2

RADIATION ONCOLOGY CASE

Brachytherapy for Cervical Cancer in an Asymptomatic Patient with Confirmed COVID-19 Diagnosis

Mark E. Hwang, MD, PhD; Cheng-Chia Wu, MD, PhD; Tony J. C. Wang, MD; Simon K. Cheng, MD, PhD; Israel Deutsch, MD; Lisa A. Kachnic, MD, FASTRO; Christine Chin, MD

CASE SUMMARY

A 58-year-old postmenopausal woman was diagnosed with FIGO IIB moderately differentiated invasive squamous cell carcinoma of the cervix. She underwent external-beam radiation therapy to the whole pelvis with concurrent weekly cisplatin chemotherapy from the first week of March to the second week of April 2020 during the height of the COVID-19 pandemic in New York City. At the end of pelvic radiation therapy, she was scheduled for a 4-fraction high-dose-rate (HDR) tandem and ring brachytherapy (BT) course. She did not exhibit any symptoms concerning for viral infection per our physician phone screening the evening before nor by nurse screening the morning of her first BT treatment.

At this time during the pandemic, our institution mandated COVID-19 nasopharyngeal swab RT-PCR testing prior to procedures involving anesthesia airway manipulation. While this patient required only intravenous sedation, a negative COVID-19 test was obtained at the recommendation of the anesthesia team prior to her first treatment. Over the next few days following her first treatment, the patient isolated at home with no sick contacts. On the morning of her second treatment, another COVID-19 test was obtained, and surprisingly detected COVID-19.

Given the high priority of the patient's therapy, it was decided with our radiation oncology COVID leadership team to proceed with her treatments donning full personal protective equipment (PPE) consisting of layered N-95 and surgical masks, disposable gown and face shield. The patient also wore a surgical mask while sedated during the procedure. The brachytherapy treatment team participated in a simulation drill to review workflow and roles to minimize staff exposures. Additionally, measures taken to minimize the patient's footprint in our department included clearing the transport route between the brachytherapy and imaging suites of noninvolved personnel and terminal cleaning of both areas. She was treated during the regular workday, and recovered from anesthesia post-treatment in the brachytherapy suite.

We were unable to perform MRI-based HDR-BT with the tandem and ring applicator in situ for her subsequent fractions due to her COVID status and the elevated exposure risk posed to other patients and staff. A second outpatient MRI of the pelvis, however, was obtained in between her second and third fractions with a Smit sleeve in place to help optimize computed tomography (CT)-based treatment planning (**Figure 1**). The Smit

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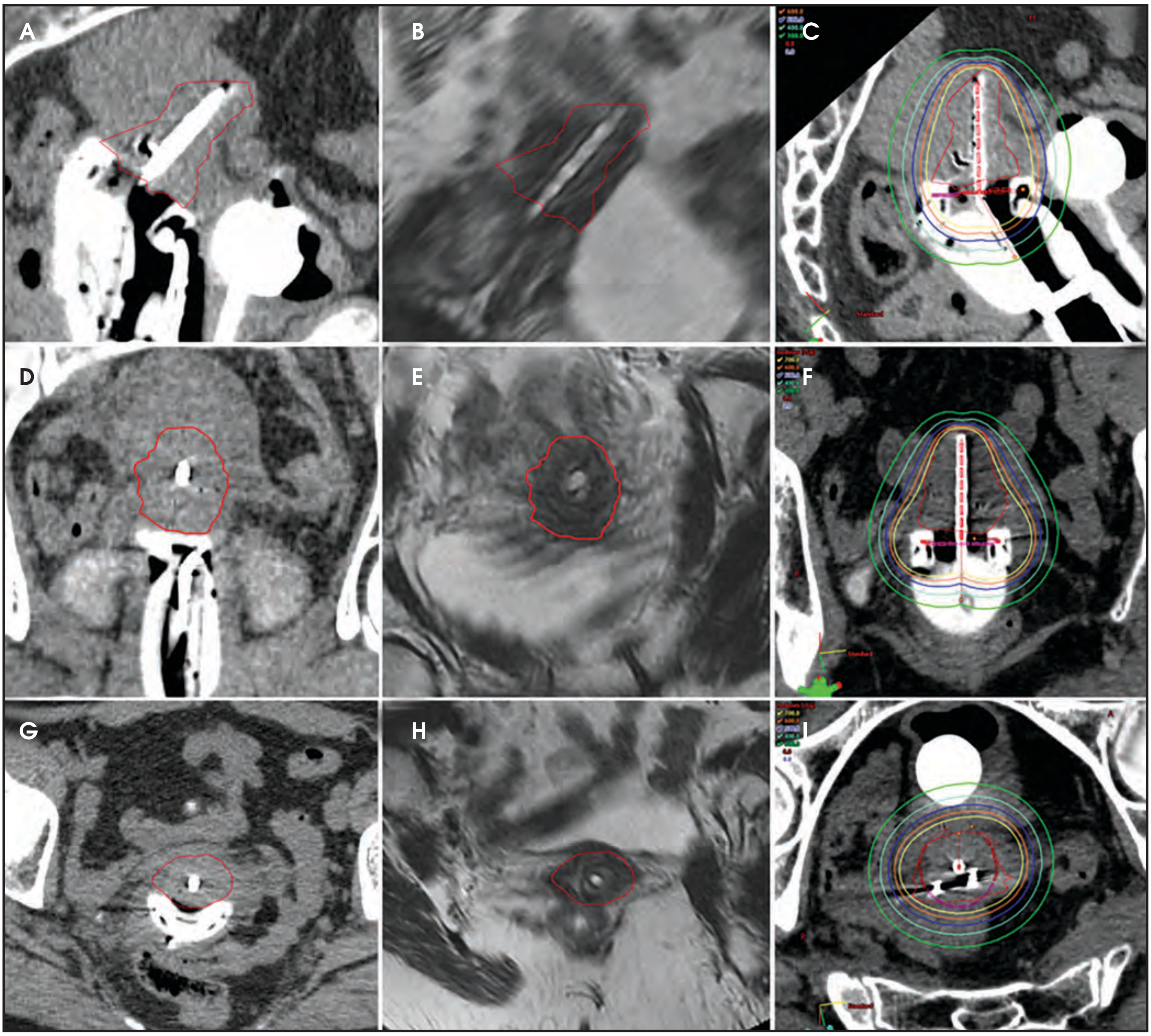

FIGURE 1. Sagittal view of (A) computed tomography (CT) simulation scan with high-risk clinical target volume (CTV) in red, (B) co-registered T2-weighted MRI with Smit sleeve only, and (C) treatment plan. Coronal (D-F) and axial (G-I) views. Isodose lines in C, F and I: 7 Gy – yellow, 6 Gy – orange, 5 Gy – blue, 4 Gy – teal, and 3 Gy – green.

sleeve was useful as a marker to help guide optimal delineation of the high-risk clinical target volume and to allow for dose escalation in the absence of MRI. Our goal was to deliver dose efficiently given the possibility that the patient could develop infectious symptoms necessitating treatment cessation prior to completing her intended 4 fractions.

As the patient remained asymptomatic from her COVID-19 infection, she was ultimately brought back for her fourth and last fraction of treatment. Prior to her last treatment, the patient underwent another COVID-19 test that did not detect virus. In total, her treatment was completed within 8 weeks from the initiation of external-beam treatments with no significant treatment delay, and she remained asymptomatic from her transient COVID-19 infection.

IMAGING FINDINGS

Interfraction T2-weighted MRI revealed a well-delineated cervical canal with a Smit sleeve in place that was co-registered to a CT simulation scan for target delineation.

DIAGNOSIS

Cervical squamous cell carcinoma FIGO IIB, with asymptomatic COVID-19 infection

DISCUSSION

Definitive concurrent chemoradiation therapy is a standard-of-care treatment for women with FIGO IB2 or greater squamous cell cervical cancer.[1] Multiple analyses have demonstrated a strong correlation between total chemoradiotherapy treatment time and pelvic disease control.[2,3] Optimal brachytherapy fractionation has not been identified;[4,5] total treatment time, patient anatomy, risk of toxicity and practitioner familiarity all influence selection of a given fractionation.

On March 24, 2020, the American Brachytherapy Society released a statement recommending against any treatment break for cervical cancer patients asymptomatic from a COVID-19 infection,[6] and the European Society for Medical Oncology soon thereafter attached "high priority" to initiation of definitive treatment.[7] Our institutional policy was to proceed with both external-beam and HDR-BT radiation therapy for cervical cancer given the impact of total treatment time on disease control. With a lack of data describing COVID-19 virus shedding and transmission in asymptomatic patients,[8] as well as reported 30% test false negative rate,[9] the decision was made to perform all brachytherapy procedures in our department with full PPE, regardless of COVID-19 status.

At the beginning of the COVID-19 pandemic, our department instituted a nightly telephone physician symptom screen of all scheduled clinic patients to minimize COVID-19 exposure to patients and staff. Screen-positive patients were referred for COVID-19 RT-PCR testing the next morning and their appointments were rescheduled pending results. All phone screen-negative patients, including this patient at the start of her treatment, were additionally screened by nurses at the department entrance with temperature measurement and provided with a surgical mask and gloves.

Infection modeling suggests the asymptomatic COVID-19 positive rates range from approximately one-fifth to one-half of all cases.[10,11] These estimates vary with incubation time, which itself is reported to range from days to weeks.[8] Prediction of where this patient was in her asymptomatic incubation period at the time of her COVID-19 diagnosis was made more difficult by recent publication of high false-negative test rates,[9] calling into question the validity of her initial negative test result. There was concern at the time of diagnosis that she might subsequently develop symptoms necessitating delay or termination of her treatment.

The patient underwent a total of 3 nasal swab COVID-19 RT-PCR tests over 17 days from her first to final HDR-BT fraction. Only the second test was positive. She likely had an asymptomatic and transient infection that was rapidly cleared if test results are accurate. While her original 4-fraction HDR-BT was ultimately implemented as planned, we adapted our approach as described due to her COVID-19 infection. This case also highlights the practice of COVID-19 testing in asymptomatic patients undergoing aerosol-producing procedures, as frequent testing allowed us to proceed in the safest manner possible.

CONCLUSIONS

Completing HDR-BT on schedule is recommended in the treatment of cervical cancer during the COVID-19 pandemic. The brachytherapy team must implement strategies to help minimize patient and staff exposure, and navigate changes in resource availability during a challenging time. Depending on the patient's clinical course following COVID infection, reduction in the number of HDR-BT fractions should be considered to facilitate timely completion of therapy.

REFERENCES

1. Monk BJ, Tewari KS, Koh W-J. Multimodality therapy for locally advanced cervical carcinoma: state of the art and future directions. *J Clin Oncol.* 2007;25: 2952-2965.
2. Fyles A, Keane TJ, Barton M, Simm J. The effect of treatment duration in the local control of cervix cancer. *Radiother Oncol.* 1992;25:273-279.
3. Song S, Rudra S, Hasselle MD, et al. The effect of treatment time in locally advanced cervical cancer in the era of concurrent chemoradiotherapy: treatment time in the era of CCRT. *Cancer.* 2013;119:325-331.
4. Petereit DG, Pearcey R. Literature analysis of high dose rate brachytherapy fractionation schedules in the treatment of cervical cancer: Is there an optimal fractionation schedule? *Int J Radiat Oncol.* 1999;43:359-366.
5. Huang E-Y, Sun L-M, Lin H, et al. A prospective cohort study to compare treatment results between 2 fractionation schedules of high-dose-rate intracavitary brachytherapy (HDR-ICBT) in patients with cervical cancer. *Int J Radiat Oncol.* 2013;85:123-128.
6. ABS releases statement on brachytherapy services during COVID-19 pandemic. Accessed May 4, 2020. https://appliedradiationoncology.com/articles/abs-releases-statement-on-brachytherapy-services-during-covid-19-pandemic
7. ESMO. ESMO management and treatment adapted recommendations in the COVID-19 era: cervical cancer. Accessed May 4, 2020. https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/gynaecological-malignancies-cervical-cancer-in-the-covid-19-era
8. Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. *Ann Intern Med.* 2020;172:577-582. doi:10.7326/M20-0504
9. Yang Y, Yang M, Shen C, et al. Evaluating the accuracy of different respiratory specimens in the laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections. Accessed May 4, 2020. http://medrxiv.org/lookup/doi/10.1101/2020.02.11.20021493. 2020 doi:10.1101/2020.02.11.20021493
10. Mizumoto K, Kagaya K, Zarebski A, Chowell, G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. *Euro Surveill.* 2020;25(10):2000180.
11. Nishiura H, Kobayashi T, Miyama T, et al. Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19). *Int J Infect Dis.* 2020;94:154-155.

RADIATION ONCOLOGY CASE

Radiation Therapy Continuation for a Patient Diagnosed with COVID-19 in a High-volume Radiation Oncology Practice

John W. Ames, MD; William C. Chen, MD; Sewit Teckie, MD; Gayle Somerstein, RN; Louis Potters MD

CASE SUMMARY

This case report describes the case of a morbidly obese woman undergoing adjuvant radiation therapy for an adrenal cortical adenocarcinoma in a busy New York academic radiation oncology practice. In the middle of her 5-week course of treatment, she developed signs and symptoms suspicious of SARS-CoV-2 infection after a known exposure to a coworker diagnosed with the virus. She ultimately tested positive. After a brief hiatus in her course of radiation, she was able to complete her course of radiation therapy employing a strict protocol to be subsequently described in detail.

INTRODUCTION

COVID-19, the disease caused by SARS-CoV-2, is a novel coronavirus pandemic that has swept the world, with most cases now concentrated in Europe and the US. In the US, New York State has the highest number of confirmed infections. Approximately 15% of all infected patients require hospitalization and approximately 2% require intensive care unit (ICU) admission.[1,2] In some populations, up to 85% of confirmed infections are asymptomatic. However, the total fraction of New York's population that is infected is unknown as a result of limited testing capacity. The pattern that is emerging shows a higher likelihood of severe infections in the elderly, the immunocompromised, those with comorbid conditions, and healthcare staff that are exposed to a high viral load. The most common cause of morbidity and death in these patients is bilateral lung pneumonia and consequent inflammatory response to the infection.[3]

In the New York metropolitan area, the high density of infected persons increases the risk of exposure and transmission, including to immunocompromised cancer patients and the health care staff who care for them.[3,4] For this reason, beginning the second week of March 2020, our radiation oncology department implemented a policy of temperature and symptom screening at the building entrance, requiring masks for all staff and patients, limiting people in the building to staff and patients only, and utilizing gloves and face shields if patient examinations were absolutely necessary. It was after this implementation that our department had its first exposure incident to a COVID-positive patient undergoing treatment.

CASE

The patient is a 36-year-old healthcare worker with T1N0M0 adrenal cortical adenocarcinoma. She underwent robotic-assisted laparoscopic right adrenalectomy in January 2020. She was referred for consideration of adjuvant radiation therapy and was offered a course of intensity-modulated radiation therapy to 45 Gy in 25 daily fractions over 5 weeks, which she began

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on March 11. She was seen by medical oncology who planned to give her mitotane after radiation therapy. Of note, she takes hydroxychloroquine for rheumatoid arthritis.

TIMELINE OF EVENTS

The patient began radiation therapy on March 11. On March 17, our department nurse practitioner (NP) had a brief telephone interview with the patient prior to treatment that day. The patient was asymptomatic, afebrile and her vital signs were stable, but she stated she had close contact with a coworker who had developed a fever and tested positive for SARS-CoV-2 infection. The patient was instructed to come in for her usual treatment and follow all previously instituted safety protocols.

At this time, the patient's office was unsure of the next steps. She had not yet been contacted by her company's employee health department or by the New York State Department of Health. We asked her to let us know if/when she received additional guidance by these other entities. In the interim, our institution adopted a standard protocol for the patient to follow, based on Centers for Disease Control and Prevention (CDC) guidelines: All patients' temperatures would be checked prior to each treatment at a screening table set up outside the department entrance, and patients would be asked a series of screening questions. In addition, patients with known close contact would be asked to check their temperature twice daily, wear a mask in the building, and report any additional symptoms.

She was tested for SARS-CoV-2 on March 24 due to the prior exposure. After receiving her radiation treatment on March 25, she was placed under mandatory quarantine beginning that day per her employer's employee health department.

On March 26, we spoke with the patient on the phone. The patient reported a temperature of 100.9 degrees Fahrenheit later on March 25, for which she took acetaminophen 1g every 6 hours around the clock; her temperature decreased to the 99s. She developed a wet cough, productive of yellowish phlegm, and generalized body aches. Her breathing felt tight, though unlabored.

The patient's test returned positive on March 26. She was then placed on a treatment break while she remained symptomatic. Her fever resolved and most symptoms, including cough and body aches, improved; by March 29, only fatigue persisted. The patient resumed treatment on March 31. A repeat COVID-19 test for the virus was not performed as per the patient's employee health protocol. At the time of this writing, there were no accepted consensus guidelines to ensure safe re-initiation of radiation therapy after a documented COVID-19 infection. Once re-testing becomes universally available, this may very well become standard of care in determining when to resume radiation therapy. In the context of the above scenario, the CDC advises that facilities use the following criteria: "at least 72 hours have passed since recovery defined as resolution of fever without the use of fever-reducing medications and improvement of respiratory symptoms (eg, cough, shortness of breath), and at least 7 days have passed since symptoms first appeared."[5]

For the safety of radiation staff and other patients, infectious disease contact and droplet precautions were implemented through the duration of our COVID-19 infected patient's course of radiation therapy. Personal protective equipment (PPE) was worn by the treating radiation therapists and other clinical staff in patient contact. The minimum PPE included an N95 respirator with a surgical mask over it, eye shield, disposable isolation gown, and gloves. Staff additionally wore disposable hair covers and shoe covers. Staff were trained in PPE donning and doffing in a systematic manner as recommended by the CDC, and staff competencies were assessed and documented.

To minimize exposure, the patient was scheduled as the last patient of the day. Additionally, the patient was escorted into the department via a back entrance closer to the linear accelerator vault and left the department via the same route. The vault was closed for at least one hour before terminal disinfection by a specially trained cleaning crew.

As of April 6, the patient was tolerating adjuvant radiation therapy well without pain or gastrointestinal distress. She continued with her usual medications and laboratory surveillance. On this date, she reported a slight cough, anosmia and ageusia, but denied fever, shortness of breath or a rash. She also reported that her husband was recently hospitalized with bilateral COVID-19 pneumonia and was clinically improving.

Also on April 6, two weeks after diagnosis, the patient was advised by employee health to undergo evaluation for return-to-work clearance per CDC guidelines for infected health care workers. She did not undergo repeat testing. She was cleared to return to work and technically considered recovered and "noninfectious" on April 7. In an abundance of caution, contact and droplet precautions were continued in our department until the patient completed her course of radiation on April 20. Although a less stringent protocol of symptom and temperature check and wearing only a face mask was now technically permissible, we continued the prior protocol of donning the full PPE to minimize exposure risk and provide treating staff additional peace of mind.

DISCUSSION

Our experience of treating a radiation patient with a highly communicable, potentially deadly virus resulted in a well-coordinated, professional, and effective response. Not only do we have an obligation to care for our cancer patients who have committed to a course of potentially life-saving radiation therapy, but we also have an equally critical obligation to keep other patients and staff safe and to minimize exposure to the virus. We were able to treat the patient on schedule while keeping our staff and other patients safe from infection. At first, the situation did cause considerable angst amongst the treating staff. We balanced real risks including affecting other patients and the small possibility of having to close our radiation facility if staff was impacted. We had to tread carefully and meticulously to honor our commitments to our patients and staff.

As an additional way to limit exposure to the virus, we have made a great effort to prioritize the treatment of various patients (urgent patients: normal timeline; semi-urgent patients: delay of 2 to 4 weeks; nonurgent patients: delay > 4 weeks) to decrease the census as a way of social distancing.[6] Moreover, we limit family or companions in the department, allowing the patient one person to accompany them only if essential for the patient's care. As we learn more about the nature of COVID-19, we have been able to adjust and refine our practices to minimize risk of exposure to our staff and other patients. In retrospect, the employee heath return-to-work policy was probably too aggressive and retesting, now more available, has been firmly incorporated into decision-making processes regarding when to return employees to work.

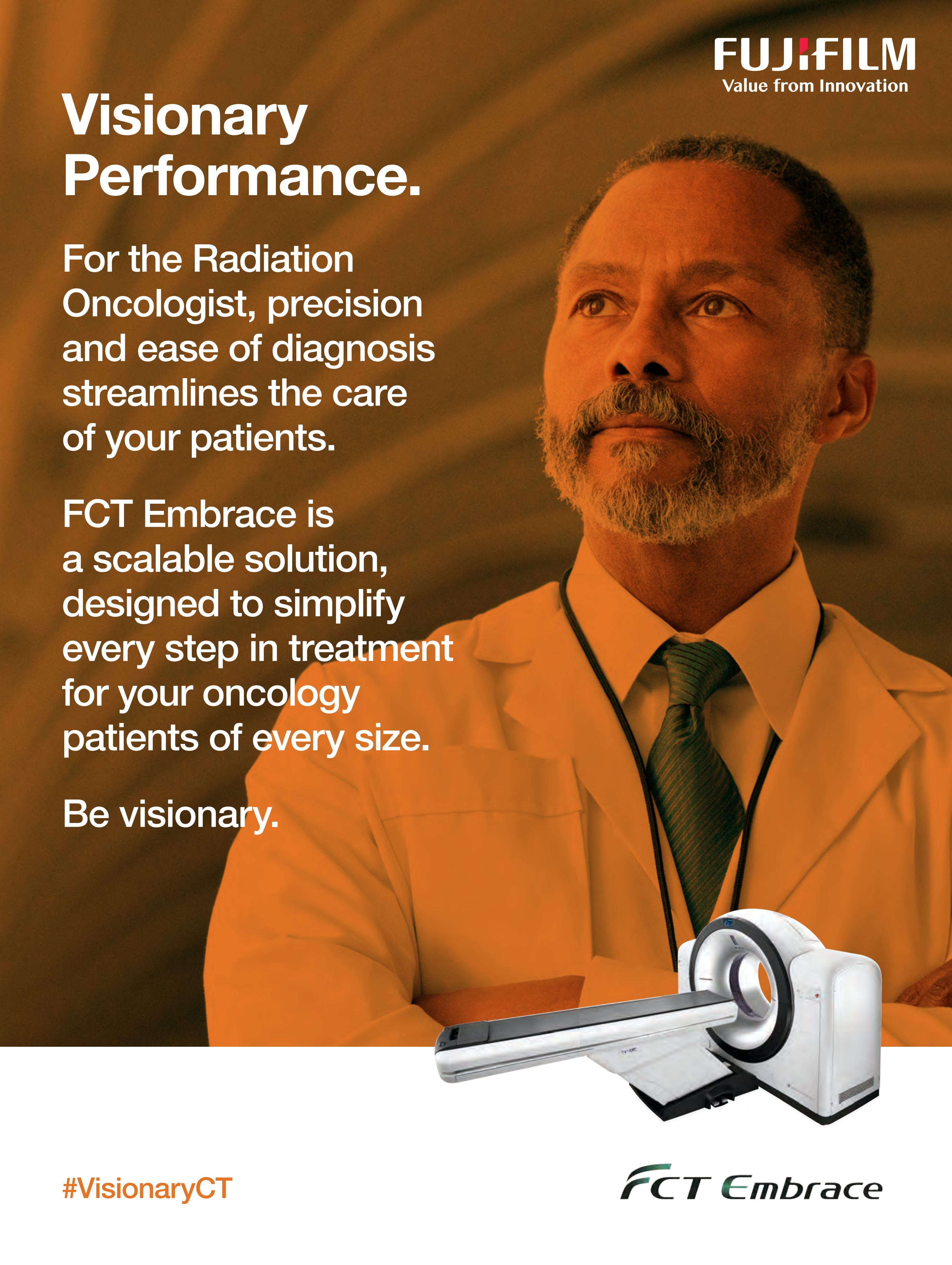
We have learned a few valuable lessons from treating a COVID-19 positive patient in our busy radiation oncology practice. We were comfortable exceeding PPE standards, particularly given the uncertainties of the virus as this provided the treating staff significant reassurance regarding adequate protection. We also appreciated the necessity of verifying the status of our patient vis-à-vis objective infectivity parameters from an official medical entity and not relying solely on the patient's account. At this moment in the pandemic, our knowledge has been increasing exponentially, which will no doubt result in our gaining control over COVID-19. That said, much remains unknown and, until then, we will exercise an abundance of caution.

CONCLUSION

Infectious pandemics are not unprecedented in the history of the world. However, the COVID-19 pandemic is arguably unprecedented in our lifetime, in particular in its sheer scale and its threat to lives, health, livelihood, and indeed our very way of life. We most certainly find ourselves on a wartime footing, requiring all hands on deck, and literally having to triage patients and priorities in, at times, an overwhelmed healthcare system. We have been forced to rapidly innovate policies and procedures (and be ready to modify them as necessary) to effectively and ethically deal with a multitude of challenging circumstances. In our department of radiation medicine, we have sought guidance from our health care institution through its Physician Partners Leadership who have drawn from national and global health leadership bodies such as the CDC, National Institutes of Health, and World Health Organization.[3] With the above-detailed case, we believe we have remained steadfast in our mission to care for our cancer patient safely even when afflicted with COVID-19. We feel having uniform policies and procedures across all of our many sites has allowed us to balance our competing obligations of keeping staff and patients safe from exposure to this highly transmissible contagion and delivering optimal oncologic care for our cancer patients.

REFERENCES

1. World Health Organization. Pneumonia of unknown cause – China. Accessed April 9, 2020. http://www.who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en/
2. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* 2020;382:1708-1720. doi:10.1056/NEJMoa2002032
3. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. Published online April 22, 2020. *J Am Med Assoc.* doi: 10.1001/jama.20206775
4. Xia Y, Jin R, Zhao J, Li W, Shen H. Risk of COVID-19 for patients with cancer. *Lancet Oncol.* 2020;21(4):e180. doi:10.1016/S1470-2045(20)30150-9
5. Pujadas-Botey A, Saxinger L, Manns B, et al. COVID-19 Scientific Advisory Group Rapid Response Report Alberta Health Services, COVID-19 Scientific Advisory Group. Published online April 16, 2020. Accessed May 23, 2020. https://www.albertahealthservices.ca/assets/info/ppih/if-ppih-covid-19-sag-starting-or-resuming-cancer-treatment-rapid-review.pdf
6. Chen WC, Teckie S, Somerstein G, Adair N, Potters L. Guidelines to reduce hospitalization rates for patients curative-intent radiation therapy during the COVID-19 pandemic: report from a multicenter new york area institution, submitted for publication to *Adv Radiat Oncol.* April 2020.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