



Prioritization of Proton Patients in the COVID-19 Pandemic: Recommendations from The New York Proton Center

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Abstract

It has been well documented from the early days of the 2019 novel coronavirus (COVID-19) pandemic that patients with a diagnosis of cancer are not only at higher risks of contracting a COVID-19 infection but also at higher risks of suffering severe, and possibly fatal, outcomes from the infection. Given that the United States has the greatest number of positive coronavirus cases, it is likely that many, if not all, radiation oncology clinics will be faced with the challenge of safely balancing a patient's risk of contracting COVID-19, while under active radiation treatment, against their risk of cancer progression if treatment is delayed. To address this challenge, the New York Proton Center established an internal algorithm that considers treatment-related, tumor-related, and patient-related characteristics. Despite having suffered staff shortages due to illness, this algorithm has allowed the center to maintain patient treatment volumes while keeping the rate of COVID-19 infection low.

Keywords: patient prioritization; proton therapy; COVID-19

Editor's Note

As we deal with the multifaceted effects of COVID-19 throughout all aspects of American life, it is helpful to look for guidance from those ahead of us in this COVID-19 experience.

Within the health care space, proton facilities may face unique challenges. Hundreds of people pass through our treatment rooms and waiting spaces each day, most with cancer and some degree of immunocompromise, others critical workers essential to carrying out daily treatments for all. Many are travelers now required to "shelter at home" in hotels, as numerous traditional housing options such as Hope lodges and Ronald McDonald houses have closed.

We, at *IJPT*, thought the following article warranted expedited publication so that others coming into the COVID-19 surge may benefit from the experience and strategy documented here by the New York Proton Therapy Center's chief medical officer, Charles B. Simone II, MD; director of research, J. Isabelle Choi, MD; and radiation oncologists Shaakir Hasan, DO, Robert H. Press, MD, and Arpit Chhabra, MD.

Please be aware that over the past few days, additional guidance for prioritization of radiation therapy resources is coming from other providers and professional societies as well, including Memorial Sloan Kettering Cancer Center, the National Accreditation Program for Breast Centers, the Society for Surgical Oncology, the Breast Cancer Consortium, and the American College of Surgeons.

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Introduction

In late December 2019, the 2019 novel coronavirus (COVID-19) was identified as the viral etiology for a clustered emergence of pneumonia cases in Wuhan, Hubei, China. Since the initial discovery of this new viral pathogen, its rapid transmission has led to the declaration of a global pandemic. Unfortunately, the United States, at the time of this writing, has the greatest number of confirmed positive coronavirus cases.

In the lessons learned to date, it has become clear that certain subgroups of patients are at higher risk of not only becoming infected with the virus but also suffering severe complications of infection, including patients with a current or past diagnosis of cancer. In a joint collaboration between the National Clinical Research Center for Respiratory Disease and the People's Republic of China, an early prospective evaluation by Liang et al [1] of 2007 positive patients revealed that 1% of COVID-19 patients had a history of cancer, compared with an overall cancer incidence of 0.29% in the Chinese population. The researchers also showed that of these cancer patients, 39.0% suffered a severe event related to their COVID-19 infection compared with a rate of 8.0% in patients with the virus who did not have cancer ($P = .0003$). The authors proposed various strategies to mitigate this risk, one of which recommended "postponing adjuvant chemotherapy or elective surgery for stable cancer." Their recommendations, however, did not include mention of strategies to triage radiotherapy treatments for patients with active cancer.

In addition, subsequent studies addressing COVID-19 infections in cancer patients found parallel results revealing high rates of severe COVID-19 infections (53.6%) and high rates of COVID-19-related mortality in cancer patients (25.0% to 28.6%) [2, 3]. These studies similarly did not provide any recommendation regarding appropriate triaging of patients with active cancer.

Balancing the risk of contracting COVID-19 and developing severe, if not fatal, complications in those with active cancer receiving immunosuppressive therapies against the risk of cancer progression due to treatment delays and increasing limitations in oncology staffing due to illness raises a significant challenge for oncologists, especially for radiation oncologists. This balance remains an ongoing challenge at our institution, the New York Proton Center (NYPC), a large freestanding proton center co-owned by Memorial Sloan Kettering Cancer Center, Montefiore Health System, and Mount Sinai Health System, which is located in New York City (NYC), the epicenter of the pandemic.

As the coronavirus incidence in NYC continues to rise, it has become clear that in order to ensure patient and staff safety, the need to continue active cancer treatments must be weighed against the risk of contracting the COVID-19 infection. Therefore, we implemented a patient prioritization process to triage incoming patient referrals for proton beam radiation therapy (PBT) into (1) patients for whom PBT simulation/treatment could not be delayed, (2) patients for whom PBT simulation/treatment could be safely delayed, and (3) patients for whom a photon-based radiotherapy option or other alternative to PBT was recommended. Of note, we have continued to proceed with all consultations for incoming patient referrals, as these are being completed through telemedicine approaches and through which we apply and refine our prioritization efforts for PBT simulation and treatments at NYPC.

It is important to note that in parallel with triaging patient referrals, our institution has also implemented daily operational and workflow adaptations to optimize the continued safety of our patients while within the center, such as, but not limited to the following: reducing and then eliminating patient visitors; spacing out treatment times; opening additional waiting-room spaces to allow patients to sit >6 feet apart; transitioning to tele-visits for consults, follow-ups, and the large majority of on-treatment visits; and conducting daily screening of all staff and patients for possible concerning symptoms or sick contacts.

Apart from limited existing radiation therapy triage recommendations for patients with prostate or breast cancer, there remains a lack of additional guidance on how best to triage patients being referred for consideration of radiation therapy across disease sites; especially limited are recommendations on triage for PBT. Given that the NYPC had the fastest ramp-up of all proton centers to date and was operating at capacity before the pandemic emerged, in combination with rising numbers of COVID-19 cases in NYC and an increasing number of NYPC staff either COVID-19 positive or quarantined due to high-risk exposure, such a need to triage is particularly critical for NYPC. One important realization from our center's experience is that staff illnesses and subsequent absences began to occur approximately 2 to 3 weeks after the first reported case of COVID-19 in NYC. Therefore, early implementation of a patient triage process can allow appropriate reduction of patient volumes in advance of any staff shortages that may arise a few weeks later. We, therefore, present here our novel approach by which we triage patients to provide guidance for other radiotherapy clinics who are or will need to undergo similar process changes.

Recommendations

Our patient referrals are either (1) self-referral submissions to our in-house intake team from patient calls, provider calls, and web consultation requests or (2) an internal referral submission through our referral management system from Memorial Sloan-Kettering Cancer Center, Mount Sinai Health System, or Montefiore Health System. To expedite the triage process, it was decided that each referral would be evaluated by a small number of physicians, specifically 2 (A.M.C., C.B.S.), to allow for same-day review for all cases and reduce delays that could occur if a larger consortium were to review referrals. Of note, both physicians have extensive and dedicated PBT experience and made their decisions in concert with one another regarding proceeding or not proceeding with simulation and treatment at NYPC.

Factors considered in triaging patients were tumor-related, treatment-related, and patient-related characteristics. These factors and their associated rationale are noted below; this list is not meant to be comprehensive but is intended to discuss factors related to the highest volume referrals received at NYPC since the start of the spread of COVID-19 in NYC.

1. Tumor Characteristics

a. Pathology (see the Table)

i. Benign

1. **Benign Processes** (ie, World Health Organization [WHO] grade 1 meningioma, schwannoma, pituitary adenoma) were delayed for PBT treatment to a later time given their low risk of progression, with each individual physician specifying the preferred duration of delay and required reimaging before PBT simulation.

ii. Malignant

1. **Central Nervous System**—Benign tumor referrals for consideration of PBT were delayed as noted above. Additionally, PBT treatment was delayed for WHO grade II, isocitrate dehydrogenase (IDH) mutant, low-grade gliomas for which observation was deferred. In contrast, we recommended proceeding with PBT treatment without delay for all WHO grade III, IDH mutant tumors. For all WHO grade IV glioblastoma referrals, our recommendation was for photon therapy given the poor long-term prognosis and limited superiority data to date for protons in this population.
2. **Base of Skull (BOS)/Spine/Chordomas**—Unless the pathology of the tumor was benign and/or the patient was having progressive, symptomatic disease, malignant tumors in the BOS/spine region were to proceed without delay to PBT treatment because of their close proximity to critical organs at risk (OARs), likely increased difficulty in adequately treating the tumors if subsequent progression occurred, and the risk of morbidity with progression/recurrence due to delay. Resectable chordomas were recommended for surgery, whenever possible, to optimize the chance of long-term local control and to delay radiotherapy, and thereafter recommended to proceed with PBT treatment without delay given higher rates of control with adjuvant PBT versus salvage PBT if recurrence were to occur [4].
3. **Head and Neck**—Given the dosimetric superiority [5], as well as the lower rates of feeding tube placement, weight loss [6], reduced patient-reported symptom burden [7], and better preservation of quality of life [8] with PBT versus IMRT, PBT treatment for head and neck referrals were generally recommended to proceed without treatment delay, particularly for paranasal sinus, nasal cavity, nasopharyngeal, and oropharyngeal cases.
4. **Lung**—With non-small cell lung cancer (NSCLC), peripheral, unresectable early-stage tumors ≤ 5 cm were recommended to undergo photon-based stereotactic body radiation therapy. For larger tumors (> 5 cm) or those centrally and ultra-centrally located, PBT treatment was recommended. The decision to proceed with PBT treatment with or without delay was dependent on the tumor size, degree of perceived further tumor growth, potential for resultant morbidity, or increased difficulty in sparing OARs with any additional growth as well as accounting for the presence of any features (age > 65 years, underlying cardiopulmonary comorbidities, presence of immunodeficiencies) that portend a higher risk of contracting a COVID-19 infection. PBT treatment without delay was recommended for locally advanced NSCLC and limited-stage small cell lung cancer given concurrent chemotherapy delivery and large treatment volumes, especially for patients with bulky or bilateral nodal involvement [9].
5. **Breast Cancer**—Early-stage node-negative breast cancers were recommended to undergo photon therapy, except for reirradiation partial breast cancer referrals or in local breast cancer recurrences, which, because of their relatively more aggressive pathology and expected higher toxicity profile with photons, were recommended to

Table. Patient triage recommendations per disease site.

	Proceed with proton therapy without delay	Safely delay proton therapy	Recommend photon-based therapy
Benign processes		✓	
Central nervous system	WHO grade III, IDH mutant glioma	WHO grade II, IDH mutant glioma	WHO grade IV glioblastoma
Base of skull/spine	✓		
Chordoma	✓		
Head and neck	✓		
Lung	<ul style="list-style-type: none"> • Peripheral ≥ 5 cm (N0) NSCLC • Central/ultra-central location (can consider delayed PBT for < 3 cm or slow-growing tumors in patients at high risk of contracting COVID-19 infection) • Stage IIb-IIIc NSCLC • Limited stage-small cell 		Peripheral ≤ 5 cm (N0) NSCLC
Breast	<ul style="list-style-type: none"> • Node positive • Reirradiation for in-breast local recurrence 		Early-stage node negative
Gastrointestinal	<ul style="list-style-type: none"> • ≥ 3 cm Hepatobiliary tumors in the dome or centrally location • Local or regionally advanced esophageal cancer 		<ul style="list-style-type: none"> • < 3 cm Hepatobiliary tumors • Caudal and left medial located hepatobiliary tumors
Gynecological	<ul style="list-style-type: none"> • Extended-field pelvic/para-aortic adjuvant radiation therapy (can consider delayed PBT for adjuvant endometrial cases in patients at high risk of contracting COVID-19 infection) • Reirradiation • Gross nodal disease requiring dose escalation (pelvic only or extended field) 		
Prostate		✓	
Pediatrics	✓		
Reirradiation	✓		

Abbreviations: WHO, World Health Organization; IDH, isocitrate dehydrogenase; NSCLC, non-small cell lung cancer; PBT, proton beam radiation therapy; COVID-19, 2019 novel coronavirus.

proceed with PBT treatment without delay [10]. Node-positive cases were recommended to proceed with PBT treatment unless adjuvant chemotherapy was planned, which could allow radiotherapy delay.

- 6. Gastrointestinal**—These were primarily hepatobiliary tumor referrals during this time period. Primary hepatobiliary tumors located in the dome or centrally located and ≥ 3 cm, which due to the dosimetric superiority of PBT in sparing normal liver tissue, were advised to proceed with PBT treatment without delay given risk of progression in the acute setting and resultant morbidity with photon radiotherapy, whereas caudal and left medial tumors and smaller tumors were recommended for photon therapy [11–13]. Similar tumor size and location considerations were given for secondary/metastatic liver tumors, as well as considerations for performance status and life expectancy; patients perceived to have limited prognosis, smaller tumors, or favorable locations were recommended to undergo photon-based radiotherapy. Locally advanced esophageal cancers were prioritized for proton therapy, especially for distal tumors, in light of the potential toxicity reduction for definitive and neoadjuvant radiation therapy when delivered with protons versus photons [14].
- 7. Gynecological**—No referrals were submitted for gynecological cases during the month after the first case of COVID-19 in NYC, but our prioritization process recommends PBT for reirradiation gynecological cases [15] as well as cases requiring dose escalation for gross nodal disease in which OARs sparing cannot be adequately achieved with photon therapy. PBT without delay was also recommended for cases warranting extended field adjuvant radiation therapy, given superior dosimetry to photon radiation therapy [16], with the exception of

endometrial pathology in which delay to PBT can be considered in patients at high risk (age >65 years, underlying cardiopulmonary comorbidities, presence of immunodeficiencies) of contracting a COVID-19 infection.

8. **Prostate**—Patients with very low, low, and favorable intermediate risk were scheduled for a delayed PBT treatment date. Patients with unfavorable intermediate-risk, high-risk, and node-positive prostate cancer were recommended to continue with and extend the duration of pre-radiotherapy androgen deprivation therapy with deferral of PBT treatment for at least 2 to 6 months [17].
9. **Pediatrics**—All nonpalliative pediatric patients, given the extensive literature supporting proton therapy over photon therapy [18–20], were recommended to proceed with PBT treatment without delay.
10. **Reirradiation**—Given the superior dosimetric ability to reduce overlap regions and thereby spare a great volume/number of OARs that previously received radiation dose, reirradiation referrals of definitive intent were cleared without delay to undergo treatment [21–24].

2. Intent of Treatment

- a. **Palliative**—Referrals for patients being treated with palliative intent were advised to undergo photon therapy, with the exception of head and neck Quad Shot, primarily because these cases were reirradiation scenarios for high performance status patients receiving short treatment courses in whom proton radiation therapy has been shown to have low acute toxicity rates with high rates of local control [25, 26].
- b. **Curative**
 - i. Refer to Section a(ii).

3. Treatment Characteristics

- a. **Dose and fractionation (hypofractionation versus conventional fractionation)**
 - i. For all referrals deemed appropriate to move forward without delay for PBT treatment, primary treating physicians were requested to provide hypofractionation alternatives, if applicable, to conventional dosing to reduce treatment days/times at NYPC and, thereby, reduce daily exposure risk to patients and staff. Certain disease sites had applicable hypofractionation schedules, including glioma reirradiation, head and neck Quad Shot, locally advanced node-positive breast, small volume reirradiation thoracic cases, and hepatobiliary tumors.

4. Patient Characteristics:

- a. **Age**
 - i. Children and younger patients were deemed appropriate to undergo PBT, with or without delay to treatment based on their pathology as noted in Section a(ii). Elderly patients for whom reduction in integral dose was not thought to be associated with appreciable or meaningful reductions in acute and/or late toxicities were advised to undergo photon therapy.
- b. **Performance Status/Prognosis**
 - i. Given the association of performance status with overall prognosis, patients with excellent/good performance statuses were considered for PBT, whereas poor performance status patients were advised to consider photon therapy, if radiation therapy was warranted. Additionally, likelihood (2 year or 5 year) rate of control and/or survival for each specific tumor site was considered when deciding between PBT and photon therapy, given the potential for PBT to provide greater benefit for long-term survivors.
- c. **Presence of underlying disease comorbidities that would portend a higher risk of acute and/or late radiotherapy toxicities**
 - i. Interstitial pulmonary fibrosis was present in 1 patient with an underlying early-stage NSCLC that was rapidly growing and not thought suitable for delayed therapy. Given the high risk of toxicity with photon-based hypofractionated thoracic radiation therapy, PBT treatment was recommended [27].

Conclusion

The algorithm presented here remains in active use to date as we continue to triage patients, especially as our center continues to adapt to rapidly increasing NYC community transmission rates and incidence of staff illness due to COVID-19 in what is now the world's epicenter of the pandemic. For those patients advised to proceed with PBT treatment without delay, we further subclassified all patients into (1) those for whom none to very few treatments could be missed, (2) those for whom up to 1 week of treatment could be missed, and (3) those who could miss more than a week of treatment, in the event the center needs to contract its volume due to staff illnesses. Factors considered in this subclassification included tumor repopulation rates as well as risk to adjacent OARs if the tumor were to grow during the break.

We feel strongly that in addition to the aforementioned factors, each radiation oncology center needs to consider the extent of COVID-19 in their community and their overall staffing requirements, personnel availability, and potential shortages when deciding the volume and complexity of patients they are able to continue treating during these dynamic times. We believe some elements of the patient triaging system will likely be required by most proton radiotherapy clinics during the COVID-19 pandemic and can also be generalizable to photon therapy clinics. Additionally, these guidelines can be helpful for proton therapy centers operating close to capacity when under non-COVID-19 conditions. As such, we hope our internal triage workflow, as highlighted in this article, will lay the foundation upon which other centers can create their own unique guidelines during this pandemic.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: The authors have no relevant conflicts of interest to disclose.

Ethical approval: All patient data have been collected under internal review board approved protocol.

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