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Brief Opinion

Practice Considerations for Proton Beam Radiation Therapy of Uveal Melanoma During the Coronavirus Disease Pandemic: Particle Therapy Co-Operative Group Ocular Experience

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Abstract

Uveal melanoma (UM) is a rare but life-threatening cancer of the eye. In light of the coronavirus disease (COVID-19) pandemic, hospitals and proton eye therapy facilities must analyze several factors to ensure appropriate treatment protocols for patients and provider teams. Practice considerations to limit COVID-19 transmission in the proton ocular treatment setting for UM are necessary. The Particle Therapy Co-Operative Group is the largest international community of particle/proton therapy providers. Participating experts have current or former affiliation with the member institutions of the Particle Therapy Co-Operative Group Ocular subcommittee with long-standing high-volume proton ocular programs. The practices reviewed in this document must be taken in conjunction with local hospital procedures, multidisciplinary recommendations, and regional/national guidelines, as each community may have its unique needs, supplies, and protocols. Importantly, as the pandemic evolves, so will the strategies and recommendations. Given the unique circumstances for UM patients, along with indications of potential ophthalmologic transmission as a result of health care providers

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working in close proximity to patients and intrinsic infectious risk from eyelashes, tears, and hair, practice strategies may be adapted to reduce the risk of viral transmission. Certainly, providers and health care systems will continue to examine and provide as safe and effective care as possible for patients in the current environment.

Introduction

Uveal melanoma (UM) threatens patients with loss of vision, a painful eye needing enucleation (ie, amputation), and metastatic disease. Metastases develop in almost 50% of patients, usually involve the liver, and rarely respond to treatment so that most patients die within a year of onset of systemic symptoms. The first choice of ocular treatment is radiation therapy, reserving enucleation for patients with advanced disease.

In light of the current coronavirus disease (COVID-19) pandemic, local hospitals and proton radiation therapy facilities are considering several factors as protocols are developed for ocular oncology patients, including (1) national, regional, and local medical system status and quarantine policies; (2) internal hospital COVID-19 policies; (3) multidisciplinary dialogue among ophthalmology and radiation oncology; and (4) status of protective equipment for patients, staff, and providers.

The American Association of Ophthalmic Oncologists and Pathologists (AAOOP) recently issued guidelines for the management and triage of ocular oncology cases during the COVID-19 pandemic.[1] Certain ocular conditions will require "emergent" care to be performed within 24 hours or as soon as possible to preserve life or sight and "urgent" to be performed within the week, considering the availability of resources. The treatment for uveal melanomas is classified as "semiurgent," that is, needing to be performed within 1 to 2 months, considering the availability of resources. The guidelines also indicate that in some cases, the balance may shift to delayed care being more appropriate for safety and conservation of limited resources.

The AAOOP practice guidelines state the importance of recognizing that there is risk for transmission of severe acute respiratory syndrome coronavirus 2 during patient care, even by asymptomatic individuals. The risk to patients, physicians and staff, and the community at large "must therefore be balanced with the necessity for urgent care." Reports from China indicate potential ophthalmologic transmission as a result of health care providers working in close proximity to patients and intrinsic infectious risk from eyelashes, tears, and hair.[2] In addition, one group noted that a third of their clinically confirmed COVID-19 patients had ocular abnormalities, and these commonly occurred in patients with a more severe form of the disease.[3]

Currently, high-priority patients with cancer are being identified using several factors, to include those (1) who are deemed critical (unstable, unbearable suffering); (2) whose condition is immediately or potentially life-threatening; and (3) who have access to effective treatment. Importantly, given the complexity of ocular oncology care, patient-specific risk factors, and capacity issues, guidelines will need to remain flexible, be revisited, and exceptions will occur.[4,5] Clinicians will certainly have to evaluate patients on a case-by-case basis and balance the potential risk and severity of outcomes, including loss of vision, loss of an eye and systemic disease progression which uniformly leads to risk of death.

Specifically, the UK National Health Service has included as priority level 1 cancer patients with curative therapy with a high (>50%) chance of success with time sensitive therapy. Radiation patients specifically are split into 5 levels, with priority 1 radiation therapy (RT) patients, including those with category 1 (rapidly proliferating) tumors for whom timely curative intent radiation therapy is needed where there is little or no scope for compensation of gaps or treatment delay. Priority level 3 radiation patients include those with category 2 (less aggressive) tumors where RT is the first definitive treatment.[5]

Uveal melanoma meets these high-priority criteria because (1) it is highly lethal, with approximately an overall 50% rate of metastasis[6,7]; (2) outcomes are potentially worse if ocular treatment is delayed[6-8]; and (3) ocular radiation therapy is highly effective at achieving local tumor control (eg, >95% rate of local tumor control after 4 to 5 fractions of proton beam radiation therapy).[6,9,10] Noteworthy, proton eye therapy for UM is delivered with significant hypofractionation (12-15 gray equivalent fractional dose) and thus in full accordance with the recently released radiation therapy guidelines during the pandemic.[11,12]

In this article, we list practice considerations to limit COVID-19 transmission in the proton ocular treatment setting for UM. Participating coauthors have past or current affiliation with member institutions of the Particle Therapy Co-Operative Group Ocular subcommittee with long-standing high-volume proton ocular programs.[13] The below comments do not supersede those of local hospitals and communities, as each of which will have its unique needs and practices, and these may change as the pandemic evolves.

Uveal melanoma proton radiation therapy general practice considerations:

1. **Adhere to clinical guidelines to minimize infectious transmission risk:** Minimize face-to-face

appointments by using telehealth technology and by increasing efficiency when in-person appointments are required. Consider measures to limit waiting room stays (eg, having patients wait outside/in their car and contacting them when they are due to be seen). Follow local protocols on daily symptomatic or temperature screening, testing, and isolation. Minimize additional visitors unless required. Use appropriate personal protective equipment and maintain physical distancing.

2. **Use clinical judgment:** Balance the risk of delayed, suboptimal treatment with the risk of transmission of COVID-19. Consider risk factors for patients who may be predisposed to severe illness due to age, comorbidities, or immunosuppression. Use the RADS principle to minimize risk (Remote, Avoid, Defer, Shorten).[14]
3. **Consider alternatives:** Enucleation, other types of radiation therapy, or surveillance may or may not be appropriate in select cases, depending on operating room, personnel, and equipment availability, tumor and patient factors, physician assessment, type and severity of risk, and so on. In some patients (eg, those with small, genetically favorable tumors or localized iris tumors), outcomes may not be compromised if treatment is delayed until the risk of infection has subsided. For patients who have undergone surgical tantalum clip placement already, clinical consideration must be given to timing of definitive treatment. In addition, if travel or hotel stay for 4 to 5 days treatment course is required for patients, this may or may not be feasible given local conditions and national quarantine policies.[15]

   Importantly, it is not known whether a delay of several months significantly increases any risk of metastasis for an individual patient. This uncertainty exists even when tumor biopsy has been performed, whatever the results of genetic tumor analysis. The risk and benefits of immediate versus delayed treatment need to be communicated with the patient when obtaining informed consent for urgent or deferred therapy.

Regarding specific potential considerations for UM proton beam radiation therapy procedures:

1. **Hypofractionation is already standard practice for UM proton RT** with a total of 4 to 5 fractions delivered in 1 week, hence shortening the window of potential exposure and compliant with current emergency guidelines for RT.[11,12]
2. **Wear protective gear in line with facility guidelines** (ie, gloves, mask, face shield, goggles, hair cover, etc) when in close physical proximity to the patient. Consider local guidelines on proper dress and avoidance of accessories, and so on.
3. **Apply infection precautions when placing eye drops and eyelid retractors.** Contact with ocular mucosa and tears is potentially contagious and technique in handling of drops or retractors should be similar to contact risk precautions for other bodily fluid. If possible, stand to one side of the patient when instilling eye drops or inserting and removing eyelid retractors to limit direct breathing space overlap and fluid exposure.

   Limit team members in immediate vicinity during such procedures. Transpalpebral technique without lid retractors may be appropriate for certain tumors.[16] Conduct appropriate cleaning or disposal of retractors.
4. **Clean immobilization head mask and mask frame thoroughly** with antiseptic and store each mask separately in designated areas or individual bags per hospital guidelines. The treatment chair and parts of the machinery as well may require appropriate cleaning/disposable coverings as per hospital guidelines.
5. **Clean bite blocks thoroughly or consider alternatives** (ie, as may be done with claustrophobic patients). A chin rest (similar to that used for a slit lamp examination) or chin strap may be an option to minimize salivary fluid and maximize positioning, reproducibility, and cleaning. Close attention must be paid to daily set-up and proton beam safety margins can be increased to avoid geographic miss as needed. Bite blocks should be handled with proper precautions in placement or removal and cleaned thoroughly after each fraction if or when used.
6. **Limit physical aperture adjustments** by considering an increased margin (~0.5-1 mm) in advance to avoid any potential adjustments for materials in close contact with the patient. All materials must be disinfected per facility guidelines, especially if transferred between team members and clinic-work areas.
7. **Follow masking policy,** which varies between centers. If resources allow, masks may be worn both by the patient being treated and by any staff who may come into close contact with each other and with machinery. Masks may need to be stored, cleaned, or reused if supply is limited. Follow hospital and national guidelines on proper surgical mask or N95/FFP2 respirator use for ophthalmic procedures based on exposure risk and supplies.[2,17]
8. **Sanitize** the patient's hands before set-up and entry, ideally upon arrival to the treatment

environment or within the treatment room as per local supplies and guidelines. Staff must also sanitize their own hands between patient setups, according to local protocols. Plan additional time per patient to allow proper sanitization.

9. **Organize clinic flow** to maximize distance between providers and team members to enhance efficiency, thereby minimizing patient time in clinic. Limit the number of staff involved with direct patient contact and optimize teams to minimize number at risk at any time.
10. **Consider testing** patients as per hospital guidelines and supplies availability. For patients testing positive for severe acute respiratory syndrome coronavirus 2, it may be most appropriate to delay proton eye treatment within the appropriate clinical window until negative testing status is confirmed to reduce risk to patients and the provider team. If or when antibody serology testing becomes available, provider teams may be tested per local guidelines and appropriate staffing decisions can be made. If a COVID + patient must be treated, follow hospital guidelines regarding timing, personal protective equipment (PPE), and protocols to separate the circuit of COVID + patients (ie, isolated path, end of day treatment, trained team in PPE, etc).
11. **Iris tumors:** Treatment of select iris melanomas with radiation therapy may be nonurgent and delayed for 2 to 3 months.[1] Some iris tumors may be urgent, especially if there is rapid growth or secondary glaucoma, and will require physician assessment to determine degree of urgency. Iris melanomas with secondary glaucoma could be due to a ring melanoma and enucleation may be the recommended treatment based on current or local circumstances and would require the appropriate ophthalmic assessment.
12. **Other ocular tumors:** Conjunctival tumors, angiomas, hemangiomas, metastatic ocular disease, and other ocular conditions should be evaluated separately to determine best safe and effective course of action per AAOOP, multidisciplinary, and other appropriate guidelines.

If tantalum ring surgery is not possible due to limited operating room facilities, there may be a limited role under special circumstances for "clipless" planning (as is done with some benign conditions, such as hemangiomas).[18] Safety margins are increased to ensure adequate treatment of the entire tumor, and additional imaging may be beneficial.[19] This is not standard of care, and if this strategy is pursued the provider team must use appropriate clinical judgment and ensure appropriate discussion and documentation of potential tumor control, visual, or other toxicity outcomes. The risks and benefits of these measures should be fully discussed with patients to ensure informed consent. Limited operating room time may also affect availability of other alternatives such as enucleation, plaque therapy, or endoresection.

The COVID-19 pandemic is a fluid situation and current best practices and institutional guidelines may need to be adjusted as resources may become limited, personnel may be on quarantine or sick leave, and different scenarios are observed.[20-24] Given the unique potential for viral spread in ophthalmology procedures and the fact that hypofractionated proton eye treatment is delivered over only 1 week, thoughtful clinical practices are essential during this pandemic and should be considered carefully. Certainly, providers and hospital systems on the front lines will continue to examine and provide as safe and effective care as possible for patients in the current environment.

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