Pseudoprogression in low-grade glioma

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Pseudoprogression (PsP) is a common phenomenon seen after radiotherapy (RT) for primary brain tumors. PsP is a post-treatment related effect that is identified by increased enhancement on T1-weighted MRI, or increased hyperintensity on T2/FLAIR, with subsequent stabilization or resolution without any intervention. This imaging finding may or may not be accompanied by clinical symptoms, and the timing of this phenomenon is thought to be subacute, or in the initial 3–6 months post-treatment. The mechanism of PsP is unclear but proposed to be due to treatment-induced endothelial cell death and subsequent disruption of the blood-brain barrier; this alteration in the blood-brain barrier contributes to the increased uptake of gadolinium seen on MRI and vasogenic edema on T2/FLAIR (1). PsP can be thought of as being on a spectrum of post-treatment effects that include mild, transient imaging changes not concerning for progression, PsP, or radiation necrosis.

PsP after treatment with RT is an entity that has been well-documented in the context of high-grade glioma and glioblastoma—being noted as early as 1979 based on CT and clinical exam (2,3). In recent years, there has been a significant increase in reports of PsP, attributable to a number of factors, including improved imaging technology to detect, the increased use of chemotherapy, RT dose escalation, and the use of advanced RT modalities such as protons. While the majority of this data has pertained to high grade gliomas, more recently has it become an area reported in the context of low-grade gliomas (LGG). PsP is of particular importance as it presents challenges in diagnosis and management; incorrect diagnosis as true tumor progression could lead to unnecessary treatment and toxicity.

The criteria that define PsP have not been well-established and most articles on PsP in LGG vary in the criteria they use to define it. These differences include definition of baseline comparison (pre-RT *vs.* initial post-RT scan), definition of time points (i.e., must occur within 12 weeks of treatment, within 12 months of treatment, etc.), but also differences in defining imaging criteria—such as type of imaging changes seen (i.e., T2/FLAIR and/or enhancement on T1 with gadolinium), measurement technique (i.e., bidimensional or volumetric, inclusion of solid tumor or cystic components, etc.), and size increase threshold (i.e., 5%, 10%, etc.). Additionally, the presence of clinical symptoms is sometimes an inclusion factor in the definition of PsP. In defining true disease progression, the Response Assessment in Neuro-Oncology (RANO) criteria include the use of bidimensional measurements, and the use of T2/FLAIR assessment; they also limit the time frame to ≥12 weeks after chemoradiotherapy unless a new lesion is outside the radiation field, and have a size increase of ≥25% (4). Neither the RANO group nor the ongoing NRG Oncology study of LGG, BN005, have a standard definition for PsP. *Table 1* summarizes the various definitions of PsP among published studies of LGG patients.

In the study by Ludmir *et al.*, the authors define PsP using the bidirectional product of solid tumor, a percentile growth minimum of 5%, and stability or decrease in size for at least 12 months (5). Importantly, they incorporated presence of symptoms into their definition. Clinical symptoms with subsequent spontaneous shrinkage was defined as symptomatic PsP, whereas symptoms with persistent or progressive growth were scored as progression.

Table 1 Criteria included in definitions of pseudoprogression in low-grade glioma studies

Patient population	Study	Enhancement only	New enhancement or increase in size	Bidimensional or volumetric	Size increase cutoff	Solid or cystic (for pilocytic astrocytoma)	Comparison (pre-RT vs. initial post-RT)	Stabilization and/or regression	Time frame required for definition PsP	Symptomatic alone as criteria for PsP
Pediatric	Ludmir et al. 2019 (present study)	No	Increase in size	Bidimensional	5%	Solid only	Pre-RT	Stabilization or reduction	Within 12 months post-completion of RT	No
	Indelicato et al. 2019	No	Both	–	–	–	–	Spontaneously resolves	No	No
	Tsang et al. 2017	No	Increase in size	Bidimensional	10%	Cystic growth only rather than solid	2–3 consecutive evaluations	Stabilization or reduction	No	No
	Mannina et al. 2016	No	Increase in size	Volumetric	–	–	Pre-RT	Regression	No	No
	Naftel et al. 2015	No	Both	Bidimensional	–	Cysts were included	Pre-RT	Stabilization or regression	No	No
	Dworkin et al. 2019	No	Both	Volumetric	40% (equivalent to 25% bidimensional)	–	Pre-RT	Stabilization or regression	No	No
Adult	Bronk et al. 2017	Yes	New	–	–	–	–	Stabilization or regression	Within 6 months post-completion of RT	No
	Van West et al. 2017	Yes	New	–	–	–	–	Stabilization for at least 1 year or regression	No	–
	Lin et al. 2016	Yes	New	–	–	–	–	Stabilization or regression	Within 6 months post-completion of RT	No
	RANO 2010 (HGG)	Yes	New	–	–	–	Pre-RT		Within 12 weeks post-completion of RT	No

–, not stated; RT, radiotherapy; HGG, high-grade glioma.

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They also note that cystic enlargement alone is not included in their definition of PsP. This is in contrast other studies in which cystic enlargement alone met criteria for PsP (6,7). This has potential to impact the PsP incidence particularly in patients with pilocytic astrocytoma (PA). These nuances in the definition of PsP limit the ability to compare rates of PsP across different studies and highlight the importance of adoption of a universal definition whether used in clinical or investigational discussions. Further to this point, a recent systematic review attempted to analyze the PsP rates for proton vs photon in LGG using the published data; however, the variable definitions of PsP across studies limited the interpretation of data (8).

There are a number of factors that are thought to influence the development of PsP in LGG, including radiation modality, radiation dose and volume, the use of chemotherapy—particularly temozolomide—tumor histology and genetics, as well as individual patient and tissue sensitivity. There is a complicated interplay between all these factors that promotes the development of PsP.

In this study, the authors document their experience of PsP in pediatric patients with low-grade glioma, specifically commenting on the difference between proton and photon RT. They found a PsP rate of 37% in their entire cohort of 83 pediatric LGG patients. PsP developed in 45% of their patients treated with proton therapy as compared to 25% of patients who received intensity-modulated radiotherapy (IMRT). Other factors that were predictive for PsP on univariate analysis were histology and RT dose. RT modality and RT dose were the only remaining significant factors on multivariate analysis.

These findings are the first report comparing IMRT and proton therapy in the pediatric LGG population. The incidence of PsP in the proton therapy cohort of this study is higher when compared to other pediatric proton therapy reports. The proton therapy cohort had a lower proportion of patients with PA compared to the IMRT group; they also found lower rates of PsP in patients with PA which is in contrast with other reports where PA patients have higher rates of PsP (6,7,9). The explanation for this discrepancy is that the definition of PsP used in this study differs from prior studies. This illustrates how the difference in PsP definitions across studies impede direct comparisons. Overall, these data suggest that proton RT may be a risk factor in the development of PsP in pediatric LGG.

There are several aspects of proton therapy that could explain an increased rate of PsP. First is the relative biological effectiveness (RBE) and linear energy transfer (LET) which these authors mention. Numerous *in vivo* and *in vitro* studies have addressed RBE of passively scattered protons and have demonstrated that RBE increases with increasing depth along the spread-out Bragg peak (SOBP), the greatest increase being at the distal edge of the beam (10-12). While there is still some degree of uncertainty in the RBE of protons relative to photons, the currently used RBE of 1.1 provides an adequate estimation with the understanding that the RBE increases significantly at the distal edge of the beam. It would be valuable to know if the areas of PsP reported in the proton patients of this study correspond to the distal edges of the proton beams used for treatment.

Radiation dose was a significant factor for the development of PsP on multivariate analysis in this study. Patients who received a dose of >50.4 Gy(RBE) were found to have higher rates of PsP compared with those who received ≤50.4 Gy(RBE). Whether 50.4 Gy(RBE) is a critical threshold for PsP is questionable given the small number of patients who received >50.4 Gy(RBE) in each cohort (8 and 5 in the IMRT and proton arms, respectively). Biologically, the effect of doses <60 Gy at standard fractionation on the vasculature is minimal and the differences between >50.4 and ≤50.4 Gy is expected to be small given the range of doses used in the study. Typically, PsP is seen more with doses approaching 60 Gy and above (1). Additionally, in the adult population receiving proton therapy, radiation dose was predictive of PsP on univariate analysis but did not remain significant upon multivariate analysis (13).

The effect of chemotherapy on PsP is difficult to elucidate from the pediatric data given that 30–40% of pediatric patients have chemotherapy prior to radiation therapy, and that there is significant variability in the agents received and number of different drugs that range in radiation sensitization. Studies that have evaluated the impact of chemotherapy on PsP development in the pediatric population have not found it to be a significant factor (5-7,9,14). In adults, the receipt of chemotherapy—particularly temozolomide—harbors increased risk for PsP (13,15,16). The same study of adult proton LGG patients found that receipt of adjuvant temozolomide was significantly associated with PsP on multivariate analysis (13).

Histology and tumor genetics play a central role in the discussion of PsP. While histology is more widely recognized in pediatric tumors, specifically the relationship of PA and PsP (6,7), genetic factors are reported more in adult tumors. MGMT promoter methylation and IDH1

mutation have predictive effect of developing PsP in glioblastoma; however, the same has not been demonstrated in LGG. 1p/19q codeletion has favorable prognostic significance in LGG with lower rates of PsP in photon-based treatment (17) and no particular association following proton therapy (13,16).

Pediatric studies have specifically investigated the impact of PA histology on the development of PsP, with early reports showing higher rates of PsP in the PA patients (6,7). In the present study, the incidence of PsP in the PA patients of 28% was not significantly higher than other histologies.

The increased prevalence of PsP presents a challenging clinical problem in terms of diagnosis and management, but also in conveying the information to patients. Currently, the best understanding of PsP is that it is a treatment-related effect that the current state of imaging is often unable to distinguish from tumor progression. This conundrum is not unique in medical imaging and is similar to treatment effect in other areas of the body such as the lung, where radiation treatment fibrosis can obscure differentiating underlying tumor progression. While the challenge in interpreting imaging findings can be frustrating, it provides an opportunity for the clinician to rely on the first principles of medicine by focusing on one's assessment of the patient's clinical status. In the presence of imaging findings suggestive of treatment effect with a patient who is asymptomatic, observation is likely the best option; if there are mild symptoms, consider conservative measures such as short course steroids and reassessment of the patient. Finally, if patient has modest imaging findings but clinically decompensating after conservative measures, the clinician would be prudent to investigate for other etiologies aside from PsP.

With ongoing investigation into this topic, we can expect more clarity in the phenomenon of PsP in the future. For the current management of this treatment-related effect, taking the entire clinical scenario into account, especially the patient's clinical status, remains the most important tool to help best care for our patients.

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