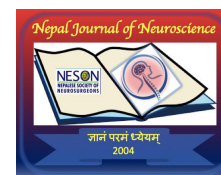


When Genomics Meets the Bragg Peak: Precision Proton Therapy for 1p/19q Co-Deleted Oligodendroglioma

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To the Editor,

Oligodendrogliomas are infiltrative primary glial tumors of the central nervous system that demonstrate a slow-growing clinical course. Accounting for 3-5 % of all the intracranial CNS tumors, with approximately 350 patients diagnosed each year in the UK, they typically present in younger individuals¹. Among various recurrent molecular alterations, IDH mutation and 1p/19q co-deletion make up the majority of the cases, and these markers carry diagnostic as well as prognostic value to guide towards different treatment modalities. Tumors with 1p/19q co-deletion have a better prognosis and take longer to progress from benign to malignant². While multimodal management begins with surgery, emerging radio-genomics strategies aim to precisely target tumor biology with Proton Beam Therapy (PBT), a promising yet underexplored modality.

Proton Beam Therapy is an emerging radiotherapy modality that uses high-energy protons to selectively target malignant cells while causing minimal damage to the surrounding cells, thereby preserving anatomical integrity due to their unique physical property known as the Bragg Peak effect. These physical characteristics significantly reduces long term neurocognitive and neuroendocrine side effects. Despite

these advantages, 1p/19q co-deletion may predict a different biological response to PBT². 1p/19q co-deletion may serve as a potential biomarker of intrinsic hypersensitivity to proton beam therapy, supporting further investigations for radio-genomics guided treatment selection.

According to clinical data, 1p/19q is a definitive marker for radiation response. In a homogeneous group with 1p/19q co-deleted tumor, there was a significant reduction in the progression risk for WHO grade 2 tumors with radiotherapy (hazard ratio <0.01 and p=0.01). Similarly, in aggressive grade 3 tumors, radiochemotherapy was associated with stability (p=0.02; HR=0.09), proving its hypersensitivity to Proton Beam Therapy (PBT)³. PBT has shown exceptional survival rates in patients with co-deleted tumors. McNamara et al. (2017) reported a 5-year overall survival rate of 91%, with grade 3 cohorts reaching 96%. Because these patients live significantly longer, radiotherapy was postponed for about 34.7 to 41.2 months to avoid neurocognitive decline. Bragg Peak of proton beams was used, which allowed exploitation of this tumor's sensitivity while protecting the healthy brain tissue of these long-term survivors⁴.

Although there is clinical superiority of the "Bragg Peak" in sparing healthy brain tissue, there is a large infrastructure requirement with limited availability and high capital cost. The infrastructure needed for PBT includes machines like a cyclotron and a proton therapy gantry, which are mostly available in specialized cancer centers, which means that most 1p/19q patients do not live within a feasible distance of a treatment center. This creates a geographic barrier where the delivery of "radio-genomic" precision is determined more by a patient's proximity to a specialized cancer center than by their molecular eligibility. Furthermore, Insurers refuse coverage for PBT due to the lack of large randomized trials. This creates a paradox for patients with 1p/19q Co-deletion, as a therapy designed to protect long-term cognitive function remains financially inaccessible⁵.

The 1p/19q co-deletion makes radiation therapy genotype-specific, preserving the healthy tissue and protecting cognition. To make this radio-genomic advantage widely available, several actions are needed. There should be development of compact

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single-room systems to improve geographic equity. Moreover, multi-institutional prospective registries focusing on long-term neurocognitive outcomes are needed. In addition, treatment plans should adjust doses based on tumor genotype to reduce brain radiation.

Competing Interests

The authors declare that they have no competing interests relevant to this manuscript.

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