**Case 10: Exploring the Role of Resection Post-Radiation Therapy in Gliomas**

A 45-year-old man was incidentally found to have a T2 hyperintense expansile anterior right frontal lobe mass during evaluation for pansinusitis. The patient underwent craniotomy with partial resection of the T2 hyperintense mass with pathology consistent with a diffuse World Health Organization grade 2 glioma, positive IDH1 mutation and 1p/q19 codeletion. The treatment team deferred completion resection. They proceeded with conventionally fractionated radiation therapy (54 Gy in 1.8 Gy daily fractions) with concurrent and adjuvant temozolomide recommended per CATNON and RTOG 9802. After 5 of 12 cycles of adjuvant temozolomide, post-chemoradiation magnetic resonance imaging was notable for a decreased expansile T2/FLAIR mass and persistent diffuse signal abnormality in the right frontal lobe. The patient's case was reviewed for a second opinion on maximally completion resection.

**Expert 1: Patience Is a Virtue**

The imaging findings described after completion of concurrent chemoradiation and part of maintenance temozolomide (TMZ) overall suggest a decreased tumor burden but with some persistent signal abnormality, possibly representing residual or recurrent disease. Despite these findings, our recommendation would be continued observation with completion of scheduled maintenance TMZ. This patient fits the most favorable molecular cohort in Radiation Therapy Oncology Group (RTOG)-9802 with isocitrate dehydrogenase (IDH) mutation and 1p/19q codeletion and, although the lack of upfront gross total resection (GTR) is suboptimal, the majority of patients (90%) in RTOG-9802 did not have a GTR. Post hoc analysis of RTOG-9802 showed excellent outcomes in patients with IDHmut/1p19q codeletion, showing a 5-year progression-free survival of nearly 90% for this cohort. Therefore, early failure would be unlikely, and given the proven survival advantage of adjuvant chemotherapy, completion of the remainder of the planned TMZ is warranted.

If significant concern remained, we would recommend additional imaging with either magnetic resonance perfusion or positron emission tomography/magnetic resonance imaging to discern possible pseudoprogression (seen in approximately 20% of patients with low-grade glioma) from actual progression. Washington University reported their experience with patients with low-grade glioma with suspected progression, and 90% of suspicious findings ultimately were found to be pseudoprogression. Of the 10 patients in their cohort who ultimately underwent surgery for reresection for progression, 80% had treatment effect with no evidence of residual or recurrent tumor. In lieu of clear evidence of progression (eg, new symptoms or radiographic evidence of progression on serial imaging), we would be hesitant to pursue surgical intervention because this would likely be low yield and without clear benefit to the patient.

**Expert 2: Back to the OR**

Low-grade gliomas (LGGs) represent an important source of morbidity and mortality in young adults. Upfront maximal safe resection is the standard of care, with adjuvant therapy used in high-risk patients. The association of molecular markers (IDH, ATRX, 1p/19q) and histology is used to stratify tumors into molecular subgroups. The 45-year-old patient highlighted had a World Health Organization grade 2, IDH-mutated, 1p/19q codeleted glioma. Such patients invariably recur in the surgical cavity, and indeed, studies demonstrate that resection extent correlates with progression-free survival and overall survival (OS). Unfortunately, this patient did not receive initial gross total resection and immediately proceeded with adjuvant chemoradiation and temozolomide. Follow-up imaging demonstrated persistent disease in the right frontal lobe.

The question posed was whether further surgery should be employed. A retrospective study of 52 patients with recurrent LGG by Ramakrishna et al found that the presence of any residual tumor after (first or second) surgery was associated with decreased OS. They also found that the use of upfront radiation and pathology at recurrence affected OS. With respect to progression-free survival after a surgically treated recurrence, significant differences were observed with higher grade tumors, extent of resection at time of first recurrence, residual disease after first operation, resectability, and Karnofsky performance status score. Such data and others highlight that patients with recurrent LGG are likely to benefit from additional surgery. Notably, such patients had low risk of surgical complications, performance status decrements, or neurologic sequelae. Thus, we would enthusiastically support reresection.

**Expert 3: Just Because You Can Does Not Mean That You Should…**

The optimal management of patients with low-grade glioma remains controversial. There currently are no randomized studies addressing the question of re-resection after adjuvant chemotherapy and radiation therapy (RT) for patients with glioma, World Health Organization grade 2, IDH1-mutant, 1p/19q codeletion, known as molecular oligodendroglioma, following initial subtotal resection. These patients typically have a long expected survival and good prognosis.

The first rationale for re-resection is to prevent the residual mass from acting as a source for malignant transformation (MT) to a high-grade glioma. However, the suggestion that RT results in MT has not been supported by data from the European Organization for Research and Treatment of Cancer 22845 (“nonbelievers”) trial, where both arms (early vs delayed RT) had similar rates of MT (approximately 70% at re-resection).1 Evidence suggests that chemotherapy, particularly temozolomide, contributes to MT. As such, our and other institutions typically would recommend treatment according to Radiation Therapy Oncology Group 9802, with sequential RT and procarbazine, lomustine, and vincristine rather than temozolomide. Whether early reresection limits the risk of MT in patients is currently uncertain.

Other reasons for re-resection do not apply to this patient. This patient is asymptomatic, but one would recommend re-resection for other patients when the residual tumor causes mass effect, symptoms such as refractory seizures, and/or herniation. Additionally, re-resection would be performed to avoid adjuvant treatment altogether in cases in which resection would not result in unacceptable neurologic deficit and would render the patient low risk by Radiation Therapy Oncology Group 9802 criteria (<40 years old and with gross total resection).

Re-resection of this right frontal tumor5 would be technically feasible. The benefits of such surgery, however, are unclear. Just because one can, does not mean one should. I would recommend continued serial observation for this patient.

ChatGPT’s initial recommendation

**Expert 4: Surgical Reevaluation and Adjuvant Therapy**

Based on the available information, our recommendation for this patient would be to consider a multidisciplinary approach that includes a thorough reevaluation of the possibility of maximal safe resection of the residual tumor, followed by continuing adjuvant temozolomide, and potentially the addition of tumor-treating fields (TTF) if deemed appropriate. This recommendation is based on the following reasoning:

1. Maximal safe resection: The patient initially underwent partial resection of the tumor, and the treatment team deferred completion resection. However, given the decrease in the expansile T2/FLAIR mass after chemoradiation, it may be worth reevaluating the feasibility of achieving a more complete resection. Maximal safe resection of low-grade gliomas has been associated with improved overall survival and progression-free survival in multiple studies. If the multidisciplinary team, including a neurosurgeon, deems it safe and feasible, this could be a beneficial step for the patient.
2. Continuing adjuvant temozolomide: The patient is currently on their 5th cycle of adjuvant temozolomide, which is in line with the treatment recommendations from the CATNON and RTOG 9802 trials. These trials demonstrated that adding temozolomide to radiation therapy in patients with grade 2 gliomas and specific molecular markers, such as IDH1 mutation and 1p/19q codeletion, led to improved overall survival. Given the patient's positive response to treatment so far, it would be reasonable to continue with the remaining cycles of adjuvant temozolomide.
3. Consideration of tumor-treating fields (TTF): TTF is a novel treatment modality that uses low-intensity, alternating electric fields to disrupt cell division in cancer cells. In the EF-14 trial, the addition of TTF to maintenance temozolomide was shown to improve overall survival and progression-free survival in patients with newly diagnosed glioblastoma. While the trial specifically focused on glioblastoma, TTF may still be considered as a potential therapeutic option for patients with grade 2 gliomas, particularly if the multidisciplinary team believes it could be beneficial in this specific case.

ChatGPT’s revised recommendation after seeing other human experts’ recommendations

**Expert 5: Observation and Surgical Consideration**

The optimal management of patients with low-grade gliomas can be challenging, and the approach should be tailored to each patient's individual case. In the current situation, we recommend the following therapeutic approach:

* Continue with observation and complete the scheduled maintenance temozolomide, as the patient has favorable molecular markers and has shown a decrease in the tumor burden after chemoradiation. This prioritizes the completion of the ongoing adjuvant therapy.
* Reevaluate the possibility of maximal safe resection of the residual tumor, involving a multidisciplinary team, including a neurosurgeon. This consideration takes into account the patient's good Karnofsky performance status and the potential benefits of achieving a more complete resection, which has been shown to correlate with progression-free survival and overall survival.
* While not a primary focus in this recommendation, the potential addition of tumor-treating fields (TTF) could be considered as an option for discussion within the multidisciplinary team, depending on the patient's response to treatment and the latest evidence supporting its use in grade 2 gliomas.

This balanced approach aims to ensure the patient receives the planned and proven effective adjuvant therapy while also considering the potential benefits of maximal safe resection if deemed appropriate by the multidisciplinary team.