Pseudoprogression

see Glioblastoma Pseudoprogression.

see also Pseudoprogression in Intracranial Metastases.

A purely radiological diagnosis of recurrence or progression can be hampered by flaws induced by pseudoprogression, pseudoresponse, or radionecrosis.

Pseudoprogression (psPD) refers to an increase in size or appearance of new areas of MRI contrast enhancement soon after completing chemoradiation. The term is largely used in brain tumours imaging follow-up, especially for high grade gliomas (e.g. glioblastoma), when observed after chemotherapy and radiotherapy treatment (in about 30% of patients submitted to these therapy) or after just radiotherapy treatment (in about 15%).

Brain post-radiation treatment effects can be divided into pseudoprogression and radiation induced necrosis.

Chemoradiotherapy followed by monthly temozolomide (TMZ) is the standard of care for patients with glioblastoma multiforme (GBM). Case reports have identified GBM patients who experienced transient radiological deterioration after concurrent chemoradiotherapy which stabilized or resolved after additional cycles of adjuvant TMZ, a phenomenon known as radiographic pseudoprogression. Little is known about the natural history of radiographic pseudoprogression.

Terminology

Due to a overlap between the definitions of both pseudoprogression and radiation necrosis, it is not incorrect to say that pseudoprogression represents a mild and self-limiting variant of treatment-related necrosis.

Currently the most reliable and robust criteria for disease progression are the Response Assessment in Neurooncology (RANO) 2D criteria established in 2010, updated from the earlier established McDonald criteria.

In particular, the newly recognized phenomenon of PsP (the transient treatment-related increase of contrast enhancement suggestive of tumor progression) and pseudoresponse (the early and rapid decrease of contrast enhancement without a true tumoricidal effect) are addressed in the RANO criteria. This pseudoresponse is most likely related to the introduction of TMZ and antiangiogenic targeted therapies in treatment protocols.

Epidemiology

In almost 60% of cases pseudoprogression occurs within the first 3 months after completing treatment, but it may occur from the first few weeks to 6 months after treatment.

PsP can develop after radiotherapy alone but more frequently is present after concomitant radiotherapy and TMZ with occurrence in up to 30% of patients, especially those with O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation.

Clinical presentation

Pseudoprogression can be observed in a context with or without clinical deterioration. However, it is
asymptomatic in most patients.

**Pathology**

It is related to endothelial damage and consequent tissue hypoxia observed after treatment and it has an early occurrence (~60%), usually in the first 3 months after the treatment, but it may occur from the first few weeks to 6 months after treatment.

**Impact of extent of resection**

MGMT status and extent of resection EOR have a significant impact on psPD. **Gross total resection** (GTR) can reduce the side effects of psPD and prolong survival.

**Diagnosis**

With conventional MRI, recurrences often have similar radiologic characteristics as therapy-related changes such as pseudoprogression (PsP) or radionecrosis, and its mutual differentiation remains challenging.

Modern multiparametric MRI techniques such as diffusion weighted imaging (DWI) with apparent diffusion coefficient (ADC) mapping, dynamic susceptibility weighted contrast enhanced perfusion imaging, and MR spectroscopy (MRS) allow a much deeper and still noninvasive insight into interpretation of brain lesions, resulting in greater specificity of diagnostic imaging, especially in combination with PET with radiolabeled aminoacid.

However, in routine practice, availability of advanced MRI as well as PET methods is limited with exception of DWI/ADC and MRS. DWI reflects changes in water diffusion as a result of changed tissue microarchitecture due to tumor infiltration and can be quantitatively assessed with the ADC. MRS enables noninvasive examination of the spatial distribution of multiple metabolite concentrations in normal and pathological tissues.

ADC mean values \( \leq 1300 \times 10^{-6} \text{ mm}^2/\text{s} \) and tCho/tNAA ratio \( \geq 1.4 \) are strongly associated with differentiating GBM recurrence from treatment-related changes indicative of PsP.

Institutional validation of cut-off values obtained from advanced MRI methods is warranted not only for diagnosis of GBM recurrence, but also as enrollment criteria in salvage clinical trials and for reporting of outcomes of initial treatment.

Surgical sampling and histologic review of MRI changes after chemoRT may not serve as a gold standard to distinguish psPD from true progression in GBM patients. Refinement of the histological criteria, careful intraoperative selection of regions of interest and advanced imaging modalities are needed for early differentiation of PsPD from progression to guide clinical management.

**Dynamic susceptibility weighted contrast enhanced perfusion imaging**

Patients with pseudoprogression (n = 13) had Vp (mean) = 2.4 and Vp (90 %tile) = 3.2; and Ktrans (mean) = 3.5 and Ktrans (90 %tile) = 4.2. Patients with tumor progression (n = 24) had Vp (mean) = 5.3 and Vp (90 %tile) = 6.6; and Ktrans (mean) = 7.4 and Ktrans (90 %tile) = 9.1. Compared with tumor progression, pseudoprogression demonstrated lower Vp perfusion values \( p = 0.0002 \) with a Vp (mean) cutoff <3.7 yielding 85 % sensitivity and 79 % specificity for pseudoprogression. Ktrans (mean) of >3.6 had a 69 % sensitivity and 79 % specificity for disease progression. DCE MRI shows lower plasma volume and time dependent leakage constant values in pseudoprogression than in...
tumor progression. A cut-off value with high sensitivity for pseudoprogression can be applied to aid in interpretation of DCE MRI 12).

**Differential diagnosis**

**Tumor progression**

**Radionecrosis**

**Case series**

Of 43 evaluable patients, 25 (58%) exhibited radiographic progression on the first MRI after concurrent treatment. Twenty of these went on to receive adjuvant TMZ, and subsequent investigation demonstrated radiographic pseudoprogression in 10 cases (50%). Median survival (MS) was better in patients with pseudoprogression (MS 14.5 months) compared to those with true radiologic progression (MS 9.1 months, p=0.025). The MS of patients with pseudoprogression was similar to those who stabilized/responded during concurrent treatment (p=0.31). Neither the extent of the initial resection nor dexamethasone dosing was associated with pseudoprogression.

These data suggest that physicians should continue adjuvant TMZ in GBM patients when early MRI scans show evidence of progression following concurrent chemoradiotherapy, as up to 50% of these patients will experience radiologic stability or improvement in subsequent treatment cycles 13).


