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# Clinical Relevance of Steroid Use in Neuro-Oncology

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**Abstract**
*Background* Corticosteroids are commonly used in the management of primary central nervous system (CNS) tumors and CNS metastases to treat cancer- and treatment-related cerebral edema and improve neurologic function. However, they are also associated with significant morbidity and mortality, given their wide range of adverse effects.
*Purpose of Review* To review the mechanism of action, pharmacology, and toxicity profile of corticosteroids and to critically appraise the evidence that supports their use in neuro-oncologic practice based on the latest scientific and clinical data.
*Recent Findings* Recent data suggest that corticosteroids may negatively impact survival in glioma patients. In addition, corticosteroids should be incorporated as a standard criterion to assess a patient's clinical and radiographic response to treatment.
*Summary* Corticosteroids should be used judiciously in neuro-oncologic patients, given the potential deleterious effects on clinical outcome and patient survival. Anti-angiogenic agents, which lack these adverse effects, may be a reasonable alternative to corticosteroids.

**Keywords** Brain tumor · Brain metastases · Corticosteroids · Steroids · Cerebral edema · Response assessment

## Introduction

Corticosteroids are widely used in the field of neuro-oncology in conjunction with chemo- and radiation therapy and in the peri- and post-operative setting. The primary purpose is to manage cancer- and treatment-associated cerebral edema and to improve neurologic deficits. Their first documented use to treat vasogenic edema was in 1952 when four pediatric patients with craniopharyngiomas received cortisone postoperatively [1]. Five years later, Kofman et al. reported significant transient neurologic improvement in patients with brain metastases who were treated with prednisolone [2]. Dexamethasone was subsequently shown to effectively decrease brain tumor-associated edema in 1961 [3] and has since become the mainstay of therapy for cerebral edema in brain tumor patients. In addition to their ability to reduce cerebral edema, corticosteroids can alleviate nausea and pain and enhance appetite and mood, all of which are desirable effects in cancer patients [4].

This review will provide an overview of the molecular effects and pharmacology of corticosteroids, their toxicity profile, and the implications of corticosteroid use on the interpretation of imaging findings in neuro-oncologic patients. We will particularly focus on dexamethasone, given its widespread use in neuro-oncology, and review recent insights into the potentially detrimental effects of corticosteroids on survival in glioma patients.

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## Mechanism of Action and Pharmacology of Corticosteroids

### Mechanism of Action

Corticosteroids exert their effects through genomic and non-genomic mechanisms. Genomic effects occur over hours, days, or years and are mediated via mRNA transcription and translation [5, 6]. Examples of genomic effects include their anti-inflammatory and immunosuppressive effects (e.g., activation of anti-inflammatory cytokines), metabolic effects (e.g., gluconeogenesis), and suppression of the hypothalamic-pituitary-adrenal (HPA) axis and osteocalcin [5]. Non-genomic mechanisms have a much more rapid onset of action (seconds or minutes), do not involve gene transcription or translation [5, 6], and are mediated through interactions with a receptor (specific) or in the absence of a receptor (non-specific). For instance, specific non-genomic effects include induction of inositol triphosphate ($IP_3$), $Ca^{2+}$, protein kinase C, and cAMP while non-specific non-genomic effects refer to direct interaction of glucocorticoids with cell membranes [5].

It is not fully understood how corticosteroids exert their anti-edema effects although numerous mechanisms have been proposed. There is evidence suggesting that dexamethasone decreases inflammation and vasogenic edema by means of partial restoration of the blood–brain barrier (BBB) and restoration of normal permeability in abnormal capillaries [6]. Corticosteroids are thought to inhibit direct modulators of BBB permeability such as occludin and members of the claudin protein family. These proteins form part of the tight junctions in blood vessel endothelium, and their expression is downregulated in vasogenic edema [6]. Dexamethasone has been shown to increase occludin expression by binding to glucocorticoid-response elements in the occludin promoter [7], thereby decreasing BBB permeability. Another proposed mechanism is related to the negative effects of glucocorticoids on vascular endothelial growth factor (VEGF) [7]. VEGF is known to impair occludin function [6], alter the extracellular matrix surrounding the tumor, and induce tumor neovascularization, thereby increasing BBB permeability [8]. Dexamethasone inhibits VEGF production by tumor cells and reduces VEGF effects on tumor vasculature [7]. Interestingly, the effects of dexamethasone on BBB permeability appear to be a glucocorticoid receptor-dependent process and a function of the intracellular density of glucocorticoid receptors [6]. For example, metastases (which express a high level of glucocorticoid receptors) tend to response better to dexamethasone than meningiomas (which exhibit lower levels of these receptors) [9].

Dexamethasone also induces changes in membrane lipid metabolism, specifically arachidonic acid which is critical in the formation of vasogenic edema [10, 11]. Arachidonic acid triggers the release of pro-inflammatory molecules (such as leukotrienes and prostaglandins) and alters the basement membrane of endothelial cells [6]. Dexamethasone modulates these metabolic pathways and produces a shift from a pro-inflammatory to anti-inflammatory environment [12].

Additional data suggest that corticosteroids enhance the uptake of serum proteins by tumor cells and thereby help normalize the perivascular-extracellular osmotic pressure gradient [6]. Lastly, dexamethasone may have a direct modulatory effect on the vasomotor state of blood vessels [13, 14], which potentially explains the rapid onset of clinical improvement after its administration.

### Pharmacology

All types of corticosteroids are readily absorbed by the gastrointestinal (GI) tract. Upon absorption, they cross the cellular membrane via passive diffusion and bind to glucorticoid (NR3C1) receptors in the cytoplasm. This ligand-receptor complex subsequently binds to glucorticoid-response elements on DNA and leads to modulation of transcription [15, 16]. The oral bioavailability of glucocorticoids ranges from 60 to 100% [5]. Protein binding varies depending on the type of glucocorticoid. Dexamethasone binds exclusively to albumin while hydrocortisone and prednisolone also bind to transcortin [17]. Glucocorticoids are metabolized through the hepatic cytochrome P450 (CYP450) system in a two-step process, consisting of addition of an oxygen or hydrogen atom, followed by conjugation via glucuronidation or sulphation [5]. The inactive metabolites are subsequently excreted by the kidneys [5].

Given their metabolism through the CYP450 system, enzyme inducers (e.g., barbiturates, carbamazepine, phenytoin, rifampin) and inhibitors (e.g., ketoconazole, clarithromycin) will affect the clearance of glucocorticoids. For instance, phenytoin significantly decreases the half-life and bioavailability of dexamethasone [18, 19] but, conversely, dexamethasone can also reduce phenytoin levels [20]. Given this complex interaction, it is recommended that phenytoin levels be closely monitored when changes in dexamethasone dosing are being made. Carbamazepine and phenobarbital have also been shown to induce hepatic metabolism of dexamethasone [21]. Co-administration of CYP 3A4 inhibitors (e.g., ketoconazole, clarithromycin) with corticosteroids decreases the clearance and increases the half-life of methylprednisolone and dexamethasone but has minimal effects on prednisolone [5]. Glucocorticoid pharmacokinetics are also influenced by renal and hepatic disease. Renal disease enhances dexamethasone clearance and reduces its plasma half-life, due to decreased binding to albumin. In patients with chronic liver disease, the

**Table 1** Recommendations for dosing and tapering of dexamethasone in patients with brain tumors based on the authors' and others' [30•, 31•] clinical experience

| Clinical scenario | Recommended dose of dexamethasone | Recommended taper |
|---|---|---|
| Asymptomatic patients | Corticosteroids not recommended | |
| Patients with mild to moderate neurologic symptoms | 4–8 mg/day (given as single dose or twice daily) | Duration and rapidity of taper depend on individual patient characteristics. Goal is to taper to lowest dose at which the patient remains asymptomatic. If symptoms recur during taper, dose should be increased to previous dose at which patient was asymptomatic |
| Patients with severe neurologic symptoms (e.g., impaired consciousness, signs of increased intracranial pressure) or radiographic evidence of impending herniation | Initial one-time dose of 10 mg, followed by 4 mg every 6 h (can consider changing dose to twice daily after patient is clinically stable) | |
| Post-operatively | 16 mg/day, given 2–4 times daily; typically determined by neurosurgeon | Authors' suggestions:<br>*In asymptomatic post-operative patients*: reduce dose by 50% every 1–2 days over 5–7 days (typically determined by neurosurgeon) |
| During radiation therapy | Corticosteroids not recommended unless patient is symptomatic | *In patients on 4–8 mg/day for ≤2 week*: reduce by 2 mg/day every 3 days until dose of 2 mg/day is reached, then 1 mg/day for 3 days, then stop |
| During chemotherapy and/or immunotherapy | Corticosteroids not recommended unless patient is symptomatic. Dosing in setting of immunotherapy administration depends on clinical trial protocol but typically should not exceed 4 mg daily | *In patients on >8 mg/day for >2 weeks*: reduce by 2 mg/day every 5–7 days until dose of 2 mg/day is reached, then 1 mg/day for 5–7 days, then stop. Patients on prolonged corticosteroid use may require taper to 0.5 mg/day for several days before they tolerate discontinuation |
| Palliation of symptoms/hospice care | Dose should balance maximizing symptom relief and minimizing side effects | |

In general, corticosteroids should be given as a daily or twice daily dose, with the second dose administered in the afternoon to reduce the risk of insomnia. Given the extensive side effects of corticosteroids, a taper should be initiated as soon as the patient is clinically stable. There is wide variety amongst neuro-oncologists on how quickly corticosteroids are tapered. In general, a more conservative taper should be performed if a patient has been on high doses of corticosteroids for several weeks and/or if the clinician is concerned about onset of adrenal insufficiency during the taper

clearance of dexamethasone is decreased and its half-life increased [22]. Patients on corticosteroids therefore warrant close monitoring of concurrent medications (especially anti-epileptics) and evaluation for co-morbid conditions to avoid side effects and maximize therapeutic benefit.

Dexamethasone is a synthetic glucocorticoid that was first synthesized in 1958 [23]. It is the agent of choice to treat cerebral edema, given its high potency (30 times as potent as cortisol, the body's endogenous glucocorticoid [24]), long biologic half-life, and low mineralcorticoid (i.e., sodium-retaining) activity [25]. The plasma half-life of oral dexamethasone is 2–4 h but the biologic half-life extends to 34–54 h [26, 27]. Thus, a once or twice daily dosing schedule is appropriate and more convenient for patients than dexamethasone given four times daily [27]. Clinical data also support the use of lower doses of corticosteroids to avoid side effects. In two consecutive randomized controlled studies, no differences in clinical outcome or quality of life, as measured by Karnofsky performance score (KPS), were seen in patients receiving a daily dose of 4, 8, or 16 mg of dexamethasone after 1 week of treatment [28]. While the frequency of side effects did not differ between the groups after 1 week, there was a significantly higher incidence of Cushingoid facies and ankle edema after 4 weeks in patients receiving ≥8 mg/day of dexamethasone. The authors also observed a higher rate of proximal muscle weakness in the ≥8-mg/day group compared to the 4-mg/day group (38 vs. 14%) at 4 weeks [28]. In general, clinical guidelines do not recommend the use of any corticosteroids in asymptomatic patients with brain metastases or high-grade glioma [29, 30•, 31•]. In symptomatic patients, starting doses of 4–8 mg/day of dexamethasone are recommended although higher doses may be needed in the presence of impaired consciousness and other signs of increased intracranial pressure [29, 30•]. Table 1 summarizes recommendations on dosing and tapering of corticosteroids based on our

own clinical practice and as supported by clinical practice guidelines.

## Adverse Effects and Toxicity of Systemic Corticosteroids

In general, adverse effects are more likely to occur with prolonged use and high doses [32]. This is particularly problematic for neuro-oncologic patients as some may require corticosteroids for the whole duration of treatment or even after treatment has been completed [33, 34]. For instance, 71% of patients with malignant gliomas who underwent radiation were still on corticosteroids 3 months after completing radiation [33]. While corticosteroids are classically associated with the development of Cushingoid features (moon face, redistribution of body fat, centripetal obesity, and development of a dorsocervical fat pad), they have a number of neurologic and non-neurologic side effects. In a survey using the Dexamethasone Symptom Questionnaire-Chronic (DSQ-C), the three most frequently reported and bothersome symptoms were sleep disturbances, increased appetite, and mood changes [35]. Difficulties with sleep and increased appetite were reported by >35% of patients. In another study, weight gain was reported by up to 70% of patients on chronic steroid therapy (mean prednisone equivalent dose of 16 mg/day) [36].

Mood disorders are common with corticosteroids and include emotional lability, depression, hypomania, mania, anxiety, and suicidality. Some patients experience psychosis, confusion, and memory difficulties [37, 38]. These symptoms can be worse in patients with pre-existing psychiatric conditions but may also develop in individuals without a known history thereof. Given the profound effects on sleep, we advocate for once or twice daily dosing of dexamethasone and administration of the second dose in the afternoon, rather than in the evening or at night time, to minimize the risk of insomnia.

Steroid-induced myopathy is a frequently observed neurologic complication and mediated by direct catabolic effects on skeletal muscle, including myocyte apoptosis [39] and reduced myocyte differentiation [40]. In one case series, 10% of brain tumor patients on 2 or more weeks of continuous daily dexamethasone developed myopathy [41]. Two-thirds developed symptoms between week 9 and 12 of therapy. Interestingly, the incidence of myopathy was reduced in patients receiving phenytoin over other anti-epileptic drugs, which is likely related to phenytoin-induced hepatic clearance of dexamethasone [41]. The pattern of weakness in steroid-induced myopathy is typically proximal and involves the lower extremities first.

Musculoskeletal complications include osteoporosis, increased fracture risk, and avascular necrosis of the bone. Osteoporosis is mediated by effects on osteoblastic and osteoclastic function [42] and occurs in as many as 30–50% of patients within the first 3 to 6 months of starting treatment [43, 44]. The risk of fractures is time- and dose-dependent and increases with daily doses of more than 5 mg of prednisone or equivalent doses [43, 45]. Fractures tend to occur in areas with high density of cancellous bone such as the femoral neck or vertebral bodies [43].

Corticosteroids increase the risk of cardiovascular disease in a dose-dependent fashion, including the incidence of myocardial infarction, heart failure, and stroke through accelerated atherosclerosis [46, 47]. In a series of rheumatoid arthritis patients treated with prednisolone (7.5 mg/day), the risk of a first-time stroke was increased by a factor of 3.7 in the first 2 years of treatment [46]. However, a similar study in brain tumor patients exposed to dexamethasone has not been conducted. Other cardiovascular effects of corticosteroids are ankle edema due to increased sodium and water retention and hypertension [48].

Common GI side effects are gastritis, peptic ulceration, and GI hemorrhage. In one study, the relative risks of peptic ulcers and GI hemorrhage in patients on corticosteroids were 2.3 and 1.5, respectively [49]. These observations provide the rationale for concurrent administration of a proton pump inhibitor or H2 antagonist during corticosteroid treatment. Intestinal perforation has been reported after corticosteroid therapy [50].

Glucocorticoids have numerous metabolic and endocrine adverse effects. Generally, they worsen pre-existing or induce new-onset diabetes mellitus [51]. The reported odds ratio of diabetes in those treated with glucocorticoids ranges from 1.5 to 2.5 [51]. Growth failure has been reported, particularly in children [52]. Glucorticoids suppress the HPA axis, resulting in inadequate cortisol secretion by the adrenal glands and adrenal atrophy with prolonged use. This becomes particularly problematic with rapid tapering of corticosteroids and can manifest with symptoms of adrenal insufficiency, such as hypotension, general malaise, nausea, and fatigue. There are no guidelines for how quickly glucocorticoids should be tapered to avoid adrenal insufficiency. In general, it is recommended to taper doses over 2–4 weeks but longer schedules should be considered if patients have been on corticosteroids for several months and if they have been receiving higher doses (Table 1) [28, 53].

Lastly, glucocorticoids increase the risk of bacterial, viral, and fungal infections in a dose-dependent fashion. This risk is augmented in the presence of other immunosuppressive conditions, such as concurrent use of immunosuppressive drugs (particularly cytotoxic drugs such as cyclophosphamide) and diabetes mellitus [54]. A higher risk of infection is also conferred by corticosteroid-induced skin thinning and impaired wound healing [55]. One of the most feared conditions is *Pneumocystis jirovecii* pneumonia (PJP). The presence of

cancer itself increases the risk of PJP, and this has traditionally been observed in hematologic malignancies. However, PJP has also been reported in 1.7% of patients with primary or metastatic CNS tumors [56, 57], after a median of 2.75 months on dexamethasone [57]. Temozolomide (TMZ), which is one component of the standard treatment for glioblastoma (GBM), causes lymphopenia and has been associated with PJP [58, 59]. It is thus recommended that all GBM patients receiving concurrent radiation and TMZ be treated prophylactically for PJP until their lymphocyte counts recover. The most commonly used agent is sulfamethoxazole/trimethoprim which reduces the incidence of PJP by 85% [60]. If this is contraindicated, alternative agents such as atovaquone, dapsone, and aerosolized pentamidine can be used.

### Effects of Dexamethasone on Survival in Glioma Patients

Reports in the literature have suggested that corticosteroid dependency in glioma patients during radiation therapy (RT) is a poor prognostic indicator of survival [61–63], perhaps because their use is linked to poorer performance status and a greater degree of residual tumor after surgery, both of which are independent negative prognostic factors. As outlined above, corticosteroids also increase morbidity and mortality through direct toxic effects. However, laboratory data and recent clinical studies have demonstrated that they negatively impact survival independent of confounding factors. Early observations were provided by Shields et al. in 2015 [64•] who found that patients treated with dexamethasone during chemoradiation had a worse overall survival (OS) than those who did not receive dexamethasone (12.7 vs. 22.5 months) on both univariate and multivariate analysis. Progression-free survival (PFS) was similarly shortened in the dexamethasone group (6.0 vs. 8.8 months). These findings were subsequently corroborated by a pooled retrospective analysis of more than 2000 GBM patients [65••]. This study demonstrated that dexamethasone administration during treatment was associated with significantly reduced OS and was an independent negative prognostic indicator, after adjusting for other prognostic factors, including age, performance status, and extent of surgery. The data were retrospectively analyzed from three large patient cohorts: 622 patients at the Memorial Sloan Kettering Cancer Center (MSKCC), 573 patients from the European Organisation for Research and Treatment for Cancer (EORTC)/National Cancer Institute of Canada (NCIC) trial, and 832 patients from the German Glioma Network (GGN). In the MSKCC cohort, patients treated with dexamethasone at the beginning of RT had an OS of 12.9 months, compared to 20.6 months in those not treated with dexamethasone. Similarly, subjects from the EORTC/ NCIC trial on baseline corticosteroids had a significantly reduced OS (12 vs. 17 months) and PFS (5.3 vs. 6.4 months) compared to those who were not on corticosteroids. The negative effects of dexamethasone were more pronounced in those treated with RT alone than concurrent chemoradiation followed by adjuvant TMZ [65••]. Data from the GGN cohort also demonstrated inferior OS and PFS in steroid-exposed patients (OS 12.1 vs. 15.7 months; PFS 6.1 vs. 7 months), which was more significant in those receiving concurrent chemoradiation.

The observations that corticosteroids abrogated the effects of radiation were then reproduced in a murine GBM model. In this model, dexamethasone given daily for 3 days before radiation (10 Gray) significantly decreased survival, particularly when a fractionated radiation scheduled was used [65••]. At a molecular level, the authors found that 19 genes involved in the cell cycle and mitosis were significantly downregulated in dexamethasone-treated mice. Using a murine in vivo assay, they demonstrated that dexamethasone decreased tumor cell proliferation [65••]. This is a significant finding since cells are most radiosensitive when they have high turnover rates [66] and when they are in G2/M phase, as opposed to G1 phase [67]. Dexamethasone may thus shift cells into a more radioresistant state by increasing the relative time spent in G1 phase and decreasing the time in G2/M phase. In addition, dexamethasone has been shown to induce the cell cycle inhibitor p21 [68], which is associated with radioresistance in human gliomas [69], and protect GBM cells from TMZ-induced apoptosis [70]. Taken together, these data provide potential mechanistic insights into how dexamethasone modulates response to cancer-directed therapies on a molecular level.

In summary, the above data provide evidence that dexamethasone may worsen clinical outcome in glioma patients independent of other known prognostic factors. In our opinion, dexamethasone should therefore only be used in symptomatic patients, including those with neurologic and radiographic signs of increased intracranial pressure. We do not recommend routine administration of dexamethasone during radiation or in the setting of adjuvant chemotherapy in asymptomatic patients. If used, it should be tapered to the lowest tolerated dose over a course of weeks, depending on the previous duration of treatment and dosing schedule.

## Alternative Treatment Strategies for Tumor-Associated Cerebral Edema

Given the significant toxicity profile of corticosteroids and their negative impact on survival in glioma patients, efforts have been underway to explore alternative therapies to treat cerebral edema in neuro-oncologic patients. One particular focus has been on anti-angiogenic agents, including bevacizumab and cediranib. These agents target vascular endothelial growth factor (VEGF), a pro-

angiogenic peptide that is upregulated in many brain tumors [71–73]. Clinical studies have demonstrated that bevacizumab (a monoclonal antibody against VEGF, administered intravenously) and cediranib (an oral tyrosine kinase inhibitor of VEGF receptors) reduce cerebral edema on MRI [74–76]. The anti-edema effects of bevacizumab were evident on MRI as early as 18 days after the start of treatment [75] and associated with a significant reduction in corticosteroid dose and neurologic improvement. In a study of patients with recurrent glioblastoma treated with cediranib, a significant reduction of cerebral edema as measured by lesion volume on T2/FLAIR sequences, apparent diffusion coefficient maps, and extracellular extravascular space fraction was apparent after a few weeks or less of treatment [74, 76]. As with bevacizumab, these imaging findings also translated into a reduction in corticosteroid requirement for all patients, with some not requiring corticosteroids at all [74].

In response to their findings that dexamethasone during radiation compromised survival in GBM patients [65••], the authors examined whether a murine bevacizumab analogue (anti-VEGF antibody B20-4.1.1) was equally effective in controlling neurologic symptoms as dexamethasone and whether it negatively affected survival. Interestingly, B20-4.1.1 independently prolonged survival in mice treated with RT and did not interfere with the efficacy of RT. On a microscopic level, B20-4.1.1 was associated with a reduction in total vessel area, average vessel size, and vessel leakage, compared to vehicle-treated mice. However, these effects were transient as vessels assumed their original morphology when B20-4.1.1 was stopped [65••]. The risk of rebound edema after cessation of therapy has been documented for anti-angiogenic agents [74] and, therefore, duration of therapy remains an open question. Overall, anti-angiogenic agents are considered relatively safe. Bevacizumab, in particular, is commonly used in neuro-oncologic practice to reduce vasogenic edema.

Other agents with documented steroid-sparing effects include corticorelin acetate (CrA) and cyclooxygenase (COX) inhibitors. CrA is a synthetic peptide formulation of endogenous human corticotrophin-releasing factor. In a phase III, double-blind randomized controlled trial, patients were treated either with CrA or placebo. All patients received concurrent dexamethasone [77]. Although the primary endpoint was not met (defined as ≥50% reduction in dexamethasone dose, at least stable neurologic examination and KPS score at week 2 of treatment, and persistent response at week 5), the maximum percent reduction in the dexamethasone dose over a 3-month period was significantly higher in the CrA than that in the placebo group. This also correlated improvement in corticosteroid-induced myopathy and a lower likelihood of developing Cushing syndrome in the CrA groups. A COX-2 inhibitor in a rat brain tumor model was associated with a similar survival benefit as dexamethasone, possibly related to anti-edema effects [78]. However, clinical studies have not been performed due to concerns for potential cardiac toxicity [23], and the clinical feasibility of this agent is unknown.

In summary, in patients who require long-term corticosteroids for edema control, have undesired corticosteroid-associated side effects, or are refractory to corticosteroids, bevacizumab should be considered as an alternative treatment strategy, given the best available clinical evidence. The use of other agents, such as CrA and COX inhibitors, remains a matter of debate and requires more validation in the clinical setting. Given the potential clinical benefit of reducing corticosteroid use, the Response Assessment in Neuro-Oncology (RANO) Working Group is developing response criteria based on corticosteroid use an as endpoint in clinical trials.

## Effects of Corticosteroids on MR Imaging

MRI is the gold standard imaging modality in neuro-oncology to monitor and assess treatment response and disease progression. Neuro-oncologists most frequently rely on post-contrast T1-weighted (T1W) and T2-weighted (T2W)/fluid-attenuated inversion recovery (FLAIR) sequences. Post-contrast T1W sequences typically capture the contrast-enhancing tumor core (commonly seen in high-grade gliomas or brain metastases) while T2/FLAIR sequences usually represent a combination of peritumoral edema and non-enhancing infiltrating tumor (commonly seen in low-grade gliomas or representative of the infiltrating edges of high-grade gliomas).

Corticosteroids can profoundly change the appearance of brain tumors on MRI and thus complicate the interpretation of imaging results. For instance, corticosteroids at a daily dose of 16 mg decreased the size of the contrast-enhancing tumor core and surrounding T2-hyperintense peritumoral edema in 90% of patients, which was most pronounced within 2 weeks of treatment [79]. In addition, anatomic and functional imaging changes have been observed at even earlier time points after exposure to corticosteroids. MRI data from GBM patients who underwent imaging 48–72 h after dexamethasone administration revealed significant changes in permeability parameters in the contrast-enhancing tumor core [80]. Changes in T1 relaxation time and mean diffusivity (measures of tissue water content and mobility of water, respectively) in the peritumoral region were also observed.

For these reasons, most clinical protocols require patients to be on a stable dose of corticosteroids for at least 5 days before the baseline MRI. In addition, corticosteroid doses have been incorporated as part of both the Macdonald criteria (a response assessment tool for high-grade gliomas) and the newer Response Assessment in Neuro-Oncology (RANO) criteria (which also specifies response criteria for other tumor entities such as low-grade gliomas and metastases). For

**Table 2** Overview of RANO criteria for high-grade gliomas, low-grade gliomas, and brain metastases

| | High-grade gliomas | Low-grade gliomas | Brain metastases |
|---|---|---|---|
| CR | • No enhancing disease for ≥4 weeks<br>• No new lesions<br>• Stable or improved T2/FLAIR<br>• No more than physiologic doses of steroids<br>• Clinically stable or improved | • No T2/FLAIR disease for ≥4 weeks<br>• No new or increased enhancement<br>• No new T2/FLAIR, other than that attributable to treatment effects<br>• No more than physiologic doses of steroids<br>• Clinically stable or improved | • Disappearance of all CNS target and non-target lesions for ≥4 weeks<br>• No new lesions<br>• No use of steroids<br>• Clinically stable or improved |
| PR | • ≥50% decrease in sum of perpendicular diameters of enhancing disease for ≥4 weeks<br>• No new lesions<br>• Stable or improved T2/FLAIR<br>• Stable or decreased steroid dose<br>• Clinically stable or improved | • ≥50% decrease in sum of perpendicular diameters of T2/FLAIR disease for ≥4 weeks<br>• No new or increased enhancement<br>• No new T2/FLAIR, other than that attributable to treatment effects<br>• No more steroids than dose at time of baseline scan<br>• Clinically stable or improved | • ≥30% decrease in sum longest diameter of CNS target lesions for ≥4 weeks<br>• Stable or improved non-target lesions<br>• No new lesions<br>• Stable or decreased steroid dose<br>• Clinically stable or improved |
| MR | N/A | • 25–49% decrease in sum of perpendicular diameters of T2/FLAIR disease for ≥4 weeks<br>• Other criteria per PR criteria | N/A |
| SD | • Does not meet criteria for CR, PR, or PD<br>• No new lesions<br>• Stable or improved T2/FLAIR<br>• Stable or decreased steroid dose<br>• Clinically stable or improved | • Does not meet criteria for CR, PR, MR, or PD<br>• No new or increased enhancement<br>• No new T2/FLAIR, other than that attributable to treatment effects<br>• No more steroids than dose at time of baseline scan<br>• Clinically stable or improved | • Does not meet criteria for PR or PD<br>• Stable or improved non-target lesions |
| PD | • ≥25% increase in sum of perpendicular diameters of enhancing disease for ≥4 weeks<br>• New lesions<br>• Substantially worse T2/LFAIR<br>• Substantial clinical decline | • New lesions or increased enhancement<br>• ≥25% increase in T2/FLAIR hyperintensity on stable or increased doses of steroids *and* not attributable to radiation effect or co-morbid events<br>• Definite clinical deterioration<br>• Death or loss of follow-up | • ≥20% increase in sum longest diameter of CNS target lesions relative to smallest sum longest diameter while on study<br>• At least one lesion increased by ≥5 mm<br>• Unequivocal progression of existing non-target lesions<br>• New lesion(s)<br>• Unequivocal progression of existing tumor-related T2/FLAIR lesions<br>• If immunotherapy given, new lesions alone may not constitute PD |

In addition to imaging criteria based on extent of contrast enhancement and T2/FLAIR hyperintensity and clinical assessment, changes in dosing of corticosteroids (referred to as "steroids" in the table) must be considered in the response assessment, given the known modulating effects of corticosteroids of imaging findings on post-contrast T1W and T2/FLAIR sequences. Adapted from [83••] with permission

*CR* complete response, *PR* partial response, *MR* minor response, *SD* stable disease, *PD* progressive disease

patients to meet criteria for a complete response (CR) with the Macdonald criteria, there must be complete resolution of contrast enhancement *and* the patient has to be off corticosteroids [81]. To fulfill criteria for a partial response (PR), there has to be at least 50% resolution of contrast-enhancing tumor on two consecutive imaging studies at least 4 weeks apart *and* a stable or decreased dose of steroids *and* a stable neurologic exam [81]. Similarly, in the RANO criteria, to achieve a CR, in addition to a complete and sustained (≥4 weeks) resolution of enhancing disease, absence of any new tumor lesions, and stable or improved extent of T2/FLAIR hyperintensity on MRI, patients have to be at most on physiologic doses of corticosteroids [82]. A patient with brain metastases must not be on any corticosteroids to fulfill CR criteria. Table 2 summarizes the RANO criteria for common types of brain tumors. A comprehensive review of the RANO criteria was recently published [83••].

## Conclusion

Corticosteroids are effective in treating and improving cancer- and treatment-associated cerebral edema and neurologic symptoms in patients with CNS tumors. However, their use should be limited to symptomatic patients and those with signs of increased intracranial pressure, given their potentially serious side effects. When administered, clinicians should aim for the lowest effective dose to improve symptoms and attempt to taper patients off corticosteroids after symptom control has been achieved. This is particularly relevant in light of recent data suggesting a potential detrimental effect of corticosteroids on survival in glioma patients. As more studies are being conducted to investigate the impact of corticosteroids on tumor-directed therapies and long-term clinical outcome, alternative treatment

approaches such as anti-angiogenic agents should be considered in patients who require long-term corticosteroids.

### Compliance with Ethical Standards

**Conflict of Interest** K. Ina Ly declares no conflict of interest.

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Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance


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