TOPIC REVIEW & CLINICAL GUIDELINES

The role of imaging in the management of progressive glioblastoma

A systematic review and evidence-based clinical practice guideline

Timothy Charles Ryken · Nafi Aygun · Johnathan Morris · Marin Schweizer · Rajeshwari Nair · Cassandra Spracklen · Steven N. Kalkanis · Jeffrey J. Olson

Abstract

Question Which imaging techniques most accurately differentiate true tumor progression from pseudo-progression or treatment related changes in patients with previously diagnosed glioblastoma?

Target population These recommendations apply to adults with previously diagnosed glioblastoma who are suspected of experiencing progression of the neoplastic process.

Recommendations *Level II* Magnetic resonance imaging with and without gadolinium enhancement is recommended as the imaging surveillance method to detect the progression of previously diagnosed glioblastoma.

Level II Magnetic resonance spectroscopy is recommended as a diagnostic method to differentiate true tumor progression from treatment-related imaging changes or pseudo-progression in patients with suspected progressive glioblastoma.

Level III The routine use of positron emission tomography to identify progression of glioblastoma is not recommended.

Level III Single-photon emission computed tomography imaging is recommended as a diagnostic method to differentiate true tumor progression from treatment-related imaging changes or pseudo-progression in patients with suspected progressive glioblastoma.

Keywords Malignant glioma · Glioblastoma · Recurrence · Progression · Pseudo-progression · Imaging · Radiology · Systematic review · Practice guideline

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Imaging rationale

Primary malignant brain tumors (malignant glioma, anaplastic astrocytoma and glioblastoma multiforme) carry a nearly uniformly dismal outcome. Even the most optimistic predictions of long term survival of greater than 5 years after diagnosis only approach 1 or 2 %, although higher 5-year survival rates have been recently published in one Phase 3 study. The median survival of patients with newly diagnosed glioblastoma has improved slightly in the last decade and may approach 15–18 months [1, 2]. Due to the dismal prognosis, patients with these tumors are treated early in the course of the disease with aggressive multimodality regimens including surgical resection, radiotherapy

and chemotherapy [3–5]. Serial imaging has been the mainstay of assessing treatment response, and therefore the decision to alter or even abandon therapy in favor of supportive care is guided heavily by non-invasive radiographic imaging techniques.

However, differentiating treatment effect from true tumor progression is challenging and has been approached with a variety of strategies [6–9].

Traditional gadolinium-enhanced magnetic resonance imaging (MRI) is confounded by overlap of findings as progressive tumor and post-radiation or treatment related effects can both show changes at or near the original tumor site, including increased contrast enhancement, mass effect, and edema. Attempts to utilize the powerful imaging capability of MRI have resulted in alternative advanced MRI techniques, including diffusion-weighted imaging (DWI), dynamic susceptibility contrast-enhanced perfusion imaging (DSC), and MR spectroscopy (MRS). [10] It is theorized that these advanced techniques may provide physiologic information not assessed using conventional anatomic MRI alone. For example the use of proton-based MRS (or 1H-MRS) yields information on the metabolic composition within a selected target area of tissue, conceptually similar to an "electronic biopsy". Comparison of the relative concentration of these metabolites provides an indication of factors such as cellular membrane turnover and neuronal viability that assists in the assessment of whether viable tumor is present in the sampled region. MRS adds little additional time (15–30 min) to the traditional MRI technique routinely utilized in malignant glioma patient management and therefore is an appealing non-diagnostic technique.

The purpose of this guideline is to assess the ability of the most widely attempted imaging techniques, primarily magnetic imaging based and radiotracer techniques, to accurately differentiate recurrent or progressive tumor (true tumor progression) from imaging artifact and treatment effect (false tumor progression), also referred to more recently as "pseudo-progression" in the setting of suspected progressive glioblastoma. This review has been structured based on the techniques involved and divided broadly into MRI based techniques and radiotracers as outlined below.

Magnetic resonance imaging techniques (MRI)

1. Contrast patterns
2. Perfusion

    (a) DSC (dynamic susceptibility contrast)
    (b) DCE (dynamic contrast enhanced)

3. DWI/ADC (diffusion weighted imaging/apparent diffusion coefficients).
4. Spectroscopy

Radiotracers

(PET Scanning—Positron Emission Tomography and SPECT—Single Photon Emission Computed Tomography).

5. FDG PET (fluoro-deoxy-glucose positron emission tomography)
6. MET PET (methionine positron emission tomography)
7. SPECT

The overall objectives of this guideline are:

1. To systematically review the evidence available for the imaging of adult patients with previously diagnosed glioblastoma suspected of having progression following initial treatment.
2. To make recommendations based on this evidence for the role of imaging in the management of these patients.

Imaging methodology

Literature review

A broad search strategy was used due to the relative small number of studies on each specific topic. PubMed (National Library of Medicine, http://www.ncbi.nlm.nih.gov) was searched using Endnote® (Thomas Reuters, Inc. http://www.endnote.com) using "ALL FIELDS" and entering "RECURRENT GLIOBLASTOMA" AND "IMAGING" without date limits for a broad initial search. The results were then hand searched based on the titles and abstracts to exclude laboratory only studies and titles not on topic. Electronic versions of relevant studies were obtained via secure access to the University of Iowa College of Medicine Hardin Library and when not available were obtained through inter-library loan with the assistance of the medical library at Covenant Medical Center, Waterloo, IA, USA. Two foreign literature papers referenced in a 2006 systematic review by Hollingworth et al. [10], one in Japanese with English abstract and one in German with English abstract were included as there was an English abstract, the abstracts could be reviewed for relevance and the data required to construct a 2 by 2 Bayesian table was available. Other foreign language papers if there was no English abstract or the table data could not be abstracted the study was excluded.

Article inclusion and exclusion criteria

All studies addressing imaging of adult patients with a known diagnosis of a glioblastoma containing information on diagnostic results of correctly identifying whether the tumor has progressed were selected for review. Exclusion criteria included: pediatric population, newly diagnosed patients as the study focus, laboratory only studies, non-human studies, and the focus of paper was a clinical trial rather than a diagnostic study.

Data collection and review

Two independent reviewers abstracted data for each article and the two sets of data were compared for agreement by a third party. Inconsistencies were re-reviewed and disagreements were resolved by consensus. Data collected included the following: author year, age of study population, study addressed previously diagnosed patients with glioblastoma, study included imaging data on the diagnosis of progressive or progressive glioblastoma, number of patients in each group, image results either positive or negative, clinical results indicating the presence of absence of progressive malignant glioblastoma, and, when possible, study allows completion of a Bayesian table for calculation of sensitivity and specificity.

Study selection and quality assessment

Following broad screening for relevance, two independent reviewers evaluated citations and full text screening of potentially relevant papers using a priori criteria for data extraction on a standardized form. Disagreements were resolved with the involvement of a third reviewer, followed by primary re-review until agreement was achieved. Both the quality of the evidence and the eventual strength of the recommendations generated by this evidence were graded according to a three-tiered system for assessing studies addressing diagnostic testing as approved by the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Committee on Guidelines criteria [4, 5, 11].

Imaging scientific foundation

Overall, 57 publications met the eligibility criteria and are included in the evidentiary tables below (see Tables 1, 2, 3, 4, 5 and 6). These included 11 focused on MRI contrast techniques (see Table 1), 8 on MRI perfusion techniques (see Table 2), 5 on MRI diffusion techniques (see Table 3), 13 on MRS (see Table 4), 10 on PET techniques (see Table 5) and 10 on SPECT techniques (see Table 6).

In addition, data extracted from 4 papers provides information on combination imaging techniques and multi-parametric analysis (see Table 7).

MRI techniques: contrast patterns

MRI with and without gadolinium contrast administration has been cited as the imaging modality of choice in previous evidence based reviews both for newly diagnosed and progressive glioblastoma, although the direct evidence supporting these recommendations is surprisingly small [3, 12]. At the present time we agree that MRI with gadolinium represents the "gold standard" as there is also little evidence to the contrary. The Level 1 recommendation made in the previously published guideline for imaging in newly diagnosed glioblastoma is based on a single blinded histopathological study including a total of 72 patients, 36 with glioblastoma, undergoing MRI imaging with pathological correlation which found a sensitivity of 0.89, specificity of 0.82, positive predictive value of 0.88, negative predictive value (NPV) of 0.88 and an overall accuracy of 0.86 for the ability of MRI to accurately diagnose glioblastoma [13]. The evidence based review of recurrent malignant glioma by Easaw et al. [3], states a Level 1 recommendation for the role of MRI, but does not cite any specific references to support this and presumably this recommendation was arrived at by consensus.

Johnson et al. [14] published the results of a study comparing T2-weighted post mortem magnetic resonance (MR) images of glioma patients and the histologic findings from whole-brain sections [15]. This study included 10 patients with recurrent glioblastoma. In general there was a high correlation of the MRI images with the pathologic findings, but resulted in overestimations (24 %) or underestimations (28 %) of tumor extent in the cases of recurrent tumor. However, the authors concluded that MRI accurately identified the presence of tumor with a high-degree of sensitivity (no false negatives were described).

The value of serial imaging in the management of glioblastoma is in early detection of treatment failure to guide intervention. The fact that progression free survival at 6 months has been shown to correlate with overall survival, to the point that is has been recommended as a primary trial endpoint, increases the importance of diagnosing early tumor progression [15–17].

Several points are of relevance when considering the situation of primary glioblastoma progression and treatment response. Although it is generally assumed that increased enhancement, edema and mass effect will accompany all cases of true tumor progression, a pooled study examining outcome measures from Phase II clinical trials for progressive glioblastoma did find that 14 of 375 (3.7 %) of patients progressed clinically without radiographic changes [18].

Table 1 MRI contrast patterns

First author and year	Description of study	Data class	Conclusions
Kleinberg 2009 [34]	Retrospective analysis of MRI contrast imaging in 20 patients with recurrent glioblastoma (GBM) treated with brachytherapy. The images were reviewed for prognostic significance	Class III	T1-weighted enhancement >1 cm median survival 13.6 months
			T1-weighted enhancement <1 cm median survival 8.5 months ($p = 0.014$)
			Increasing T2-weighted hyper intensity surrounding the resection cavity associated with decreased survival ($p = 0.027$)
			The authors conclude that T1-weighted enhancement without edema suggests pseudoprogression
Aiken 2008 [31]	Retrospective analysis of MRI enhancement patterns in 15 patients with recurrent GBM treated with brachytherapy plus external beam radiotherapy (EBRT) or EBRT alone. The pattern of contrast enhancement (linear, nodular, feathery, or solid) was compared with clinical course	Class II	Bayesian analysis of enhancement pattern and tumor recurrence versus necrosis

	Tumor	Radiation Necrosis
Nodular	19	1
Feathery	5	10

Sensitivity = 0.95

Specificity = 0.67

The authors conclude that nodular enhancement strongly suggests tumor recurrence and feathery enhancement suggests radiation necrosis (seen in brachytherapy group)

First author and year	Description of study	Data class	Conclusions
Taal 2008 [37]	Retrospective analysis of MRI enhancement patterns consistent with early progression in 36 patients treated with radiotherapy and temozolamide	Class III	Bayesian analysis of enhancement pattern and tumor recurrence versus pseudoprogression

	Neuro Decline	Neuro Stable
Progression	12	6
Pseudo	6	12

Sensitivity 0.67

Specificity 0.67

The authors conclude that up to 50 % of patients treated with radiochemotherapy will develop pseudoprogression and this should be considered carefully before altering therapy when progression is suspected

First author and year	Description of study	Data class	Conclusions
Wick 2008 [17]	Validated longitudinal analysis of prospectively collected MRI data acquired on 63 patients with progressive GBM treated on European Organization for Research and Treatment of Cancer (EORTC) 26981/22981/National Cancer Institute of Canada (NCIC) to examine changes of site and distance between the initial and the recurrent tumor on the group level	Class III	There was no difference in the patterns noted between study groups but the authors conclude that the data show the feasibility of group-wise recurrence pattern analysis
			There were no patients reported to progress without MRI detection. 20 % of tumors progressed away from original center of tumor mass
Valery 2001 [38]	Prospective analysis of 16 patients with recurrent GBM analyzed by the three-dimensional relationship of the tumor and the surrounding normal brain. The authors define a new parameter surface tumor volume (STV)	Class III	STV was significantly negatively correlated with survival (Spearman test: $r = -0.54$, $p = 0.03$),
	The use of the three-dimensional value, tumor volume rather than the two-dimensional, cross-sectional area is the focus of this study		The authors conclude that STV may be a useful tool for predicting the evolution of malignant glioma
Kumar 2000 [20]	Prospective analysis of MRI enhancement patterns in 148 patients on a uniform radiochemotherapy regimen	Class III	Unable to perform Bayesian analysis
			The authors conclude the following
			findings favor radiation necrosis:
			(1) appearance of necrosis in a previously non-enhancing area after treatment
			(2) enhancing focus developing at a distance
			(3) enhancement near periventricular white matter tracts
			(4) soap bubble or Swiss cheese pattern

Table 1 continued

First author and year	Description of study	Data class	Conclusions
Sneed 1994 [36]	Retrospective analysis of 381 scans from 25 patients with glioblastoma treated with brachytherapy in addition to standard radiochemotherapy to evaluate sites of progression	Class III	Local 17 (77 %) Distant 3 (14 %) Subependymal 1 (5 %) Systemic 1 (5 %) The authors conclude that there was a significant risk of separate brain lesions or subependymal spread over time, local tumor progression was the predominant pattern of failure. The study demonstrated the role of MRI in posttreatment monitoring for progression
Agbi 1992 [30]	Retrospective review of recurrence pattern in 68 patients with malignant glioma monitored by CT	Class III	Location of recurrence: Initial tumor site 88 % (including 72 % within 2 cm) Outside original tumor margin 6 % Spinal metastases 1 % Systemic metastases 2 %
Johnson 1989 [14]	Retrospective post-mortem descriptive report comparing postmortem T2-weighted MR and human brain glioma specimens histologic findings including 10 cases with progressive GBM	Class III	MR imaging findings resulted in overestimation (24 %) or underestimation (28 %) of tumor distribution in the recurrent GBM cases Overall the authors felt the T2 images were representative of the pathologic state of the tumor progression
Curnes 1986 [32]	Retrospective review of nine patients with GBM treated with radiotherapy and followed with MRI and CT	Class III	The authors conclude that MRI is uniquely suited to detect radiation injury to the brain because of its extreme sensitivity to white-matter edema
Dooms 1986 [33]	Retrospective analysis of 55 malignant primary tumor patients treated with radiation and monitored with imaging for progression with CT and MRI	Class III	The authors concluded that MR can depict radiation lesions with great sensitivity but is not very helpful for discrimination between recurrent or residual brain tumor, radiation necrosis, and other brain lesions

Pseudo-progression and pseudo-response are recent phenomena that are causing increasing discussion. Pseudo-progression has been defined as an increase in contrast enhancement and/or edema on MRI without true tumor progression and has most often been associated with the combination or radiotherapy and temozolamide [7, 8, 19, 20]. In contrast pseudo-response, refers to a decrease in enhancement on MRI without a true antitumor effect, generally associated with anti-angiogenic targeted therapy [21–25]. Both of these radiographic based phenomena are having an increasing impact on treatment planning due to the increasing use of both temozolomide and the anti-angiogenic agents, bevacizumab or cediranib. The traditional Macdonald response assessment generally based on MRI data interpretation is particularly prone to problems as a result of the variable pathological progression and treatment response of the glioblastoma [26]. Irregular growth patterns, irregular contrast-enhancement and infiltration all complicate methodology based on cross-sectional expansion alone. The more recently proposed RANO criteria have been proposed specifically to address this shortcoming and

provide a more realistic set of parameters to determine true progression. These proposed criteria take into account not just MR enhanced response but T2 changes, steroid use and clinical status. It is assumed that as new studies are designed, these potentially more relevant criteria will be utilized and therefore it will be possible to assess whether they truly represent an improved response assessment. They are, however, currently not validated [27–29].

The pattern of MRI contrast enhancement has been investigated in a number of studies [30–38].

This set of publications includes one Class II study using criteria for diagnostic testing and is listed in evidentiary Table 1 below [31]. In the study by Aiken et al., the authors describe the differentiation of true progression from pseudo-progression with a sensitivity of 0.95 and specificity of 0.67 using the pattern of recurrence as the differentiating criteria with nodular enhancement strongly suggesting tumor progression and feathery enhancement suggesting radiation necrosis (seen in the group receiving brachytherapy).

Supporting Class III studies are also listed in evidentiary Table 1 below [14, 17, 30]. The study by Taal et al. [37]

Table 2 MRI perfusion DSC and dynamic contrast enhanced (DCE)

First author and year	Description of study	Data class	Conclusions
Hu 2012 [41]	Prospective study of 25 patients undergoing craniotomy for suspected progressive GBM examining the correlation of histologic tumor fraction and overall survival (OS) correlate pMRI-based metrics within CE-MRI enhancing lesions: rCBV mean, mode, maximum, width, and define a new threshold metric called pMRI fractional tumor burden (pMRI-FTB)	Class III	Histologic tumor fraction correlated most strongly with pMRI-FTB ($r = 0.82$; $p < 0.0001$), which was the only imaging metric that correlated with OS ($p < 0.02$) The authors propose pMRI-FTB as biomarker for future study Study support metrics derived from contrast enhanced MRI correlate with histologic tumor fraction and overall survival Note: The pMRI-FTB metric is calculated by coregistering the volume of interest with the rCBV. Based on signal intensity ranges within the volume of interest a lesion "mask" is created that includes enhancing voxels and excludes nonenhancing necrotic voxels. Following coregistration with the rCBV map, the lesion mask voxels are categorized as tumor voxels or non-tumor voxels. pMRI-FTB is defined as the percentage of tumor voxels relative to total lesion mask voxels
Al Sayyari 2010 [39]	Prospective correlative imaging study (contrast MRI and ACD mapping) of 17 patients undergoing treatment for high grade glioma	Class III	The authors concluded that an increase in enhancement volume and a reduction in ADC supports a diagnosis of recurrent tumor
Ringelstein 2010 [42]	Prospective study of 12 patients with recurrent high-grade glioma assessing the prognostic value of ADC mapping Not able to determine how many GBM Decreased ADC values correlate with decreased Brownian motion and increased cell density consistent with progression or recurrence	Class III	Accuracy of ADC mapping to predict tumor response was 10 of 12 (83 %) The author conclude that ADC mapping predicts patient response to treatment and provides and early indicator for recurrence or progression
Sawlani 2010 [43]	Retrospective 16 patients with recurrent GBM treated with bevacizumab as part of a clinical trial. rCBV maps were created from analysis of MR perfusion images to calculate the following parameters: size, mean rCBV, mean leakage coefficient K (2), and HPV, which is the fraction of the tumor with an rCBV higher than a predetermined threshold	Class III	This pilot study derived an imaging metric (HPV) that reflects local perfusion changes in GBMs The authors conclude that this metric was found to show a significantly improved correlation to time to progression
Vrabec 2010 [46]	Retrospective analysis of 32 follow-up MRI examinations in eight patients with possible recurrent malignant glioma Three groups: 0-obtained in patients that remained stable during the follow-up period, 1a-obtained in progressive-tumor patients at time points before definite progression 1b-obtained in patients at or after progression	Class III	Maximum lesional rCBV ratios Group 1b (9.25 ± 2.68; $p < 0.001$) Group 1a (4.87 ± 1.61, $p < 0.001$) Group 0 (1.22 ± 0.47) ADCs in the contrast-enhancing regions Group 1b (0.76 ± 0.08) ($p = 0.02$) Group 1a ($0.62 \pm 0.06 \times 10^{-3}$) Group 0 ($1.03 \pm 0.43 \times 10^{-3}$, $p = 0.01$) Minimum ADCs in the FLAIR-hyper intense region w Group 1b (0.68 ± 0.07) from groups 0 and 1a ($p = 0.33$, $p = 0.10$)

Table 2 continued

First author and year	Description of study	Data class	Conclusions
			Group 1a (0.62 ± 0.06, $p = 0.02$) Group 0 (0.76 ± 0.16) The authors conclude that maximum rCBV and minimum ADC corresponds to tumor recurrence or progression
Barajas 2009 [40]	Retrospective study of 57 patients with recurrent GBM to investigate whether CBV, PH, and PSR measurements derived from the results of T2-weighted dynamic susceptibility-weighted contrast material-enhanced (DSC) MR imaging performed after external beam radiation therapy (EBRT) can be used to distinguish recurrent glioblastoma multiforme (GBM) from radiation necrosis	Class III	Mean, maximum, and minimum relative PH and relative CBV were significantly higher ($p < .01$) in patients with recurrent GBM than in patients with radiation necrosis. Mean, maximum, and minimum relative PSR values were significantly lower ($p < .05$) in patients with recurrent GBM than in patients with radiation necrosis. The authors conclude that DSC perfusion MR imaging may be used to differentiate recurrent GBM from EBRT-induced radiation necrosis
Sorensen 2009 [44]	Retrospective analysis of a prospective trial of 31 recurrent glioblastoma patients enrolled in a phase II trial of cediranib, an oral pan-VEGF receptor tyrosine kinase inhibitor. The correlation between clinical outcome and MRI-measured changes in vascular permeability/flow, in microvessel volume, and circulating collagen IV level	Class III	Three parameters were combined to create a VNI that correlated with overall survival (R = 0.54; $p = 0.004$) and progression-free survival (R = 0.6; $p = 0.001$). This metric has not been validated
Stenberg 2006 [45]	Retrospective review of 79 imaging enhanced and perfusion MRI studies from 6 patients with GBM to assess the value of the combined use of DSC-enhanced perfusion MRI and conventional contrast-enhanced MRI for the follow-up of treatment of glioblastoma multiforme (GBM)	Class III	The authors concluded that the combination of perfusion and contrasted MRI provides useful information. Elevated rCBV supports the diagnosis of recurrent or progressive tumor. However, a mismatch can be seen with rapidly growing lesions that might otherwise be taken for reactive non-tumor changes (pseudoprogression)

Table 3 MRI diffusion weighted imaging (DWI) and ADCs

First author and year	Description of study	Class	Conclusions
Paldino 2011 [47]	Retrospective study of images obtained from 15 recurrent GBM patients to determine the prognostic significance of changes in parameters derived from DTI that occur in response to treatment with bevacizumab (BEV) and irinotecan in patients with recurrent glioblastoma multiforme (GBM)	Class III	DTI detected a change in ADC within the flair signal abnormality (FSA) after therapy in nine patients (5 increased, 4 decreased)
			Patients with a change in ADC within FSA had significantly shorter overall survival ($p = 0.032$) and progression free survival ($p = 0.046$) than those with no change
			The authors concluded that in recurrent GBM patients treated with BEV and irinotecan, a change in ADC after therapy in FSA is associated with decreased survival
Al Sayyari 2010 [39]	Prospective study of 17 patients previously treated for high-grade glial neoplasms presenting with new enhancing lesions to evaluate the relationship between contrast enhancement and ADC mapping	Class III	The authors conclude that an increased in enhancement coupled with a reduction in ADC support a diagnosis of tumor recurrence or progression
Zeng 2007 [50, 61]	Prospective single center study of 55 patients with suspected recurrent GBM examining a variety of imaging techniques	Class III	ADC value and ADC ratios (ADC of contrast-enhancing lesion to matching structure in the contralateral hemisphere) were significantly higher in radiation injury regions than in recurrent tumor ($p < 0.01$)
			The authors summarize by indicating that the ADC value can be added to discriminant analysis, to improve the ability to differentiate recurrent glioma and radiation injury
Rollin 2006 [48]	Prospective study of 28 patients with intraaxial brain tumors underwent conventional MR imaging (T2- and T1-weighted sequences after gadobe-nate dimeglumine injection), diffusion imaging and T2*-weighted echo-planar perfusion imaging	Class III	rCBV values were increased in all recurrent tumors,
	Determinations of rCBV and ADC were performed in the solid parts of each tumor, peritumoral region and contra-lateral white matter		Diffusion and perfusion imaging, even with relatively short imaging and data processing times, provide important information for lesion characterization
Sundgren 2006 [49]	Retrospective review of 28 patients with recurrent malignant glioma using mean ADC, FA and eigenvalue	Class III	ADC recurrence group
			mean = $1.27 \pm 0.15 \times 10^{-3}$ mm^2/s)
			ADC nonrecurrence group
	The purpose of this study was to assess the use of DTI in the evaluation of new contrast-enhancing lesions and peri-lesional edema in patients previously treated for brain neoplasm in the differentiation of recurrent neoplasm from treatment-related injury		$1.12 \pm 0.14 \times 10^{-3}$ mm^2/s ($p = 0.01$)
			ADC ratios in the white matter tracts in peri-lesional edema trended higher ($p = 0.09$) in treatment-related injury than in recurrent neoplasm (mean $\pm$ SD = 1.85 ± 0.30 vs 1.60 ± 0.27, respectively)
			FA ratios were significantly higher in normal-appearing white matte) tracts adjacent to the edema in the nonrecurrence group (mean $\pm$ SD = 0.89 ± 0.15) than in those in the recurrence group (mean $\pm$ SD = 0.74 ± 0.14; $p = .03$)
			The authors conclude that the assessment of diffusion properties, (ADC values and ADC ratios), in contrast-enhancing lesions, peri-lesional edema and normal white matter adjacent to the edema can differentiate radiation injury from tumor recurrence

found a sensitivity and specificity of 0.67 in determining true from pseudo-progression and conclude that pseudo-progression is common and needs to be high in the differential diagnosis of increasing enhancement on serial imaging. Of note factors suggestive of pseudoprogression included T1 enhancement without edema [34], appearance of necrosis in a previously non-enhancing area after treatment, enhancing focus developing at a distance from the original occurrence, enhancement near periventricular white matter tracts, and soap bubble or Swiss cheese pattern [35]. Other authors noted that 80–90 % of all progression occurred with 2 cm of the original tumor bed [30, 36] and that increasing surface tumor volume was associated with decreased survival [38].

Table 4 Magnetic resonance imaging spectroscopy (MRS)

First author, year	Description of study	Data Class	Conclusions
Matsusue 2010 [54]	Retrospective single center non-blinded study that included 6 patients with recurrent GBM A multiparametric scoring system including MR DWI, DSC-enhanced perfusion imaging, and MRS techniques was proposed to improve diagnostic accuracy	Class III	For MRS alone 		Tumor	No Tumor
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MRS +	3	1
MRS -	1	1 | | Sensitivity	0.75
Specificity	0.50
Accuracy	0.67	 Optimum thresholds for ADC ratio (1.30), rCBV ratio (2.10), and either combined Cho/Cr (1.29) and Cho/NAA (1.06) yielded diagnostic accuracies of 86.7, 86.7, and 84.6 %, respectively ($p < 0.05$) A combined multiparametric score improved diagnostic accuracy to 93.3 % ($p < 0.05$) Downgraded due to design and size
Srinivasan 2010 [57]	Retrospective single center non-blinded study examining MRS prediction of recurrent tumor with pathological correlation	Class III	For MRS alone 		Tumor	No Tumor
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MRS +	27	0
MRS -	2	11 | | Sensitivity	0.93
Specificity	1.00
Accuracy	0.95	 Downgraded due to design
Chuang 2007 [52]	Prospective single center non-blinded study examining MRS prediction of recurrent tumor	Class III			Tumor	No Tumor
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MRS +	4	0
MRS -	0	11 | | Sensitivity	1.0
Specificity	1.0
Accuracy	1.0	 Downgraded due to design and size
Zeng 2007 [50, 61]	Prospective study of 55 patients with recurrent GBM undergoing imaging to determine the likelihood of recurrent or progressive tumor Spectral data for *N*-acetylaspartate (NAA), choline (Cho), creatine (Cr), lipid (Lip), and lactate (Lac) were analyzed in conjunction with the ADC were correlated with histopathology in all patients	Class III	Cho/NAA and Cho/Cr ratios were significantly higher in recurrent tumor than in regions of radiation injury ($p < 0.01$). Cho/NAA and Cho/Cr ratios combined differentiated recurrent glioma from radiation injury in 85.5 % of the total subjects Cho/NAA, Cho/Cr, and ADC ratio correctly classified 96.4 % of total subjects were correctly classified The authors conclude that discriminant analysis with these factors led to high rate of correctly identifying progressive tumor from radiation necrosis This method of analysis has not been validated

Table 4 continued

First author, year	Description of study	Data Class	Conclusions
Zeng 2007 [50, 61]	Prospective single institution study of 28 patients with recurrent GBM studied with MRS and compared with histopathology	Class III	<table><tr><td></td><td>Tumor</td><td>No Tumor</td></tr><tr><td>MRS +</td><td>16</td><td>0</td></tr><tr><td>MRS -</td><td>1</td><td>9</td></tr></table> <table><tr><td>Sensitivity</td><td>.94</td></tr><tr><td>Specificity</td><td>1.0</td></tr><tr><td>Accuracy</td><td>.96</td></tr></table> Cho/NAA and Cho/Cr ratios were significantly higher in recurrent tumor than in radiation injury ($p < 0.01$) NAA/Cr ratios were lower in recurrent tumor than in radiation injury ($p = 0.02$) Cut-off value for Cho/Cr and Cho/NAA 1.71 The authors conclude that 3D (1)H-MRS could differentiate recurrent tumor from radiation injury Study downgraded on size and design. It is likely that some if not all of the patients described here are also included in the previous study by Zeng et al. listed above
Hollingworth 2006, Am J Neuroradiol [10]	Systematic review of studies published from 2002 to 2004 addressing diagnostic accuracy MRS in patients with CNS tumors, including progressive GBM	Systematic review	The authors concluded that several studies found that MRS was highly accurate for distinguishing high- and low-grade gliomas, though the incremental benefit of MRS in this setting was less clear in demonstrating progression versus non-progression (see Text for more detail on included studies)
Weybright 2005 [60]	Retrospective single institution non-blinded study of 28 patients with recurrent GBM evaluating the ability of MRS to differentiate recurrent tumor from radiation necrosis	Class II	<table><tr><td></td><td>Tumor</td><td>No Tumor</td></tr><tr><td>MRS +</td><td>15</td><td>0</td></tr><tr><td>MRS -</td><td>1</td><td>12</td></tr></table> <table><tr><td>Sensitivity</td><td>0.94</td></tr><tr><td>Specificity</td><td>1.00</td></tr><tr><td>Accuracy</td><td>0.96</td></tr></table> Mean Cho/Cr ratios were 2.52 for tumor, 1.57 for radiation injury, and 1.14 for normal-appearing white matter Mean Cho/NAA ratios were 3.48, 1.31, 0.79, and mean NAA/Cr ratios were 0.79, 1.22, and 1.38, respectively Cho/Cr (choline/creatine) and Cho/NAA (choline/*N*-acetyl aspartate) ratios were significantly higher, and the NAA/Cr ratios significantly lower, in tumor than in radiation injury (all three differences, $p < 0.0001$)

Table 4 continued

First author, year	Description of study	Data Class	Conclusions
			The Cho/Cr and Cho/NAA ratios were significantly higher in radiation injury than in normal-appearing white matter ($p < 0.0003$ and $p < 0.0001$, respectively), whereas NAA/Cr ratios were not different ($p = 0.075$)
			Cutoff value for Cho/Cr and/or Cho/NAA of 1.8 correctly classified 27 of 28 patients could be correctly classified. The authors conclude MRS can differentiate tumor from radiation injury in patients with recurrent contrast-enhancing transcranial lesions
			Despite retrospective nature this study potentially represents Class I diagnostic data. Downgraded from a potential Class I study to Class II on design and size
Ando 2004 [51]	Retrospective single institution study of 20 patients treated for glioma including 2 with progressive GBM evaluated with MRS. Cho/Cr ratio of 1.5 or greater used as an indicator of tumor presence	Class III	(see table below)
Lichy 2004 [62]	Prospective imaging study of 24 patients diagnosed with a glioma and treated with radiotherapy	Class III	Sensitivity 87 % (95 % CI 60–98) Specificity 89 % (95% CI 52–100) Not able to separate by pathology Included here for completeness as it is included in the systematic review of MRS as noted in the text
Plotkin 2004 [63]	Prospective single institute non-blinded study of MRS (Cho/Cr and Cho/NAA ratio as tumor criterion of 1.11 and 1.17, respectively) and SPECT in 25 patients with treated for glioma including 10 with suspected progressive GBM	Class III	(see table below)

Ando 2004 [51]:

	Tumor	No Tumor
MRS +	9	1
MRS -	5	5

Sensitivity	0.64
Specificity	0.83
Accuracy	0.70

The authors conclude that Cho/Cr ratio of 1H-MRS differentiate residual/recurrent gliomas from non-neoplastic lesions

Plotkin 2004 [63]:

	Tumor	No Tumor
MRS +	17	0
MRS -	2	5

Sensitivity	0.89
Specificity	1.00
Accuracy	0.92

SPECT 123I-IMT uptake cut-off of 1.62

Sensitivity 0.95

Specificity 1.00

Accuracy 0.96

1H-MRS

sensitivity 0.89

specificity 0.83

accuracy 0.88

Table 4 continued

First author, year	Description of study	Data Class	Conclusions
			Both SPECT and MRS were successful in in differentiating recurrent tumor from radiation necrosis. 123I-IMT SPECT yielded slighltly more favorable results in this study.
			Downgraded from Class II to III based on limited numbers, mixed pathologies and design
Rabinov 2002 [56]	Prospective single institution study of 17 patients with progressive glioma including 4 with progressive GBM evaluated with MRS. Cho/Cr ratio of 1.3 or greater used as an indicator of tumor presence. Diagnosis was confirmed by means of histopathologic analysis of the biopsy samples in all cases	Class III	*(see table below)*
Traber 2002 [58]	Prospective single institution study of including data on 43 patients with progressive malignant glioma (including 34 patients with progressive GBM) evaluated with MRS. Diagnosis was confirmed by means of by biopsy or clinical followup	Class II	*(see table below)*
Wald 1997 [59]	Prospective single institution study of 12 patients with recurrent glioblastoma evaluated with MRS	Class II	*(see table below)*

Rabinov 2002 [56] — Conclusions

	Tumor	No Tumor
MRS +	9	1
MRS -	0	7

Sensitivity	1.00
Specificity	0.88
Accuracy	0.94

The authors conclude that In 3-MRS has sufficient spatial resolution and chemical specificity to allow distinction of recurrent tumor from radiation effects in patients with treated gliomas

Downgraded to Class III based on limited numbers, mixed pathologies and design

Traber 2002 [58] — Conclusions

	Tumor	No Tumor
MRS +	23	2
MRS -	9	9

Sensitivity	0.72
Specificity	0.82
Accuracy	0.74

The authors conclude that MRS techniques are able to diagnose tumor recurrence early and unambiguously in cases where focal choline accumulation is detected

This study is a high quality study that included predominately GBM patients but does not differentiate the results for anaplastic astrocytoma from GBM results and therefore is downgraded to Class II

Wald 1997 [59] — Conclusions

	Tumor	No Tumor
MRS +	6	0
MRS -	5	1

Sensitivity	0.55
Specificity	1.00
Accuracy	0.58

The authors conclude that MRS imaging discriminates between contrast-enhancing radiation necrosis and residual or recurrent tumor

Class II based on size and restricted population

Table 5 Radiotracers-PET

First author and year	Description of study	Data class	Conclusions
Enslow 2012 [65]	Prospective study of 15 patients with suspected progressive malignant glioma (including 10 progressive GBM) comparing F-fluorodeoxyglucose (FDG) and F-fluorothymidine (FLT) PET in differentiating radiation necrosis from recurrent glioma. On the basis of follow-up Gd-enhanced MRI, lesion-specific recurrent tumor was defined as a definitive increase in size of the lesion, and radiation necrosis was defined as stability or regression	Class II on comparison Class III on diagnosis	FDG PET Sensitivity 0.91 Specificity 0.50 PPV 0.80 NPV 0.20 FLT PET Sensitivity 0.82 Specificity 0.50 PPV 0.73 NPV 0.27 The authors conclude that both methods could differentiate recurrent tumor from necrosis and that the use of fluoro-thymidine offered no advantage over fluoro-glucose. The study is downgraded mainly because of size. The low specificity and very low NPV support concerns over the routine role of PET techniques for recurrent primary brain tumors
Tripathi 2012 [67]	Prospective comparative study of F-18 FDG PET and C-11 MET PET for the evaluation of recurrence in primary brain tumors in 35 patients with recurrent primary brain tumors (including 7 progressive GBM)	Class II	Tumor recurrence 24 patients No recurrence/stable 11 patients. FDG predicted recurrence in 15/35 (42 %) MET predicted recurrence in 24/34 (70.5 %) <table><tr><td></td><td>sens</td><td>spec</td><td>kappa</td></tr><tr><td>FDG</td><td>0.81</td><td>0.89</td><td>0.23 (fair)</td></tr><tr><td>MET</td><td>0.95</td><td>0.89</td><td>0.93 (good)</td></tr></table> The authors conclude that MET should be the radiotracer of choice based better on accuracy of diagnosis and reliability. Class II due to limited number of GBM patients
Galldiks 2010 [69]	Two patients reported with an unusually stable clinical course and long-term survival who were treated after surgery and radiotherapy with adjuvant temozolomide (TMZ) chemotherapy for 17 and 20 cycles, respectively. Ithe biologic activity of the tumors was monitored by repeated methyl-11C-L-MET and 3'-deoxy-3'-18F-fluorothymidine (FLT) PET studies	Class III	Repeated MET- and FLT-PET imaging accurately documented complete initial response and subsequent failure of the treatment regimen. The authors suggest that repeated MET- and FLT-PET imaging provide information on the biologic activity of a tumor that can be used to monitor and detect changes in activity
Galldiks 2010 [69]	Prospective comparison of MET-PET and contrast-enhanced MRI with Gd-DTPA in 12 uniformly pretreated patients with recurrent GBM	Class III	MET volume 30.2 ± 22.4 cm^3 Gd-DTPA volume 13.7 ± 10.6 cm^3 ($p = 0.04$). MET uptake and Gd-DTPA volume were positively correlated r = 0.76, $p = 0.003$, index 1.3 or more r = 0.74, $p = 0.005$ index 1.5 or more The authors conclude that active tumour volume is underestimated by Gd-DTPA enhancement and that complementary information derived from MET uptake and Gd-DTPA enhancement will assist in developing individualized, patient-tailored therapy strategies in patients with recurrent GBM. Limited data on determining progression versus pseudoprogression

Table 5 continued

First author and year	Description of study	Data class	Conclusions
Schnell 2009 [71]	Prospective study of 12 patients with suspected recurrent GBM imaged with (18)F-labeled glycosylated Arg-Gly-Asp peptide ([(18)F]Galacto-RGD) PET and the studies fused with cranial MR images for image-guided surgery. Tumor samples taken from areas with intense tracer accumulation in the [(18)F]Galacto-RGD PET images and were analyzed histologically and immunohistochemically	Class III	Normal brain tissue did not show significant tracer accumulation (mean SUV, 0.09 ± 0.04),
			GBMs demonstrated significant but heterogeneous tracer uptake, with a maximum in the highly proliferating and infiltrating areas of tumors (mean SUV, 1.6 ± 0.5)
			Immunohistochemical staining was prominent in tumor microvessels as well as glial tumor cells
			In areas of highly proliferating glial tumor cells, tracer uptake (SUVs) in the [(18)F]Galacto-RGD PET images correlated with immunohistochemical alpha(v)beta(3) integrin expression of corresponding tumor samples
			The authors conclude that [(18)F] Galacto-RGD PET successfully identifies alpha(v)beta(3) expression in patients with GBM
Potzi 2007 [66]	Prospective comparative study of F-18 FDG PET and C-11 MET PET for the evaluation of recurrence in primary brain tumors in 28 patients with progressive GBM	Class II on comparison Class III on diagnosis	Mean overall survival 12.7 months
			Focally increased uptake:
			MET PET 24/28
	The patients were divided into two groups: those that survived less than 12 months and those that survived longer than 12 months		FDG PET 2/28
			MRI in 18/28
			Neither FDG nor MET uptake correlated with either survival time or disease duration.
			MET PET correlated with survival group
			Sensitivity of 86 %
			Specificity of 8 %
			The authors conclude that FDG PET is of limited value in the work-up of recurrent GBM because of its lower sensitivity than MET PET and the fact that it allows no prediction of the outcome. MET PET visualizes viable tumor tissue without adding any prognostic information
Yamamoto 2006 [73]	Retrospective correlation analysis of predicted tumor volume using 3′-deoxy-3′-[F-18]fluorothymidine (FLT) on PET images and gadolinium enhanced MR images (GdMRI) in 10 patients with progressive GBM	Class III	A significant correlation between the tumor volume identified by FLT and GdMRI was found ($p < 0.0001$) although there was a difference in the areas of Gd-DTPA enhancement and FLT uptake
			The authors concluded that while FLT PET may be useful for the detection of recurrent glioblastoma multiforme, their data did not support a clear-relationship between FLT accumulation and Gd-DTPA enhancement
Eary 1999 [70]	Prospective comparison of thymdine PET, FDG PET and MRI in 13 patients including 4 with recurrent GBM	Class III	In the four GBM patients both thymidine and FDG imaging increased with suspected tumor although in different patterns
			The authors conclude that imaging brain tumor cellular proliferation provides unique information for guiding patient treatment
Ishizu 1994 [72]	Propsective study adding glucose uptake to FDG PET in 3 patients with recurrent GBM	Class III	FDG uptake ratio (tumor:normal) had a mean increase of 27 % with glucose loading
			The authors conclude that glucose loading might improve the ability of FDG-PET to detect recurrent or residual tumors

Table 5 continued

First author and year	Description of study	Data class	Conclusions
Chin 1991 [68]	Retrospective report on 2 patients with recurrent GBM imaged with FDG PET	Class III	In these cases PET was useful in monitoring the progression of GBM
			Quote, "PET has a promising role in neuroradiology for accurate diagnosis and prognostication of malignant tumors as well as differential diagnosis of radiation necrosis and recurrent tumors. Particularly, PET has proven its ability to accurately differentiate radiation necrosis from recurrent brain tumor."

Based on the Class II and supporting Class III data discussed above and summarized in Evidentiary Table 1, the following Level 2 recommendation is made: MRI with and without gadolinium enhancement is recommended as an imaging surveillance method to detect the progression of previously diagnosed glioblastoma, with a sensitivity of 0.95, a specificity of 0.67 and an overall accuracy of 0.83.

MRI techniques: perfusion DSC and on DCE

Developing MRI techniques include the ability to study the perfusion of central nervous system tissue using DSC and dynamic contrast enhancement. Eight studies were reviewed and included in evidentiary Table 2 below [39–46]. All were considered Class III studies, primarily due to lack of control groups, inability to create Bayesian tables and lack of relevant validation groups.

Barajas et al. [40] retrospectively evaluated 57 patients with progressive glioblastoma to investigate whether cerebral blood volume (CBV), peak height (PH), and percentage of signal intensity recovery (PSR), all measurements derived from the results of T2-weighted dynamic susceptibility-weighted contrast material-enhanced (DSC) MRI performed after external beam radiation therapy (EBRT) could be used to distinguish progressive glioblastoma multiforme from pseudo-progression or radiation necrosis. Both PH and CBV were significantly higher ($p < 0.01$) in patients with recurrent GBM than in patients with radiation necrosis. Additionally, the PSR values were significantly lower ($p < 0.05$) in patients with recurrent GBM than in patients with radiation necrosis. Although a non-validated study and no specific guidelines were proposed, the authors conclude that the use of DSC perfusion MRI may allow differentiation of recurrent GBM from pseudo-progression.

Vrabec et al. [46] retrospectively reviewed 32 imaging studies in 8 patients with glioblastoma to evaluate patients at various stages of follow-up: stable, prior to progression and following clear progression. They evaluated the regional CBV (rCBV) and the apparent diffusion coefficient (ADC—see also next section) and concluded that maximum rCBV and minimum ADC correspond to tumor recurrence or progression. Ringelstein et al. [42] prospectively studied 12 patients with progressive high-grade glioma (number of GBM patients not specified) and found that ADC mapping was predictive of tumor response to treatment in over 80 % of the patients and gave an indication of which patients were at highest risk of progression. In a similar prospective study of 17 patients undergoing treatment for high grade glioma (including 11 patients with GBM), Al Sayyari et al. [39] concluded that an increase in enhancement volume (as well as a reduction in ADC, see further discussion below) supports a diagnosis of progressive tumor. Although these studies are small and non-validated, the high rate of identifying responding versus progressive tumor was encouraging.

Several authors have proposed new metrics using MRI perfusion data. Hu et al. [41] published a prospective series of 25 patients with suspected progression of GBM at craniotomy and defined a new metric called pMRI fractional tumor burden (see entry in Evidentiary Table 2 for definition) showing that when compared to other blood volume parameters this variable demonstrated a significant correlation with overall survival ($r = 0.82$, $p < 0.0001$). Sawlani et al. [43] also describe a novel imaging metric, the hyperperfusion volume (HPV), which reflects local perfusion change in progressive GBM and correlated significantly with time to progression. Sorenson et al. [44] used three parameters (changes in vascular permeability/flow, in microvessel volume, and circulating collagen IV level) to create a vascular normalization index (VNI) that correlated with overall survival ($R = 0.54$; $p = 0.004$) and progression-free survival ($R = 0.6$; $p = 0.001$). Stenberg et al. [45] that elevated rCBV suggests progressive tumor; however, rapidly growing lesions can be misinterpreted as reactive non-tumor changes (pseudoprogression).

While potentially significant metrics, incorporation into recommendations will await further study and validation in independent relevant populations. The planning and execution of well-designed clinical trials for these promising techniques is strongly encouraged.

Table 6 Radiotracers-CT SPECT

First author and year	Description of study	Data class	Conclusions
Vos 2012 [82]	Prospective trial involving 22 patients with progressive glioma (including 8 progressive GBM) patients undergoing both MRI and (201)Tl SPECT imaging procedures to compare their prognostic value	Class III	Both strongly related to OS ($p < 0.02$)
			The addition of one imaging modality to the other did not contribute to the prediction of OS
			The authors conclude that both MRI and (201)Tl SPECT are valuable in the prediction of OS. It is adequate to restrict to one of both modalities in the radiological follow-up during treatment
			Well conducted study but of limited value specifically for progressive GBM
Vos 2007 [74]	Systematic review to determine the diagnostic accuracy of 201Tl SPECT in the detection of glioblastoma recurrence in patients with previous radiotherapy for supratentorial glioma. Studies included minimum of 6 patients with 201Tl SPECT study and pathological confirmation	Systematic Review	Eight studies met the inclusion criteria but only one considered high quality
		Class III	Sensitivity 0.43–1.00
			Specificity 0.25–1.00
			Diagnostic odds ratio greater than 1 in all studies included
	Sensitivity, Specificity and Diagnostic odds ratio of 201Tl SPECT was calculated. A quantitative meta-analysis was not performed due to study heterogeneity		The authors conclude that 201Tl SPECT seems a valuable method in the detection of tumor recurrence in patients treated with radiotherapy for supratentorial glioma. The evidence is not robust because of the low quality and high heterogeneity of the studies included
			Downgraded to Class III due to quality of studies cited
Plotkin 2004 [63]	Prospective single institute non-blinded study of MRS (Cho/Cr and Cho/NAA ratior as tumor criterion of 1.11 and 1.17, respectively) and SPECT (cut-off of 1.62) in 25 patients with suspected progressive of malignant glioma (including 10 progressive GBM)	Class III	SPECT 123I-IMT uptake
			Sensitivity 0.95
			Specificity 1.00
			Accuracy 0.96
			1H-MRS
			sensitivity 0.89
			specificity 0.83
			accuracy 0.88
			Both SPECT and MRS were successful in in differentiating recurrent tumor from radiation necrosis. 123I-IMT SPECT yielded slightly more favorable results in this study
			Downgraded due to restricted population
Schwartz 1998 [79]	Prospective study 201Tl SPECT and 99mTc-hexamethypropyleneamine oxime (HMPAO) performed 1 day prior to reoperation in 47 patients with recurrent glioblastoma multiforme	Class III	Group I (201Tl ratio <2 and 99mTc-HMPAO ratio <0.5) showed radiation changes in their biopsy specimens: 83.3 % 1-year survival rate
			Group II patients (201Tl ratio <2 and 99mTc-HMPAO ratio of ≥0.5 or 201Tl ratio between 2 and 3.5 regardless of 99mTc-HMPAO ratio) 29.2 % 1-year survival rate
			Group III (201Tl ratio >3.5 and 99mTc-HMPAO ratio ≥0.5) 6.7 % 1-year survival rate

Table 6 continued

First author and year	Description of study	Data class	Conclusions
Kline 1996 [76]	Retrospective analysis of 33 adult patients with progressive malignant glioma undergoing Tl 201 SPECT imaging. Outomce (included 21 GBM) correlated by histologic analysis (28 cases) clinical course(14 cases) Tumor/scalp (T/S) ratios were calculated for all patients	Class III	SPECT grouping was more closely associated with 1-year survival ($p < 0.001$) than histological data were associated with 1-year survival ($p < 0.01$) and was the only variable significantly associated with long-term survival ($p < 0.005$) The authors conclude that SPECT data correlates with pathological findings and survival. Excellent study downgraded only due to restricted population
Namba 1996 [84]	Prospective study assessing the effect of steroid on thallium-201 uptake in four patients with recurrent malignant glioma (included 2 GBM)	Class III	Sensitivity 0.94 Specificity 0.63 T/S ratios >2.0 had a positive predictive value for tumor recurrence of 92 % T/S ratios less than 0.5 had a NPV for tumor recurrence of 83 % The authors conclude that Thallium-201 SPECT is a sensitive and accurate test to differentiate tumor recurrence from radiation necrosis Steroid administration reduced uptake by over 20 % (<0.05 paired t test) The authors conclude that the effect of steroid has to be taken into account when interpreting the 201Tl index
Lorberboym 1995 [77]	Prospective study of SPECT compared to CT including 31 patients with progressive glioblastoma	Class III	The authors conclude that SPECT was more reliable than CT in identifying progression, improvement, or no change in brain tumor burden
Kosuda 1994 [83]	Prospective study including patients with progressive GBM assessing whether quantitative 201Tl SPECT as a prognostic test L/N ratio defined as the ratio of the count from lesion to normal brain	Class III	201Tl index (L/N ratio) negatively correlated with short survival ($r = -0.502$, $p < 0.05$) The authors conclude that quantitative 201Tl SPECT may be a useful tool for predicting survival of patients with suspected recurrent cerebral tumor and may be used in place of fluorine-18-2-fluoro-D-glucose (18F-FDG) scan
Vertosick 1994 [85]	Prospective study of 16 patients with progressive GBM studied with thallium-201 (Tl-201) SPECT T/C ratio defined as the ratio of Tl-201 uptake in tumor to Tl-201 uptake in myocardium	Class III	Significant negative correlation between the T/C ratio at failure and the time interval between failure and death ($r = -0.602$, $p = 0.014$). Patients with T/C ratios of less than 0.3 lived an average of 13 months, whereas patients with T/C ratios of more than 0.3 lived an average of only 4 months Not able to calculate sensitivity or specificity from data provided The authors conclude that SPECT is of prognostic benefit and identifies recurrence accurately
Kosuda 1993 [83]	Prospective study of Tl-201 brain SPECT including 14 patients with progressive GBM and 6 with radiation necrosis L/N ratio defined as the ratio of the count from lesion to normal brain	Class III	Tl-201 brain SPECT using a L/N ratio of 2.5 as a cutoff accurately discriminated between recurrent tumor and radiation necrosis in all cases. Not able to calculate sensitivity or specificity The authors conclude that quantitative Tl-201 brain SPECT can discriminate radiation necrosis from recurrent tumor and estimating residual tumor burden

Table 7 Combination studies and multi-parametric analysis

First author and year	Description of study	Data class	Conclusions
Galban 2011	Prospective analysis of 37 patients at risk for progressive GBM undergoing chemoradiation monitored prospectively with quantitative MRI, including ADC and rCBV. PRM, a voxel-by-voxel image analysis method, was evaluated as an early prognostic biomarker of overall survival. Clinical and conventional MR parameters were also evaluated	Class III	Multivariate analysis showed that PRM (ADC+) in combination with PRM (rCBV−) obtained at week 3 had a stronger correlation to 1-year and overall survival rates than any baseline clinical or treatment response imaging metric
			The composite biomarker significantly correlated with survival ($p = 0.00010$) and identified three distinct patient groups:
			Non-responders ($n = 13$) median survival (MS) of 6.0 months
			Partial responders ($n = 16$) (MS of 12.8 months)
			Responders ($n = 8$) (MS over 30 months had not yet been reached)
			The authors conclude that the inclusion of PRM (ADC+) and PRM (rCBV−) into a single imaging biomarker metric provided early identification of patients resistant to standard chemoradiation
			This well-conducted study strongly suggests the value of multiparametric analysis to identify progression of GBM. It is downgraded due to lack of validation group
Matsusue 2010 [54]	Retrospective review of fifteen patients with glioma (including 5 with GBM) with suspected progression following radiation. All had undergone advanced MRI imaging allowing the following parameters to be measured:	Class III	Optimum thresholds for ADC ratio (1.30), rCBV ratio (2.10), and either combined Cho/Cr (1.29) and Cho/NAA (1.06) yielded diagnostic accuracies of 86.7, 86.7, and 84.6 %, respectively ($p < 0.05$)
	Minimum ADC ratio,		A combined multi-parametric score threshold of 2 improved diagnostic accuracy to 93.3 % ($p < 0.05$)
	Maximum rCBV ratio		The authors conclude that incorporating the diagnostic results of DWI, DSC, and MRS using a multi-parametric scoring system has the potential to assist in differentiating tumor progression from treatment effect
	Maximum MRS choline/creatine (Cho/Cr) and choline/*N*-acetyl-aspartate (Cho/NAA) metabolic peak-height ratios		
	Each parameter was scored as either glioma progression (one) or radiation change (zero) based upon thresholds derived from our own data		Downgraded due to study size and lack of a validation group
	For each lesion, the combined parameters yielded a multiparametric score (0–3) for prediction of tumor progression or post-radiation change		
Zeng 2007 [50, 61]	Retrospective review of 55 patients with malignant glioma (including 5 with GBM) with suspected progression following radiation	Class III	Cho/NAA and Cho/Cr ratios correctly classified 85.5 % of the subjects
	All had undergone advanced MRI imaging allowing the following parameters to be measured:		Discriminant analysis of MRS imaging plus DWI (combining Cho/NAA, Cho/Cr, and ADC ratio) improved this to 96.4 %. (Chi square = 3.96, $p = 0.046$)
	Spectral data for *N*-acetylaspartate (NAA), choline (Cho), creatine (Cr), lipid (Lip), and lactate (Lac)		The authors conclude that using discriminant analysis, MRS in combination with ADC may identify progression versus treatment effect
	ADC in all patients		It is downgraded due to lack of validation group
	Diagnosis of these lesions was assigned by means of follow-up or histopathology		

MRI techniques: perfusion DWI and ADC

Additional MRI based techniques include diffusion weighted imaging (DWI) and ADC mapping, as introduced along with CBV determination in the section above. All data reviewed was Class III, but promises with additional study to provide valuable information in the patient with progressive glioblastoma [39, 47–50] The details of these studies are included in evidentiary Table 3 and the conclusions are highlighted below.

Paldino et al. [47] retrospectively reviewed images obtained from 15 patients with progressive GBM evaluating the prognostic significance of diffusion tensor imaging (DTI) following treatment with bevacizumab (BEV) and irinotecan. DTI detected changes in ADC within the flair signal abnormality after therapy, which correlated with a significantly shorter overall survival ($p = 0.032$) and progression free survival ($p = 0.046$).

Al Sayyari et al. [39] prospectively studied 17 patients previously treated for high-grade glial neoplasms (including 11 patients with GBM) presenting with new enhancing lesions to evaluate the relationship between contrast enhancement and ADC mapping. The presence of new enhancement coupled with a reduction in ADC supports a diagnosis of tumor progression.

Zeng et al.'s prospective single-center study of 55 patients with suspected recurrent GBM examined a variety of imaging techniques. ADC value and ADC ratios (ADC of contrast-enhancing lesion to the matching structure in the contralateral hemisphere) were significantly higher in radiation injury regions than in recurrent tumor ($p < 0.01$). The authors summarize by indicating that the ADC value can be added to discriminant analysis, to improve the ability to differentiate recurrent glioma and radiation injury [50].

Rollin et al. published their prospective study of 28 patients with intraaxial brain tumors who underwent conventional MR imaging (T2- and T1-weighted sequences after gadolinium injection), diffusion imaging and T2 weighted echo-planar perfusion imaging. Determinations of rCBV and ADC were performed in the solid parts of each tumor; peritumoral region and contra-lateral white matter. They found that rCBV values were increased in all recurrent tumors. Diffusion and perfusion imaging, even with relatively short imaging and data processing times, provided important information for lesion characterization [48].

Sundgren et al. conducted a retrospective review of 28 patients with progressive malignant glioma (including 4 patients with GBM) using mean ADC, fractional anisotropy (FA) and eigenvalues to assess the use of DTI in the evaluation of new contrast-enhancing lesions and peri-lesional edema to differentiate progressive neoplasm from treatment-related injury. The mean ADC was significantly greater comparing progressive to non-progressive groups ($1.27 \pm 0.15 \times 10^{-3}$ mm²/s vs $1.12 \pm 0.14 \times 10^{-3}$ mm²/s, $p = 0.01$). ADC ratios in the white matter tracts in peri-lesional edema trended higher ($p = 0.09$) in treatment-related injury than in recurrent neoplasm (mean ± SD = 1.85 ± 0.30 vs 1.60 ± 0.27, respectively). FA ratios were significantly higher in normal-appearing white matter) tracts adjacent to the edema in the non-recurrence group (mean ± SD = 0.89 ± 0.15) than in those in the recurrence group (mean ± SD = 0.74 ± 0.14; $p = 0.03$). The authors conclude that the assessment of diffusion properties, (ADC values and ADC ratios), in contrast-enhancing lesions, peri-lesional edema and normal white matter adjacent to the edema can differentiate radiation injury from tumor progression [49].

While these studies represent intriguing possibilities, incorporation into recommendations will await further study and validation in independent relevant populations. As with the MRI perfusion techniques, the planning and execution of well-designed clinical trials for these promising techniques is strongly encouraged.

MRI techniques: spectroscopy

One of the earliest specialized MRI techniques was MRS, which has been increasingly utilized to monitor treatment effect and tumor growth. The use of proton-based MRS (or 1H-MRS) yields information on the metabolic composition within a selected target area of tissue, conceptually similar to an "electronic biopsy". Comparison of the relative concentration of these metabolites provides an indication of factors such as cellular membrane turnover and neuronal viability that assists in the assessment of whether viable tumor is present in the sampled region. MRS adds little additional time (15–30 min) to the traditional MRI technique routinely utilized in progressive glioblastoma patient management and therefore is an appealing non-diagnostic technique. Multiple publications addressing the role of MRS are available for review in Evidentiary Table 4) [10, 50–61].

Only one previous systematic review on the topic was identified [10]. Hollingworth et al. [10] evaluated the role of MRS in characterizing brain tumors and included differentiating radiation necrosis from progressive tumor in patients with primary brain tumors in papers published between 2002 and 2004. This paper included four studies that are included in this guideline. Although no combined summary statistic was calculated the results indicated a range of sensitivity of 64–89 % and specificity of 82–89 % as follows:

Traber et al. [58] sensitivity 72 % (95 % CI 53–86 %) specificity 82 % (95 % CI 48–98 %). Ando et al. [51] sensitivity 64 % (95 % CI 35–87 %) specificity 83 % (95 % CI 36–100 %). Lichy et al. [62] sensitivity 87 % (95 % CI 60–98 %) specificity 89 % (95 % CI 52–100 %). Plotkin et al. [63] 89 % sensitivity 83 % specificity (no CI). Three studies containing Class II data are included in evidentiary Table 4 below, [58–60] only one of which is included in the above systematic review [58].

In the study by Weybright et al. [60], the ability of MRS to differentiate progressive tumor from radiation necrosis was evaluated in 28 patients in a single institution non-blinded retrospective study. Cho/Cr (choline/creatine) and

Cho/NAA (choline/*N*-acetyl aspartate) ratios were significantly higher, and the NAA/Cr ratios significantly lower, in tumor than in radiation injury (all three comparisons, $p < 0.0001$). Cho/Cr and Cho/NAA ratios were significantly higher in radiation injury than in normal-appearing white matter ($p < 0.0003$ and $p < 0.0001$, respectively), whereas NAA/Cr ratios were not ($p = 0.075$). Using a cutoff value of 1.8 for Cho/Cr and/or Cho/NAA, 27 of 28 patients were correctly classified (accuracy 0.96). The authors conclude MRS can differentiate tumor from radiation injury in patients with suspected progressive glioblastoma with a high degree of sensitivity and specificity (0.94 and 0.96 respectively).

Traber et al. [58] described a prospective single-institution study of 42 patients with suspected progressive glioma including 34 patients with progressive GBM and 8 patients with anaplastic astrocytoma evaluated with MRS. In this study the sensitivity was 0.72, the specificity was 0.82 and the overall accuracy was 0.74. This study is a well-conducted prospective study that has an unrestricted study population that is predominately GBM. It is downgraded to Class 2 only because it is not possible to create a completely separate Bayesian analysis that excludes the 8 anaplastic astrocytoma patients from the data presented.

Finally, in an older study Wald et al. [59] published their small series of 12 patients with progressive GBM evaluated with serial MRS with sensitivity of 0.55 and specificity of 1.00 and an overall accuracy of 0.58. This is an older study and small in size but well-conducted. A well conducted meta-analysis creating a summary statistic for sensitivity and specificity would address this issue more appropriately.

Three high-quality studies provide additional supportive data that would be at least Class II for imaging in progressive glioblastoma but contains either a less uniform patient population or the results specifically for GBM are not clear and are therefore lowered to Class III for the purposes of this study [51, 55, 56]. Ando et al. [51] published a retrospective single institution study of 20 patients with progressive glioblastoma evaluated with MRS using Cho/Cr ratio of 1.5 or greater used as an indicator of tumor presence. This small series (published in Japanese) found a sensitivity of 0.64 and a specificity of 0.83 with an overall accuracy of 0.70. The authors conclude that Cho/Cr ratio of 1H-MRS differentiate residual/recurrent gliomas from non-neoplastic lesions.

Plotkin et al. [63] published a prospective single-institute non-blinded study of MRS (Cho/Cr and Cho/NAA ratio of 1.11 and 1.17, respectively). MRS resulted in sensitivity of 0.89, specificity 1.00 and overall accuracy of 92 %. The authors conclude that MRS was successful in differentiating progressive tumor from radiation necrosis although in this study SPECT yielded slightly more favorable results, as discussed below. Rabinov et al. [56]

reported a prospective single institution study of 17 patients with recurrent glioma evaluated with MRS using a Cho/Cr cutoff ratio of 1.3 to differentiate progressive tumor from inactive tumor or treatment effect. In this study the sensitivity was 1.00, the specificity was 0.88 and the overall accuracy was 0.94.

An additional six papers containing Class 3 data are summarized in Evidentiary Table 4 below [50, 52, 54, 57, 61, 62], This additional Class 3 data indicates that MRS identifies progressive tumor from treatment effect/necrosis with a sensitivity ranging from 0.55 to 1.00, a specificity ranging from 0.50 to 1.00 and an overall accuracy ranging from 0.58 to 1.00. The two largest series had sensitivities of 0.9 and 0.93, specificity of 1.00 and accuracy of 0.95 and 0.96, providing additional supporting evidence for the ability of MRS to discriminate progression from treatment effect.

Based on the Class II and supporting Class III data discussed above and summarized in Evidentiary Table 4, the following Level 2 recommendation is made: MRS is recommended as a diagnostic method to differentiate true tumor progression from treatment-related imaging changes or pseudo-progression in patients with suspected progressive glioblastoma with a sensitivity ranging from 0.72 to 0.94, a specificity ranging from 0.82 to 1.00 and an overall accuracy ranging from 0.58 to 0.96.

Radiotracers

FDG PET (fluoro deoxy-glucose positron emission tomography) and MET PET (methionine positron emission tomography)

PET is used widely in non-CNS cancer paradigms to differentiate progressive tumor from treatment effect due to the metabolic incorporation of the tracer molecule into the dividing tumor cells. From review of the available studies the role of radiolabelled tracers (fluoro-deoxy glucose (FDG) and MET) has yet to establish a role in the routine evaluation of primary central nervous system tumor progression, however, further work will determine if this technique will add significantly to the discrimination of progression from treatment effect. Petrirena et al. [64] provide an optimistic view of the continuing role of PET in brain imaging but provides no usable data for the purposes of this guideline.

There are several papers evaluating the role of PET included in the evidence Table 5 providing Class II data [65–67]. Of note, however, is the fact that the Class II nature of this data addresses the choice of radiotracer and provides information at that level if the choice has already been made to use PET in this type of imaging. They are not high-level comparative studies to other techniques such as

MRS or SPECT. Therefore, they do not support a Level II recommendation for or against the overall role of PET imaging. Taken together there is insufficient data to support the routine use of PET imaging in the evaluation of progressive glioblastoma and therefore the routine use is not recommended. The strength of this recommendation is Level 3.

Enslow et al. [65] prospectively evaluated 15 patients with suspected recurrent glioma. The study compared the role of F-fluorodeoxyglucose (FDG) and F-fluorothymidine (FLT) PET in differentiating radiation necrosis from progressive glioblastoma, and while this provides Class 2 data on the comparison (and found that the use of FLT did not improved the predictive ability of PET over the more established FDG), it found a sensitivity of 0.91, a specificity of 0.50, a positive predictive value (PPV) of 0.80 and a NPV of 0.20. Despite the prospective study design, the low specificity and very low NPV argue against recommendation and the small size reduces the value of the study for either technique alone and underscores concerns over the routine role of PET techniques for recurrent primary brain tumors.

Tripathi et al. [67] reported their prospective comparative study of F-18 flurodeoxyglucose (FDG) PET and C-11 MET PET for the evaluation of in 35 patients with recurrent primary brain tumors. FDG predicted recurrence in 15/35 (42 %) and MET predicted recurrence in 24/34 (70.5 %) with sensitivities of 0.81 and 0.95 and specificities of 0.89 and 0.89 respectively. The authors conclude that if PET imaging is employed then MET should be the radiotracer of choice.

Potzi et al. [66] also published a prospective comparative study of F-18 FDG PET and C-11 MET PET for the evaluation of 28 patients with suspected progressive brain tumors and added an evaluation of the results predicting survival. Neither FDG nor MET uptake correlated with either survival time or disease duration, although similar to the Tripathi study, these authors found the sensitivity of MET uptake was better than FDG.

Additional Class III data is provided in the evidence Table 5 evaluating the role of PET imaging in recurrent malignant glioma including the role of monitoring chemotherapy or treatment response [68–70], improved targeting of biopsy with radiolabelled peptides [71], the role of glucose improving fluoro-deoxy-glucose (FDG) [72] and failure of fluoro-thymidine (FLT) to correlate with MRI gadolinium uptake (Table 5) [73].

In 1991, Chin et al. [68], described in a retrospective report of 2 patients followed with serial PET imaging concluded that, "PET has a promising role in neuroradiology for accurate diagnosis and prognostication of malignant tumors as well as differential diagnosis of radiation necrosis and recurrent tumors. Particularly, PET has proven its ability to accurately differentiate radiation necrosis from recurrent brain tumor." From a review of the subsequent available studies, this statement appears to have been overly optimistic.

Based on Class III data discussed above and summarized in Evidentiary Table 5, high-quality comparative studies of PET with other techniques such as MRS or SPECT are not available resulting in a Level 3 recommendation that the routine use of PET imaging in the evaluation of progressive glioblastoma is not recommended.

Radiotracers: CT SPECT

A systematic review published in 2007 by Vos et al. [74], determined the diagnostic accuracy of 201Tl SPECT in the detection of recurrence in patients with previous radiotherapy for supratentorial glioma. Studies included a minimum of 6 patients with 201Tl SPECT study and pathological confirmation. Eight studies met the inclusion criteria for this systematic review but only one was considered high quality and a meta-analysis could not be performed due to methodological variability [73, 75–81] The sensitivities reported ranged from 0.43 to 1.0, specificities ranged from 0.25 to 1.00 and the diagnostic odds ratio was significant in all eight studies ranging from 2 to over 350, for detecting tumor progression for supratentorial glioma. However, in seven of the eight studies it was not possible to differentiate the patients with progressive glioblastoma and therefore only one of the studies is included in this review [79]. In follow up of this review, Vos et al. [82] published a prospective trial in 2012 involving 46 patients undergoing both MRI and (201)Tl SPECT imaging procedures to compare their prognostic value. Both strongly related to OS ($p < 0.02$) but the addition of one imaging modality to the other did not contribute to the prediction of OS. This was considered Class II data based on prognosis but not on diagnosis but is included as important data supportive of both MRI and SPECT.

Several studies provide Class 3 data in support of SPECT imaging in progressive glioblastoma [63, 79], Plotkin et al. [63] reported their prospective single institute non-blinded study including 25 patients undergoing SPECT imaging (cut-off value 1.62) with suspected progressive malignant glioma and found a sensitivity of 0.95, a specificity of 1.00 and an accuracy of 1.00 which was slightly superior to the MRS in the same population (described above). The authors conclude that both SPECT and MRS were successful in differentiating recurrent tumor from radiation necrosis. 123I-IMT SPECT yielded slightly more favorable results in this study.

Schwartz et al. [79] published a prospective study of 47 patients undergoing reoperation for suspected progressive

glioblastoma imaged with 201Tl SPECT and 99mTc-hexamethypropyleneamine oxime (HMPAO). The patients were divided into three groups based on pathological findings and imaging as indicated in the evidentiary table. The authors conclude that SPECT data correlates with pathological findings and survival.

Additional Class III data is included in the evidentiary tables as supporting information including data on supporting the role of SPECT differentiating progressive tumor from radiation necrosis [76, 83], comparison with FDG PET, [77], impact of steroid use reducing uptake [84] and impact on prognostic ability [85].

Based on the Class III data discussed above and summarized in Evidentiary Table 6, the following Level III recommendation is made: SPECT imaging is recommended as a diagnostic method to differentiate true tumor progression from treatment-related imaging changes or pseudo-progression in patients with suspected progressive glioblastoma with expected sensitivity ranging from 0.94 to 0.95 and an expected specificity ranging from 0.63 to 1.00. One study reported a positive predictive value of 0.92.

Combination studies and multi-parametric analysis

Several investigators have described methodologies to combine or model the combination of multiple imaging modalities to improve the diagnostic and prognostic accuracy of available techniques. All of these studies represent Class 3 data and lack validation and therefore are not suitable for use in recommendations at this time (see Table 7). They are all exciting possible techniques to foster additional study.

Zeng et al. [61] analyzed the combination of various MRS generated values including N-acetylaspartate (NAA), choline (Cho), creatine (Cr), lipid (Lip), and lactate (Lac) in conjunction with the ADC and correlated with histopathology (gold standard) using discriminant analysis. After analyzing various combinations, the authors described a predictive accuracy of over 96 % in predicting tumor progression. If this type of analysis were validated in larger independent study populations, it would be of potential benefit in redefining the optimal imaging protocol for detecting tumor progression.

Similarly, in a pilot study, Matsusue et al. [54] describe using a multiparametric scoring system including MR DWI, DSC-enhanced perfusion imaging, and MRS based on a retrospective single center non-blinded study that included 6 patients with recurrent GBM. The optimum thresholds for ADC ratio (1.30), rCBV ratio (2.10), and either combined Cho/Cr (1.29) and Cho/NAA (1.06) yielded diagnostic accuracies of 86.7, 86.7, and 84.6 %, respectively ($p < 0.05$). In this study the accuracy of MRS alone was only 67 % whereas the combined multiparametric score improved diagnostic accuracy to 93.3 % ($p < 0.05$). As with the study by Zeng et al., this model remains non-validated but does offer the promise of improving diagnostic accuracy to the point of limiting the need for invasive diagnostic procedures.

Galban et al. prospectively studied 45 patients with high grade glioma who underwent surgical resection followed by radiotherapy and concurrent temozolamide treatment with MRI using DWI and DSC-MRI at 3 and 10 weeks after treatment and found that a composite of ADC and rCBV, as analyzed by parametric response map enhanced the sensitivity of the biomarker for predicting those patients resistant to chemo-radiation at 3 weeks post treatment initiation [86].

The combination of multiple imaging results and multiparametric analysis may well represent the solution to improving the diagnostic accuracy of imaging for progressive glioblastoma. However, as stated for the advanced MRI techniques, these studies represent intriguing possibilities; incorporation into recommendations will await validation in independent relevant populations.

Imaging summary and discussion

The current data on the role of imaging in progressive or recurrent glioblastoma available is lacking in high levels of evidence due primarily to poor study design, heterogeneity of the patient population, and variability in practices at the time of progression and general lack of prospectively collected data with comparable groups in this challenging patient population. Despite these shortcomings, recommendations can be formulated from the available data.

Based on our current review, Class II data supports a recommendation for MRI with and without gadolinium enhancement in the evaluation of patients with suspected progressive glioblastoma with a reasonable diagnostic accuracy. In order to improve the sensitivity, specificity and diagnostic accuracy of imaging, based on Class II data, MRS be recommended to further differentiate true tumor progression from treatment-related imaging changes or pseudo-progression in patients with suspected progressive malignant glioma. Similarly, Class III data supports the role of SPECT, but with a larger range of sensitivity and specificity. The reviewed data on PET indicates that the routine use of PET to identify progression of glioblastoma is not recommended. Additional high-quality studies to clarify the appropriate role of MRI-based perfusion and diffusion techniques, and to evaluate the combination of imaging results are strongly encouraged.

Although the current status of non-invasive imaging in progressive glioblastoma remains controversial, a detailed

review of the relevant literature suggests that available imaging techniques are of benefit in the follow up care of glioblastoma patients and may add additional prognostic information.

A primary goal of serial imaging is to establish the time point when progression occurs in order to appropriately guide subsequent clinical decision-making. While the current recommendations are made on the best available information, the goal of future studies and updates to these recommendations will be to more accurately determine the optimal technique, timing and interpretation of non-invasive imaging in the management of patients with progressive glioblastoma.

Conclusions and key issues for future investigation

The recent review of the phenomena of "pseudoprogression" published by Sanghera et al. [87], highlights the importance of this area of study. The ability to detect early progression is critical to responding early with a change of treatment strategy in this deadly progressive tumor. In contrast, it is also critically important to identify treatment strategies which may benefit the patient but which may simultaneously also result in radiographic changes such as additional contrast enhancement not indicative of true progression. Being aware of such treatment effects whenever possible prevents the clinician from discarding a treatment strategy too early in the course of therapy as there are limited options available and each need to be used to its maximal potential benefit in order to have any impact on overall survival. Although the pathophysiology of pseudoprogression is poorly understood, it is important that it be recognized promptly. Current recommendations for imaging follow-up are based on less than optimal data and increase the rationale to provide the best quality studies and meta-analyses available to guide future recommendations. A series of well-designed studies would greatly clarify the issue of the diagnostic accuracy of current and future imaging techniques in identifying progressive tumor. Larger and more diverse study populations and studies performed in prospective fashion using validated criteria would address two major concerns in study design. A more specific definition of the "gold standard" (either tissue diagnosis or clinical signs of progression or some combination of the two) and a more specified definition of a "positive" versus "negative" test result would reduce heterogeneity. Attempts to blind the interpretation of results would also improve the quality of the design. In the future, this study design could be used to facilitate comparison between non-invasive imaging techniques of potential benefit in identifying true tumor progression. If all techniques prove roughly equivalent, a cost-effective analysis would be of significant impact and benefit.

The level of recommendation is based on the best available evidence, so the quality of the studies and data collected requires continued improvement and education of the investigators. Several investigators have described methodologies to combine or model the combination of multiple imaging modalities to improve the diagnostic and prognostic accuracy of available techniques.

References

1. Darefsky AS, King JT Jr, Dubrow R (2012) Adult glioblastoma multiforme survival in the temozolomide era: a population-based analysis of surveillance, epidemiology, and end results registries. Cancer 118(8):2163–2172
2. Koshy M, Villano JL, Dolecek TA et al (2012) Improved survival time trends for glioblastoma using the SEER 17 population-based registries. J Neurooncol 107(1):207–212

3. Easaw JC, Mason WP, Perry J et al (2011) Canadian recommendations for the treatment of recurrent or progressive glioblastoma multiforme. Current Oncol 18(3):e126–e136

4. Olson JJ, Fadul CE, Brat DJ, Mukundan S, Ryken TC (2009) Management of newly diagnosed glioblastoma: guidelines development, value and application. J Neurooncol 93(1):1–23

5. Olson JJ, Ryken T (2008) Guidelines for the treatment of newly diagnosed glioblastoma: introduction. J Neurooncol 89(3):255–258

6. Brandes AA, Tosoni A, Spagnolli F et al (2008) Disease progression or pseudoprogression after concomitant radiochemotherapy treatment: pitfalls in neurooncology. Neuro Oncol 10(3):361–367

7. Brandsma D, Stalpers L, Taal W, Sminia P, van den Bent MJ (2008) Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. Lancet Oncol 9(5):453–461

8. Brandsma D, van den Bent MJ (2009) Pseudoprogression and pseudoresponse in the treatment of gliomas. Curr Opin Neurol 22(6):633–638

9. Sanghera P, Perry J, Sahgal A et al (2010) Pseudoprogression following chemoradiotherapy for glioblastoma multiforme. Can J Neurol Sci 37(1):36–42

10. Hollingworth W, Medina LS, Lenkinski RE et al (2006) A systematic literature review of magnetic resonance spectroscopy for the characterization of brain tumors. AJNR Am J Neuroradiol 27(7):1404–1411

11. Matz PG, Anderson PA, Kaiser MG et al (2009) Introduction and methodology: guidelines for the surgical management of cervical degenerative disease. J Neurosurg Spine 11(2):101–103

12. Mukundan S, Holder C, Olson JJ (2008) Neuroradiological assessment of newly diagnosed glioblastoma. J Neurooncol 89(3):259–269

13. Dean BL, Drayer BP, Bird CR et al (1990) Gliomas: classification with MR imaging. Radiology 174(2):411–415

14. Johnson PC, Hunt SJ, Drayer BP (1989) Human cerebral gliomas: correlation of postmortem MR imaging and neuropathologic findings. Radiology 170(1 Pt 1):211–217

15. Ballman KV, Buckner JC, Brown PD et al (2007) The relationship between six-month progression-free survival and 12-month overall survival end points for phase II trials in patients with glioblastoma multiforme. Neuro Oncol 9(1):29–38

16. Lamborn KR, Yung WK, Chang SM et al (2008) Progression-free survival: an important end point in evaluating therapy for recurrent high-grade gliomas. Neuro Oncol 10(2):162–170

17. Wick W, Stupp R, Beule AC et al (2008) A novel tool to analyze MRI recurrence patterns in glioblastoma. Neuro Oncol 10(6):1019–1024

18. Hess KR, Wong ET, Jaeckle KA et al (1999) Response and progression in recurrent malignant glioma. Neuro Oncol 1(4):282–288

19. Brandes AA, Franceschi E, Tosoni A et al (2008) MGMT promoter methylation status can predict the incidence and outcome of pseudoprogression after concomitant radiochemotherapy in newly diagnosed glioblastoma patients. J Clin Oncol 26(13):2192–2197

20. Gerstner ER, McNamara MB, Norden AD, Lafrankie D, Wen PY (2009) Effect of adding temozolomide to radiation therapy on the incidence of pseudo-progression. J Neurooncol 94(1):97–101

21. Batchelor TT, Duda DG, di Tomaso E et al (2010) Phase II study of cediranib, an oral pan-vascular endothelial growth factor receptor tyrosine kinase inhibitor, in patients with recurrent glioblastoma. J Clin Oncol 28(17):2817–2823

22. Vredenburgh JJ, Desjardins A, Herndon JE 2nd et al (2007) Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol 25(30):4722–4729

23. Friedman HS, Prados MD, Wen PY et al (2009) Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 27(28):4733–4740

24. Kreisl TN, Kim L, Moore K et al (2009) A phase I trial of enzastaurin in patients with recurrent gliomas. Clin Cancer Res Off J Am Assoc Cancer Res 15(10):3617–3623

25. Kreisl TN, Kim L, Moore K et al (2009) Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol 27(5):740–745

26. Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG (1990) Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 8(7):1277–1280

27. Wen PY, Macdonald DR, Reardon DA et al (2010) Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 28(11):1963–1972

28. Wen PY, Norden AD, Drappatz J, Quant E (2010) Response assessment challenges in clinical trials of gliomas. Curr Oncol Rep 12(1):68–75

29. van den Bent MJ, Vogelbaum MA, Wen PY, Macdonald DR, Chang SM (2009) End point assessment in gliomas: novel treatments limit usefulness of classical Macdonald's Criteria. J Clin Oncol 27(18):2905–2908

30. Agbi CB, Bernstein M, Laperriere N, Leung P, Lumley M (1992) Patterns of recurrence of malignant astrocytoma following stereotactic interstitial brachytherapy with iodine-125 implants. Int J Radiat Oncol Biol Phys 23(2):321–326

31. Aiken AH, Chang SM, Larson D, Butowski N, Cha S (2008) Longitudinal magnetic resonance imaging features of glioblastoma multiforme treated with radiotherapy with or without brachytherapy. Int J Radiat Oncol Biol Phys 72(5):1340–1346

32. Curnes JT, Laster DW, Ball MR, Moody DM, Witcofski RL (1986) MRI of radiation injury to the brain. AJR. Am J Roentgenol 147(1):119–124

33. Dooms GC, Hecht S, Brant-Zawadzki M, Berthiaume Y, Norman D, Newton TH (1986) Brain radiation lesions: MR imaging. Radiology 158(1):149–155

34. Kleinberg L, Yoon G, Weingart JD et al (2009) Imaging after GliaSite brachytherapy: prognostic MRI indicators of disease control and recurrence. Int J Radiat Oncol Biol Phys 75(5):1385–1391

35. Kumar AJ, Leeds NE, Fuller GN et al (2000) Malignant gliomas: MR imaging spectrum of radiation therapy- and chemotherapy-induced necrosis of the brain after treatment. Radiology 217(2):377–384

36. Sneed PK, Gutin PH, Larson DA et al (1994) Patterns of recurrence of glioblastoma multiforme after external irradiation followed by implant boost. Int J Radiat Oncol Biol Phys 29(4):719–727

37. Taal W, Brandsma D, de Bruin HG et al (2008) Incidence of early pseudo-progression in a cohort of malignant glioma patients treated with chemoirradiation with temozolomide. Cancer 113(2):405–410

38. Valery CA, Marro B, Boyer O et al (2001) Extent of tumor-brain interface: a new tool to predict evolution of malignant gliomas. J Neurosurg 94(3):433–436

39. Al Sayyari A, Buckley R, McHenery C, Pannek K, Coulthard A, Rose S (2010) Distinguishing recurrent primary brain tumor from radiation injury: a preliminary study using a susceptibility-weighted MR imaging-guided apparent diffusion coefficient analysis strategy. AJNR Am J Neuroradiol 31(6):1049–1054

40. Barajas RF Jr, Chang JS, Segal MR et al (2009) Differentiation of recurrent glioblastoma multiforme from radiation necrosis after external beam radiation therapy with dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. Radiology 253(2):486–496

41. Hu LS, Eschbacher JM, Heiserman JE et al (2012) Reevaluating the imaging definition of tumor progression: perfusion MRI quantifies recurrent glioblastoma tumor fraction, pseudoprogression, and radiation necrosis to predict survival. Neuro Oncol 14(7):919–930

42. Ringelstein A, Turowski B, Gizewski ER et al (2010) Evaluation of ADC mapping as an early predictor for tumor response to chemotherapy in recurrent glioma treated with bevacizumab/irinotecan: proof of principle. RoFo : Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin 182(10):868–872

43. Sawlani RN, Raizer J, Horowitz SW et al (2010) Glioblastoma: a method for predicting response to antiangiogenic chemotherapy by using MR perfusion imaging—pilot study. Radiology 255(2):622–628

44. Sorensen AG, Batchelor TT, Zhang WT et al (2009) A "vascular normalization index" as potential mechanistic biomarker to predict survival after a single dose of cediranib in recurrent glioblastoma patients. Cancer Res 69(13):5296–5300

45. Stenberg L, Englund E, Wirestam R, Siesjo P, Salford LG, Larsson EM (2006) Dynamic susceptibility contrast-enhanced perfusion magnetic resonance (MR) imaging combined with contrast-enhanced MR imaging in the follow-up of immunogene-treated glioblastoma multiforme. Acta Radiol (Stockholm, Sweden: 1987) 47(8):852–861

46. Vrabec M, Van Cauter S, Himmelreich U et al (2011) MR perfusion and diffusion imaging in the follow-up of recurrent glioblastoma treated with dendritic cell immunotherapy: a pilot study. Neuroradiology 53(10):721–731

47. Paldino MJ, Desjardins A, Friedman HS, Vredenburgh JJ, Barboriak DP (2011) A change in the apparent diffusion coefficient after treatment with bevacizumab is associated with decreased survival in patients with recurrent glioblastoma multiforme. Br J Radiol 13(12):1349–1363

48. Rollin N, Guyotat J, Streichenberger N, Honnorat J, Tran Minh VA, Cotton F (2006) Clinical relevance of diffusion and perfusion magnetic resonance imaging in assessing intra-axial brain tumors. Neuroradiology 48(3):150–159

49. Sundgren PC, Fan X, Weybright P et al (2006) Differentiation of recurrent brain tumor versus radiation injury using diffusion tensor imaging in patients with new contrast-enhancing lesions. Magn Reson Imaging 24(9):1131–1142

50. Zeng QS, Li CF, Liu H, Zhen JH, Feng DC (2007) Distinction between recurrent glioma and radiation injury using magnetic resonance spectroscopy in combination with diffusion-weighted imaging. Int J Radiat Oncol Biol Phys 68(1):151–158

51. Ando K, Ishikura R, Nagami Y et al (2004) Usefulness of Cho/Cr ratio in proton MR spectroscopy for differentiating residual/recurrent glioma from non-neoplastic lesions. Nihon Igaku Hoshasen Gakkai Zasshi 64(3):121–126

52. Chuang CF, Chan AA, Larson D et al (2007) Potential value of MR spectroscopic imaging for the radiosurgical management of patients with recurrent high-grade gliomas. Technol Cancer Res Treat 6(5):375–382

53. Lichy MP, Henze M, Plathow C, Bachert P, Kauczor HU, Schlemmer HP (2004) Metabolic imaging to follow stereotactic radiation of gliomas—the role of 1H MR spectroscopy in comparison to FDG-PET and IMT-SPECT. RoFo : Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin 176(8):1114–1121

54. Matsusue E, Fink JR, Rockhill JK, Ogawa T, Maravilla KR (2010) Distinction between glioma progression and post-radiation change by combined physiologic MR imaging. Neuroradiology 52(4):297–306

55. Plotkin M, Gneveckow U, Meier-Hauff K et al (2006) 18F-FET PET for planning of thermotherapy using magnetic nanoparticles in recurrent glioblastoma. Int J Hyperth 22(4):319–325

56. Rabinov JD, Lee PL, Barker FG et al (2002) In vivo 3-T MR spectroscopy in the distinction of recurrent glioma versus radiation effects: initial experience. Radiology 225(3):871–879

57. Srinivasan R, Phillips JJ, Vandenberg SR et al (2010) Ex vivo MR spectroscopic measure differentiates tumor from treatment effects in GBM. Neuro Oncol 12(11):1152–1161

58. Traber F, Block W, Flacke S et al (2002) 1H-MR spectroscopy of brain tumors in the course of radiation therapy: use of fast spectroscopic imaging and single-voxel spectroscopy for diagnosing recurrence. RoFo : Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin 174(1):33–42

59. Wald LL, Nelson SJ, Day MR et al (1997) Serial proton magnetic resonance spectroscopy imaging of glioblastoma multiforme after brachytherapy. J Neurosurg 87(4):525–534

60. Weybright P, Sundgren PC, Maly P et al (2005) Differentiation between brain tumor recurrence and radiation injury using MR spectroscopy. AJR Am J Roentgenol 185(6):1471–1476

61. Zeng QS, Li CF, Zhang K, Liu H, Kang XS, Zhen JH (2007) Multivoxel 3D proton MR spectroscopy in the distinction of recurrent glioma from radiation injury. J Neurooncol 84(1):63–69

62. Lichy MP, Bachert P, Henze M, Lichy CM, Debus J, Schlemmer HP (2004) Monitoring individual response to brain-tumour chemotherapy: proton MR spectroscopy in a patient with recurrent glioma after stereotactic radiotherapy. Neuroradiology 46(2):126–129

63. Plotkin M, Eisenacher J, Bruhn H et al (2004) 123I-IMT SPECT and 1H MR-spectroscopy at 3.0 T in the differential diagnosis of recurrent or residual gliomas: a comparative study. J Neurooncol 70(1):49–58

64. Petrirena GJ, Goldman S, Delattre JY (2011) Advances in PET imaging of brain tumors: a referring physician's perspective. Curr Opin Oncol 23(6):617–623

65. Enslow MS, Zollinger LV, Morton KA et al (2012) Comparison of 18F-fluorodeoxyglucose and 18F-fluorothymidine PET in differentiating radiation necrosis from recurrent glioma. Clin Nucl Med 37(9):854–861

66. Potzi C, Becherer A, Marosi C et al (2007) [11C] methionine and [18F] fluorodeoxyglucose PET in the follow-up of glioblastoma multiforme. J Neurooncol 84(3):305–314

67. Tripathi M, Sharma R, Varshney R et al (2012) Comparison of F-18 FDG and C-11 methionine PET/CT for the evaluation of recurrent primary brain tumors. Clin Nucl Med 37(2):158–163

68. Chin HW, Fruin AH, Bertoni JM et al (1991) Application of positron emission tomography to neurological oncology. Neb Med J 76(3):70–73

69. Galldiks N, Kracht LW, Burghaus L et al (2010) Patient-tailored, imaging-guided, long-term temozolomide chemotherapy in patients with glioblastoma. Mol Imaging 9(1):40–46

70. Eary JF, Mankoff DA, Spence AM et al (1999) 2-[C-11]thymidine imaging of malignant brain tumors. Cancer Res 59(3):615–621

71. Schnell O, Krebs B, Carlsen J et al (2009) Imaging of integrin alpha(v)beta(3) expression in patients with malignant glioma by [18F] galacto-RGD positron emission tomography. Neuro Oncol 11(6):861–870

72. Ishizu K, Sadato N, Yonekura Y et al (1994) Enhanced detection of brain tumors by [18F]fluorodeoxyglucose PET with glucose loading. J Comput Assist Tomogr 18(1):12–15

73. Yamamoto Y, Wong TZ, Turkington TG, Hawk TC, Reardon DA, Coleman RE (2006) 3'-Deoxy-3'-[F-18]fluorothymidine positron emission tomography in patients with recurrent glioblastoma multiforme: comparison with Gd-DTPA enhanced magnetic resonance imaging. Mol Imaging Biol 8(6):340–347

74. Vos MJ, Tony BN, Hoekstra OS, Postma TJ, Heimans JJ, Hooft L (2007) Systematic review of the diagnostic accuracy of 201Tl single photon emission computed tomography in the detection of recurrent glioma. Nucl Med Commun 28(6):431–439

75. Carvalho PA, Schwartz RB, Alexander E 3rd et al (1992) Detection of recurrent gliomas with quantitative thallium-201/technetium-99m HMPAO single-photon emission computerized tomography. J Neurosurg 77(4):565–570

76. Kline JL, Noto RB, Glantz M (1996) Single-photon emission CT in the evaluation of recurrent brain tumor in patients treated with gamma knife radiosurgery or conventional radiation therapy. AJNR Am J Neuroradiol 17(9):1681–1686

77. Lorberboym M, Baram J, Feibel M, Hercbergs A, Lieberman L (1995) A prospective evaluation of thallium-201 single photon emission computerized tomography for brain tumor burden. Int J Radiat Oncol Biol Phys 32(1):249–254

78. Schwartz RB, Carvalho PA, Alexander E 3rd, Loeffler JS, Folkerth R, Holman BL (1991) Radiation necrosis vs high-grade recurrent glioma: differentiation by using dual-isotope SPECT with 201TI and 99mTc-HMPAO. AJNR Am J Neuroradiol 12(6):1187–1192

79. Schwartz RB, Holman BL, Polak JF et al (1998) Dual-isotope single-photon emission computerized tomography scanning in patients with glioblastoma multiforme: association with patient survival and histopathological characteristics of tumor after high-dose radiotherapy. J Neurosurg 89(1):60–68

80. Slizofski WJ, Krishna L, Katsetos CD et al (1994) Thallium imaging for brain tumors with results measured by a semiquantitative index and correlated with histopathology. Cancer 74(12):3190–3197

81. Sonoda Y, Kumabe T, Takahashi T, Shirane R, Yoshimoto T (1998) Clinical usefulness of 11C-MET PET and 201Tl SPECT for differentiation of recurrent glioma from radiation necrosis. Neurol Med Chir 38(6):342–347 (discussion 347–348)

82. Vos MJ, Berkhof J, Hoekstra OS et al (2012) MRI and thallium-201 SPECT in the prediction of survival in glioma. Neuroradiology 54(6):539–546

83. Kosuda S, Fujii H, Aoki S et al (1994) Prediction of survival in patients with suspected recurrent cerebral tumors by quantitative thallium-201 single photon emission computed tomography. Int J Radiat Oncol Biol Phys 30(5):1201–1206

84. Namba H, Togawa T, Yui N et al (1996) The effect of steroid on thallium-201 uptake by malignant gliomas. Eur J Nucl Med 23(8):991–992

85. Vertosick FT Jr, Selker RG, Grossman SJ, Joyce JM (1994) Correlation of thallium-201 single photon emission computed tomography and survival after treatment failure in patients with glioblastoma multiforme. Neurosurgery 34(3):396–401

86. Galban CJ, Chenevert TL, Meyer CR et al (2011) Prospective analysis of parametric response map-derived MRI biomarkers: identification of early and distinct glioma response patterns not predicted by standard radiographic assessment. Clin Cancer Res Off J Am Assoc Cancer Res 17(14):4751–4760

87. Sanghera P, Rampling R, Haylock B et al (2012) The concepts, diagnosis and management of early imaging changes after therapy for glioblastomas. Clin Oncol (Royal College of Radiologists (Great Britain)) 24(3):216–227