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[Diagnostic Test Accuracy Review]

Magnetic resonance perfusion for differentiating low-grade from high-grade gliomas at first presentation

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ABSTRACT

Background

Gliomas are the most common primary brain tumour. They are graded using the WHO classification system, with Grade II-IV astrocytomas, oligodendrogliomas and oligoastrocytomas. Low-grade gliomas (LGGs) are WHO Grade II infiltrative brain tumours that typically appear solid and non-enhancing on magnetic resonance imaging (MRI) scans. People with LGG often have little or no neurologic deficit, so may opt for a watch-and-wait-approach over surgical resection, radiotherapy or both, as surgery can result in early neurologic disability. Occasionally, high-grade gliomas (HGGs, WHO Grade III and IV) may have the same MRI appearance as LGGs. Taking a watch-and-wait approach could be detrimental for the patient if the tumour progresses quickly. Advanced imaging techniques are increasingly used in clinical practice to predict the grade of the tumour and to aid clinical decision of when to intervene surgically. One such advanced imaging technique is magnetic resonance (MR) perfusion, which detects abnormal haemodynamic changes related to increased angiogenesis and vascular permeability, or "leakiness" that occur with aggressive tumour histology. These are reflected by changes in cerebral blood volume (CBV) expressed as rCBV (ratio of tumoural CBV to normal appearing white matter CBV) and permeability, measured by K^{trans}.

Objectives

To determine the diagnostic test accuracy of MR perfusion for identifying patients with primary solid and non-enhancing LGGs (WHO Grade II) at first presentation in children and adults. In performing the quantitative analysis for this review, patients with LGGs were considered disease positive while patients with HGGs were considered disease negative.

To determine what clinical features and methodological features affect the accuracy of MR perfusion.

Search methods

Our search strategy used two concepts: (1) glioma and the various histologies of interest, and (2) MR perfusion. We used structured search strategies appropriate for each database searched, which included: MEDLINE (Ovid SP), Embase (Ovid SP), and Web of Science Core Collection (Science Citation Index Expanded and Conference Proceedings Citation Index). The most recent search for this review was run on 9 November 2016.

We also identified 'grey literature' from online records of conference proceedings from the American College of Radiology, European Society of Radiology, American Society of Neuroradiology and European Society of Neuroradiology in the last 20 years.

Selection criteria

The titles and abstracts from the search results were screened to obtain full-text articles for inclusion or exclusion. We contacted authors to clarify or obtain missing/unpublished data.

We included cross-sectional studies that performed dynamic susceptibility (DSC) or dynamic contrast-enhanced (DCE) MR perfusion or both of untreated LGGs and HGGs, and where rCBV and/or K^{trans} values were reported. We selected participants with solid and non-enhancing gliomas who underwent MR perfusion within two months prior to histological confirmation. We excluded studies on participants who received radiation or chemotherapy before MR perfusion, or those without histologic confirmation.

Data collection and analysis

Two review authors extracted information on study characteristics and data, and assessed the methodological quality using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. We present a summary of the study characteristics and QUADAS-2 results, and rate studies as good quality when they have low risk of bias in the domains of reference standard of tissue diagnosis and flow and timing between MR perfusion and tissue diagnosis.

In the quantitative analysis, LGGs were considered disease positive, while HGGs were disease negative. The sensitivity refers to the proportion of LGGs detected by MR perfusion, and specificity as the proportion of detected HGGs. We constructed two-by-two tables with true positives and false negatives as the number of correctly and incorrectly diagnosed LGG, respectively, while true negatives and false positives are the number of correctly and incorrectly diagnosed HGG, respectively.

Meta-analysis was performed on studies with two-by-two tables, with further sensitivity analysis using good quality studies. Limited data precluded regression analysis to explore heterogeneity but subgroup analysis was performed on tumour histology groups.

Main results

Seven studies with small sample sizes (4 to 48) met our inclusion criteria. These were mostly conducted in university hospitals and mostly recruited adult patients. All studies performed DSC MR perfusion and described heterogeneous acquisition and post-processing methods. Only one study performed DCE MR perfusion, precluding quantitative analysis.

Using patient-level data allowed selection of individual participants relevant to the review, with generally low risks of bias for the participant selection, reference standard and flow and timing domains. Most studies did not use a pre-specified threshold, which was considered a significant source of bias, however this did not affect quantitative analysis as we adopted a common rCBV threshold of 1.75 for the review. Concerns regarding applicability were low.

From published and unpublished data, 115 participants were selected and included in the meta-analysis. Average rCBV (range) of 83 LGGs and 32 HGGs were 1.29 (0.01 to 5.10) and 1.89 (0.30 to 6.51), respectively. Using the widely accepted rCBV threshold of $\leq$1.75 to differentiate LGG from HGG, the summary sensitivity/specificity estimates were 0.83 (95% CI 0.66 to 0.93)/0.48 (95% CI 0.09 to 0.90). Sensitivity analysis using five good quality studies yielded sensitivity/specificity of 0.80 (95% CI 0.61 to 0.91)/0.67 (95% CI 0.07 to 0.98). Subgroup analysis for tumour histology showed sensitivity/specificity of 0.92 (95% CI 0.55 to 0.99)/0.42 (95% CI 0.02 to 0.95) in astrocytomas (6 studies, 55 participants) and 0.77 (95% CI 0.46 to 0.93)/0.53 (95% CI 0.14 to 0.88) in oligodendrogliomas+oligoastrocytomas (6 studies, 56 participants). Data were too sparse to investigate any differences across subgroups.

Authors' conclusions

The limited available evidence precludes reliable estimation of the performance of DSC MR perfusion-derived rCBV for the identification of grade in untreated solid and non-enhancing LGG from that of HGG. Pooled data yielded a wide range of estimates for both sensitivity (range 66% to 93% for detection of LGGs) and specificity (range 9% to 90% for detection of HGGs). Other clinical and methodological features affecting accuracy of the technique could not be determined from the limited data. A larger sample size of both LGG and HGG, preferably using a standardised scanning approach and with an updated reference standard incorporating molecular profiles, is required for a definite conclusion.

PLAIN LANGUAGE SUMMARY

How accurate is MR perfusion, an advanced MRI method, for differentiating low-grade gliomas from high-grade gliomas in children and adults?

Why is differentiation of low-grade and high-grade gliomas important?

Low-grade gliomas (LGGs) are slow growing brain tumours that have a typical appearance on standard MRI. Patients with LGGs who have few or no symptoms may prefer to delay treatment until such time they experience progression of their symptoms or appearance of the tumour on MRI; this is called the watch-and-wait approach. However occasionally, high-grade gliomas (HGGs), which are aggressive and require early treatment, can mimic the appearance of LGGs. It is only by examining tissues obtained by surgery - either through sampling (biopsy) or removal of tumour (resection) - can LGG and HGG be definitively differentiated. But a patient with few or no symptoms may want to avoid risking early neurologic disability resulting from surgery. Thus an accurate noninvasive method to differentiate gliomas can aid patients' decision making whether to opt for a watch-and-wait approach or undergo early treatment.

What is the aim of this review?

The review aims to determine how accurate MR perfusion is for differentiating LGGs and HGGs, and what factors affect its accuracy. Researchers in Cochrane included seven studies to answer this question.

What was studied in this review?

An advanced MRI technique called MR perfusion was studied. This method detects abnormal blood vessels which are increased from low- to high-grade gliomas. Unlike surgery, MR perfusion is noninvasive and allows clinicians to determine if a watch-and-wait approach can be adopted by patients, i.e. delay treatment including the initial tissue examination which requires surgery.

What are the main results of the review?

The analysis included results from 115 patients. The results indicate that in theory, if MR perfusion were to be used in 100 patients with brain tumours that look like LGG on standard MRI scan, of whom 72 actually have LGG, then:

- an estimated 74 will have an MR perfusion result indicating that they have LGGs, and of these 15 will have HGGs;

- an estimated 26 will have an MR perfusion result indicating that they have HGGs, and of these 13 will have LGGs.

How reliable are the results of the studies in this review?

In the included studies, the diagnosis of LGG or HGG was made by assessing all patients with tissue examination, and a majority underwent resection. This is considered a reliable method for deciding whether patients actually had LGGs or HGGs.

The small number of patients that were included in this review is a major limitation to the analysis. Estimates from individual studies and pooled data were variable and/or had a wide range. The numbers reported in the main results above are an average across studies in the review, but it is unknown if MR perfusion will always produce these results. Further, the included studies differed in how MR perfusion was performed, and pooling of data for the analysis may be inappropriate.

Who do the results of this review apply to?

The included studies were carried out in Europe (Italy, Sweden, Spain, France), Asia (Japan) and South America (Brazil) and MR perfusion was mostly performed in university hospitals. Most studies recruited adults so the results may not be representative of children.

What are the implications of this review?

Our results based on 115 patients showed that MR perfusion may detect 66% to 93% of LGGs, which means that 7% to 34% of people with LGGs may be misclassified as having HGGs and thus may undergo early invasive treatment with an accompanying risk of adverse events. Meanwhile, around half of people with HGGs may be misclassified as having LGGs, and thus may suffer from delayed treatment. Due to uncertainty in the estimates this may range from 9% to 90% of patients. Given the wide range of estimates, currently, it cannot be determined how accurate MR perfusion is for differentiating LGGs and HGGs. Future studies to inform evidence would need to include larger numbers of patients with LGG and HGG.

How up to date is this review?

We searched for and used studies published from 1990 to November 2016.

BACKGROUND

Target condition being diagnosed

Epidemiology and pathology

Gliomas are tumours that arise from glial cells which form the supporting architecture of the brain. In the USA, around 18,000 gliomas are diagnosed each year, giving an incidence rate of 6.6 per 100,000. Over 90% of gliomas occur in adults (Dolecek 2012). The incidence rate is less in Europe (Crocetti 2012) and lesser still in Asia and Africa, although the rate is similar when comparing developed or industrialised countries (Ohgaki 2005). This variation may result from underestimate of case ascertainment rather than a different genetic predisposition (Crocetti 2012; Ohgaki 2005). Using the World Health Organization (WHO) classification of brain tumours, gliomas are graded I-IV to reflect increasing growth rate based on histology (Louis 2007). The recent 2016 WHO classification includes molecular information in addition (Louis 2016). Grade II gliomas (commonly known as 'low-grade gliomas' (LGGs)) predominantly comprise astrocytomas, oligodendrogliomas and mixed oligoastrocytomas. LGGs tend to be diffuse and infiltrative tumours with a growth rate between that of grade I and grade III tumours. Despite growing slowly initially, they usually transform to high-grade gliomas (HGGs) with time. The timing of this transition is highly variable and difficult to predict for an individual (Rees 2002). Approximately 50% of people with LGGs will experience malignant transformation usually within five years (Afra 1999; Piepmeier 1996), although more protracted growths of up to 20 years have been described (Claus 2006; Recht 1992). Once transformation occurs, the tumours are highly resistant to therapy. Prognostic factors for survival include age, presence of seizures alone, histology, and larger tumour size (Nicolato 1995; Pignatti 2002).

Clinical features and investigations

People with LGGs usually present with seizures, headaches or focal neurological features (for example, weakness). A classical presentation is a focal seizure in an otherwise healthy young adult. Other people may present with a LGG as an incidental finding after investigation for another condition (e.g. dizziness or blackouts) or after screening for employment purposes and be essentially asymptomatic. Regardless of presentation, the first-line investigation is a contrast-enhanced magnetic resonance imaging (MRI) scan. LGGs are solid tumours located within the brain itself and often have a characteristic appearance of poorly defined margins and little mass effect despite often large tumour volumes. Certain features strongly suggest a higher grade tumour, including contrast enhancement, signs of mass effect and significant peri-tumoural vasogenic oedema. If any of these features is present, people often undergo early surgery (either biopsy or resection), followed by definitive oncological treatment (if appropriate).

Management

If a tumour appears to be an LGG (based on a contrast-enhanced MRI scan), optimal management is debated (Whittle 2004) and varies between treating centres (Jakola 2012; Soffietti 2010; van den Bent 2005). Certain authorities would often recommend early surgical resection (Dolecek 2012). Case series of people undergoing surgical resection for LGG, often utilising advanced neurosurgical techniques such as awake craniotomy and brain mapping (Bello 2010), have demonstrated impressive outcomes (Duffau 2005). However, studies are limited by selection bias and other methodological issues. Other management options might be conservative management or observation in selected patients. This is often known as 'watch-and-wait' (NCCN Guidelines 2016). In particular, when people have no or few symptoms, have deep and inaccessible tumours located in/near 'eloquent' regions of the brain, or have significant co-morbidity which can complicate the peri-operative setting, conservative management becomes attractive because it decreases the risk of developing neurologic deficits from surgery (Reijneveld 2001).

Determining optimal management is complicated by tumours that appear to be LGGs on contrast-enhanced MRI scans but turn out to be higher grade tumours (or non-glial tumours) when subsequently biopsied. The accuracy of a standard contrast-enhanced MRI scan in distinguishing a grade II from a grade III astrocytoma is only approximately 30% to 50% because morphologic features of LGGs and HGGs may overlap (Heiss 2011; Kondziolka 1993; Piepmeier 2009; Scott 2002). Although LGGs are typically solid and non-enhancing, HGGs may mimic this appearance in the ultra-early stage of development (Barker 1997; Bernstein 1994; Cohen-Gadol 2004). Enhancement usually reflects a HGG but can be seen in some LGGs where it may indicate a more aggressive tumour (Pallud 2009). Histological analysis is the most reliable method of diagnosing LGGs but requires a surgical procedure, either taking a small tissue sample for diagnostic purposes only (biopsy), or a larger tissue sample when removal of the tumour is attempted (resection). Both of these procedures are invasive and have a risk of adverse events.

Index test(s)

Magnetic resonance (MR) perfusion

Advanced MRI techniques could provide additional information on the aggressiveness of the tumour. One such technique that is becoming routinely employed in clinical centres is magnetic resonance (MR) perfusion, which identifies tumour angiogenesis

or the proliferation of abnormal vessels in tumours. Tumoural vessels are tortuous, immature and leaky, and result in abnormal blood flow (haemodynamics) in the brain. On MR perfusion, these are depicted in colour maps of cerebral blood volume (CBV) and vessel wall permeability, which are quantitatively expressed as the ratio of tumoural CBV to normal-appearing white matter CBV (relative CBV or rCBV), and the volume transfer constant K^{trans} (Provenzale 2006), respectively. High-grade tumours show increased CBV and increased K^{trans} on MR perfusion.

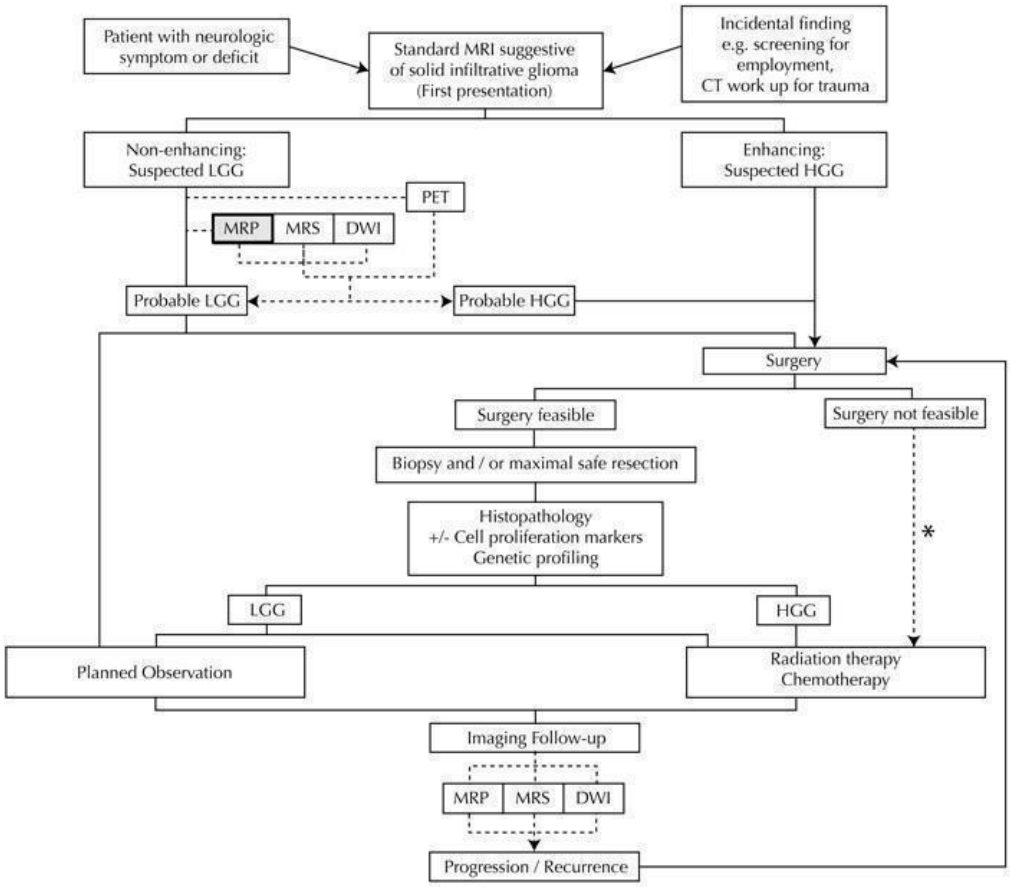
Most studies utilising MR perfusion have been in the context of suspected HGGs (Al-Okaili 2006; Law 2003; Provenzale 2006). In this tumour group, MR perfusion can reliably demonstrate evidence of tumour angiogenesis, and an rCBV higher than 1.75 reliably associates with histological diagnosis (Law 2003). However, the role of MR perfusion for the identification of suspected LGGs has not been described. Specifically, it is not known if MR perfusion can differentiate between grade II gliomas and grade III/IVtumours that otherwise may appear the same on standard MRI scans.

Abnormalities on MR perfusion may also have a role in detecting grade transformation (increased malignancy) during follow-up or as an independent biomarker of increased malignancy by itself, however neither of these roles were considered in this review.

Clinical pathway

Figure 1 summarises the pathway by which people with infiltrative gliomas are typically managed in the clinical setting. The role of imaging in the identification of primary disease as well as in surveillance for recurrence is incorporated.

Figure 1. Diagram shows the clinical management algorithm for patients with infiltrative glioma. The role of the index test (MRP) for differentiating LGGs and HGGs at first presentation is shown with alternative tests (MRS, DWI, PET). These advanced MRI techniques are also used to identify progression or recurrence during interval scanning and are included, although they are outside the scope of this review. *May or may not be offered, depending on institutional/regional practice.Abbreviations: LGG: Low-grade glioma, HGG: High-grade glioma,MRP: Magnetic resonance perfusion, MRS: magnetic resonance spectroscopy, DWI: Diffusion-weighted imaging, PET: Positron emission tomography



This review focuses on primary tumours, determining the accuracy of MR perfusion in differentiating LGGs from HGGs. Such characterisation may improve decision-making towards conservative management or active treatment (surgery or chemotherapy/ radiotherapy).

Prior test(s)

People, whether symptomatic or asymptomatic, are identified as having primary infiltrative gliomas on a standard contrast-enhanced MRI scan as baseline imaging investigation. However MR alone is insufficient for definite classification into low grade or high grade. Typically, tumours that appear solid, non-enhancing and associated with little mass effect are suspected to be LGGs, however occasionally HGGs may have the same appearance.

Role of index test(s)

In addition to a standard contrast-enhanced MRI scan, people with tumours may also undergo MR perfusion as part of their diagnostic work-up, both of which are performed before surgery. The aim is to detect those tumours that are not LGGs but rather higher grade tumours on histology.

Alternative test(s)

Other imaging methods can be used to increase the accuracy of diagnosing LGGs. These include other MRI techniques such as diffusion weighted imaging and magnetic resonance spectroscopy, and positron emission tomography. These methods may also play a role in predicting tumour grading but they are not included in this review.

Rationale

Imaging features often play a major role in the initial management pathway of people with a brain tumour. There is interest in more accurate diagnosis and, in particular, in identifying when grade II tumours start to transform to grade III/IV tumours as early as possible in order to initiate treatment. If MR perfusion can reliably identify higher grade features in a tumour that otherwise appears like a grade II glioma on standard MRI scan, then possibly intervention would be more appropriate than a conservative 'watch-and-wait' approach. Conversely, if the MR perfusion findings reliably predict a grade II glioma, then a conservative 'watch-and-wait' approach could continue.

Experience with MR perfusion is relatively limited and only a few large centres publish their own small case series. Interpretation is limited by variability in the conditions assessed and technical details of the scanning. To our knowledge, no previous reviews have tried to systematically analyse all available imaging studies on magnetic resonance perfusion for the diagnosis of solid and non-enhancing LGGs.

OBJECTIVES

To determine the diagnostic test accuracy of MR perfusion for identifying primary solid and non-enhancing low-grade (WHO Grade II) gliomas at first presentation in children and adults. In performing the quantitative analysis for this review, patients with LGGs were considered disease positive while patients with high-grade (Grade III and IV) gliomas, being non-LGGs, were considered as disease negative.

Secondary objectives

To determine what clinical features and methodological features affect the accuracy of MR perfusion.

METHODS

Criteria for considering studies for this review

Types of studies

We included cross-sectional studies with retrospective or prospective design, and excluded case-control studies. Non-English literature studies were eligible for inclusion.

Participants

We considered studies that enrolled paediatric and adult patients with solid and non-enhancing infiltrative tumours on standard contrast enhanced MRI and who had subsequent WHO grade histologic classification following biopsy or resection. The interval period between MR perfusion and histologic diagnosis must be within two months, as LGGs can transform into HGGs over that period of time. As this review focused on primary and not recurrent disease, participants who had received previous surgery (either biopsy or resection) or oncological treatment (chemotherapy or radiotherapy) prior to the index test were excluded.

Index tests

Studies that employed dynamic susceptibility (DSC) and/or dynamic contrast-enhanced (DCE) MR perfusion were considered for the review. They were included when data on rCBV and/or K^{trans} were provided, regardless of the method of acquisition, imaging analysis or post-processing performed. Studies that used arterial spin labelling MR perfusion were excluded, as this method has been largely utilised as a research tool.

For DSC MR perfusion, we adopted a common rCBV threshold of 1.75 following the landmark study of Law and colleagues (Law 2003). This value is widely accepted and is used and recommended in clinical practice (Al-Okaili 2006). In this review, a positive test or rCBV $\leq$ 1.75 implied an LGG diagnosis while a negative test or rCBV > 1.75 suggested an HGG diagnosis (Appendix 1). With reference to the seven studies included in this review, five studies did not report an rCBV threshold, while the other two studies used or reported various rCBV thresholds (1.29, 1.5, 5.66).

For DCE MR perfusion, there is no consensus in the field regarding a threshold. Only one out of seven included studies reported K^{trans} and did not use a threshold.

The generation of MR perfusion data is a multistep process involving acquisition, post-processing and imaging analysis. Technical differences may arise at each step, which can ultimately influence the perfusion value obtained. Thus it is acknowledged that there may not be an appropriate single threshold when using multicentre MR perfusion data.

Target conditions

The target condition is LGGs (disease positive in quantitative analysis), with the alternative condition being HGGs (i.e. non-LGG or disease negative in quantitative analysis). Studies must have both conditions to be included in the review.

We included studies that enrolled WHO Grade II diffuse astrocytomas, oligodendrogliomas and oligoastrocytomas, their Grade III anaplastic counterparts and glioblastomas (see Table 1). Other WHO Grade II-IV gliomas of different histologic type were excluded, because they are rare and usually have distinct clinical characteristics. Grade I tumours were also excluded because their distinct clinical and radiological features separate their management from that of grade II tumours. In this review, gliomas were included irrespective of patient age and tumour location, although it is recognised that paediatric and adult gliomas, and supratentorial and brainstem gliomas may be histologically similar but have biologic and molecular differences (Paugh 2010).
Tumour histologies outside of these target conditions but having similar solid, non-enhancing appearance as LGGs were recorded and excluded from the analysis.

Reference standards

The reference standard is histological diagnosis assessed according to the WHO 2007 criteria (Table 1). We recorded the method of tumour sampling (biopsy or resection) per study. Reference test failures were treated as no histologic confirmation, and excluded from the analysis.
There are two potential limitations with histology. First, histological diagnosis can be subjective and suffer from significant intra- and inter-observer variability, even among neuropathologists (Brat 2008). Recently, the WHO classification (Louis 2016) has been substantially updated to incorporate molecular profiles in the diagnosis of diffuse gliomas, providing a layer of objectivity to tumour evaluation. However, these are not always available or reported, and were not used in this review. Second, tissue sampling is constrained by the surgical technique of tissue acquisition. Because gliomas are morphologically heterogeneous, they are susceptible to sampling errors, particularly in biopsies. Small volumes of tissue may not be representative of the most malignant component and are therefore less ideal compared with full tissue evaluation afforded by maximal resections. In fact, agreement in histological typing and grading between biopsies and resections has been found to be low (Muragaki 2008).

Search methods for identification of studies

No language or document-type restrictions were applied.

Electronic searches

We performed a systematic search for literature with quantitative data. Articles were retrieved from the following electronic databases.

1. MEDLINE via OvidSP (Appendix 2, 1996 to 9 November 2016).
2. Embase via OvidSP (Appendix 3, 1996 to 9 November 2016).
3. Web of Science Core Collection, specifically Science Citation Index Expanded and Conference Proceedings Citation Index - Science via Thomson Reuters Web of Science (Appendix 4 1990 to 9 November 2016).

The search was restricted to studies in humans, and was limited to studies in the last 20 years, since MR perfusion is a relatively recent MRI technique.

Searching other resources

Additional references were identified by manually searching the references of relevant review articles. We also used the 'related articles' feature in PubMed to identify articles similar in keywords and database subject headings to the original included studies.
We sought unpublished studies by searching the conference proceedings, available online, of the following radiologic and neuroradiologic societies (years accessed).

1. The Radiology Society of North America (2003 to 2016).
2. The American Society of Neuroradiology (1996 to 2016).
3. The European Society of Radiology (1999 to 2016).
4. The European Society of Neuroradiology (1995 to 2016).

Data collection and analysis

We followed the guidelines outlined in the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy* (Macaskill 2010).

Selection of studies

Prior to abstract review, two review authors (JMA, MGH) performed preliminary screening of titles to exclude irrelevant references. Subsequent screening was carried out by at least two authors (JMA, DMF, MGH, EKCL or JMP). Disagreements were resolved by consensus or third person.
During the abstract review, potentially eligible publications were selected based on the following criteria.

1. Did the study include participants suspected to have primary infiltrative gliomas (including LGG)?
2. Were brain tumours confirmed by histology?
3. Was MR perfusion performed?

An initial review of full-text publications was then conducted to establish that they meet the following criteria.

1. Did the study enrol participants with solid non-enhancing brain tumours on standard contrast-enhanced MRI scan?
2. Were measurements on rCBV and/or K^{trans} given?
3. Can a two-by-two table be extracted from the provided data?

When this information was not readily available from the published data, we contacted primary authors for clarification. In particular, information on the MRI appearance of the gliomas, i.e. if

they were solid and non-enhancing, and were not always explicitly reported in studies. We also requested for patient-level data from authors to allow selection of tumours relevant to our review. The data included the individual perfusion values, the method of histologic confirmation, and interval period between the index test and histologic confirmation.

Detailed data extraction of full-text paper or conference abstract was carried out to determine final eligibility based on the inclusion criteria (see Criteria for considering studies for this review).

Data extraction and management

Two review authors (JMA, DMF) independently completed a data extraction form on all included studies. The following data were retrieved.

1. General information: title, journal, year, publication status, and study design (prospective versus retrospective).
2. Sample size: number of participants included, those meeting the target and alternative conditions (i.e. other-gliomas and non-gliomas), and reference test failures.
3. Study setting: country and type of hospital.
4. Baseline characteristics: age, sex.
5. Clinical reference standard test: method of tissue sampling (biopsy or resection), blinding from MR perfusion results, interval period between MR perfusion and tissue diagnosis.
6. Histologic diagnosis and WHO grade of tumour. In this review, LGGs are considered disease positive, and HGGs are disease negative.
7. Details of the index test, including the strength of the MRI scanner, method of MR perfusion performed (DCE or DSC), pulse sequence, use of contrast preload, post-processing algorithm, imaging analysis, blinding from histological analysis if retrospectively processed.
8. Quantitative results of the index tests, including but not limited to rCBV, $K^{trans.}$
9. Authors' recommended threshold.
10. Number of true positive, false positive, true negative, false negative, and area under the receiver operating characteristic (ROC) curve, extracted based on authors' pre-specified and recommended thresholds, and based on Law's threshold of 1.75.

During the course of this review, we found that authors' pre-specified and recommended thresholds were either missing or when available, heterogeneous, therefore we only used Law's threshold to construct the two-by-two contingency tables. A positive index test implied a diagnosis of LGG while a negative test suggested HGG. Thus, true positives are correctly diagnosed LGGs, false negatives are LGGs incorrectly labelled as HGG, true negatives are correctly diagnosed HGGs, while false positives are HGGs incorrectly labelled as LGG (Appendix 1).

We contacted primary authors via e-mail for missing data and to obtain clarification on study methods.

Assessment of methodological quality

Each study was assessed for methodological quality using the revised Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS 2) (Whiting 2011). QUADAS 2 assesses study quality through the use of signalling questions which facilitate assessment of risk of bias in four domains: patient sampling; index test; reference standard; and flow and timing. In addition, concerns regarding applicability were also rated in the first three domains. The QUADAS 2 tool for this review is described in Appendix 5 and was applied on study design and on the included patient data. To reduce uncertain risks, we sought clarification from authors when information was missing. e.g. blinding between MR perfusion and histology, details on the MRI acquisition and post-processing.

Summative data from QUADAS 2 were used to describe the numbers of studies with high/low/unclear risk of bias as well as concerns regarding applicability. All studies with sufficient data were included in the general analysis, but studies with low risk of bias in the domains of reference standard and flow and timing were used in the sensitivity analysis.

Statistical analysis and data synthesis

The reported number of true positive, false positive, false negative and true negative cases were used to construct two-by-two tables based on the author's pre-specified and recommended thresholds, and Law's threshold. When these counts could not be determined from published data, we contacted authors for individual patient-level data.

Of the seven included studies, five studies did not report an rCBV threshold, while two studies pre-specified or determined different rCBV thresholds (1.29, 1.5 and 5.66). One study used a pre-specified threshold of 1.5, which was chosen as a mean between literature values (Law 2003; Zonari 2007). Thus, we used Law's threshold of 1.75 as a common threshold in the quantitative analysis for DSC perfusion, as this is more widely accepted in the field. Individual patient-level data were classified using this common threshold to construct the two-by-two table per study.

Meanwhile, of the seven included studies, only one study reported K^{trans} results, precluding quantitative analysis for DCE MR perfusion.

Coupled forest plots showing pairs of sensitivity and specificity, with their 95% confidence intervals (CI), were constructed for each study using RevMan 5.3 (Macaskill 2010; Review Manager 2014).

To estimate the summary sensitivity and specificity, we applied the bivariate model (Reitsma 2005), which accounts for between-study variability in estimates of sensitivity and specificity through the inclusion of random effects for the logit sensitivity and logit specificity parameters of the bivariate model. To generate the bivariate model parameters required to construct the SROC plot in Revman 5.3 (Review Manager 2014), the model was fitted us-

ing the lme4 package of R (R Core team 2013) following Partlett 2016.

Investigations of heterogeneity

As part of the secondary objective, we planned to investigate heterogeneity potentially arising from differences in participant characteristics and study design:

1. tumour histology (subgroups for astrocytomas, oligodendrogliomas, and oligoastrocytomas);
2. MRI strength (1.5T versus 3T);
3. MR perfusion technique (DSC versus DCE);
4. use of contrast preload;
5. post-processing technique (arterial input function versus gamma variate fitting; region of interest versus histogram analysis);
6. method of histological sampling (biopsy versus resection).

Due to the insufficient number of studies, we were unable to perform regression approach to explore heterogeneity.

Subgroup analysis was conducted for tumour histology (astrocytomas versus oligodendrogliomas plus oligoastrocytomas) based on the bivariate model. As the data are sparse, the bootstrap method was used to compute the 95% confidence intervals for the estimates through the boot package of R (R Core team 2013). Other subgroup analyses were not possible due to the small number of studies and participants.

Sensitivity analyses

To determine the robustness of the outcome of the meta-analysis, we conducted sensitivity analysis on good quality studies, defined as those with low risk of bias in domains 3 (reference standard) and 4 (flow and timing) as specified in the QUADAS 2 criteria (Appendix 5).

We also initially intended to conduct sensitivity analysis based on tumour status outside the target and alternative conditions (i.e. including other-gliomas and non-gliomas), but no data were available to perform this.

Assessment of reporting bias

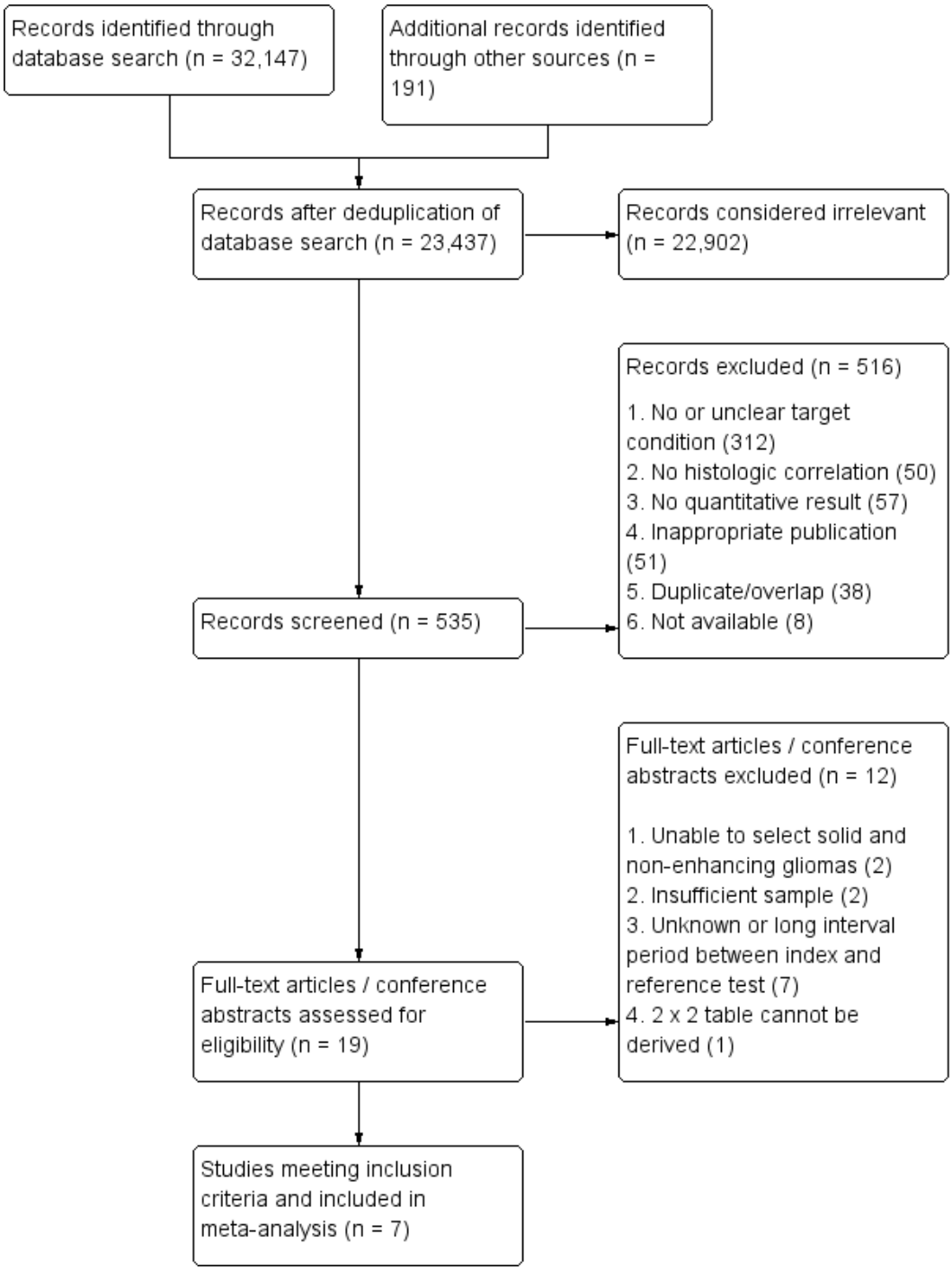
We did not assess reporting bias as there are no clear-cut methods to perform this for studies of diagnostic accuracy (Brazzelli 2009). It is noted that the index test under review is a widely available MRI technique and could be routinely employed in clinical practice (NCCN Guidelines 2016). As such, it would be unlikely to have a record of all attempted evaluations using this technique and therefore positive results are more likely to be reported in the literature (Irwig 1995). To minimise this, we included radiology and neuroradiology conference proceedings in our literature search, where negative results could be documented which may not have been published. Further, the small number of included studies was also inadequate to assess reporting bias by funnel plot (Deeks 2005).

RESULTS

Results of the search

The study selection process is summarised in a PRISMA flow chart (Figure 2). The literature search performed on 11 Nov 2016 identified 32,338 records, after de-duplication and preliminary screening we identified 535 potentially relevant citations. After a further screening of titles and abstracts, we identified 19 studies for full-text review. Of these, we excluded two which reported gliomas of mixed morphology that precluded selection of solid and non-enhancing types (Law 2003; Sugahara 1998), two were excluded due to insufficient samples (no solid non-enhancing HGGs) (Rollin 2006; Senturk 2009), seven excluded due to an unclear time interval between the index test and reference standard (protocol specified less than two months) (Fan 2006; Gaudino 2010; Lev 2004; Liu 2011; Romano 2011; Sahin 2013; Whitmore 2007), and one excluded as no two-by-two table could be derived (Morita 2010). Thus seven studies met all inclusion criteria.

Figure 2. Flow diagram.



Methodological quality of included studies

We judged the methodological qualities of each of the seven included studies according to the modified QUADAS-2 criteria (Appendix 5) and the results are presented in the respective sections below and summarised in Figure 3 and Figure 4. Often the research questions of the accepted studies did not match our review question, and we assessed studies for their risk of bias and concerns regarding applicability based on the study design and the extracted included patient data.

Figure 3. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study using QUADAS 2 tool, applied on study design and included patient data

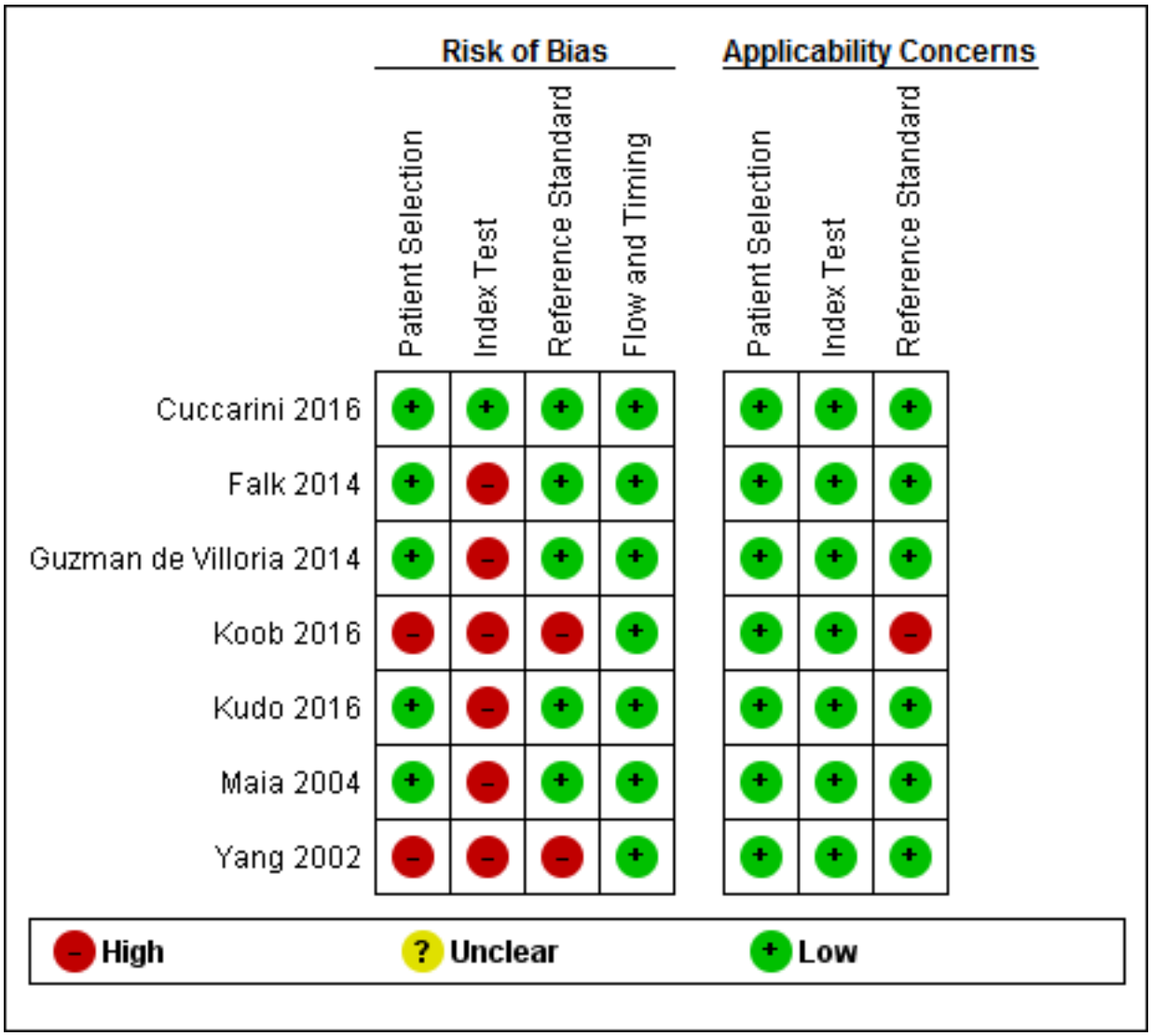
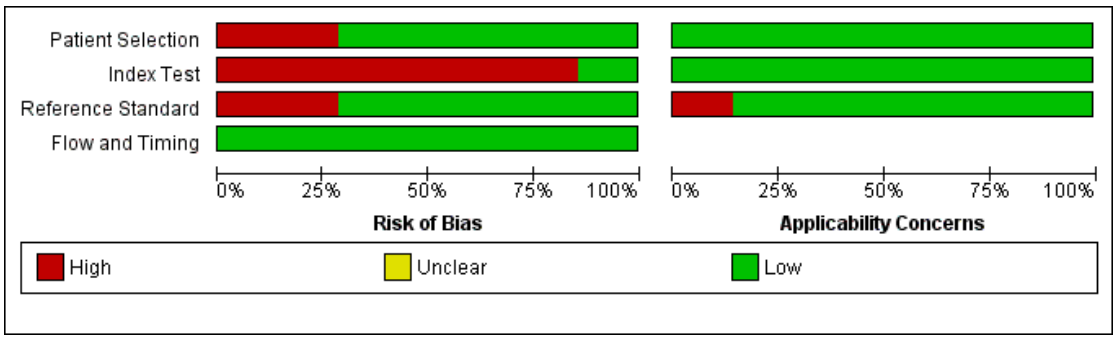


Figure 4. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies



Only one study had low risk of bias and low concern for applicability across all domains (Cuccarini 2016). Five studies had low risk of bias in the domains of reference standard and flow & timing and were deemed of good quality (Cuccarini 2016; Falk 2014; Guzman de Villoria 2014; Kudo 2016; Maia 2004).

Participant Selection

Risk of bias for participant selection was low in five out of seven studies (Cuccarini 2016; Falk 2014; Guzman de Villoria 2014; Kudo 2016; Maia 2004). The other two studies had high risk due to unclear patient sampling (Yang 2002) and inappropriate exclusion of small tumours (Koob 2016). Although many studies had different objectives from our review and also reported contrast enhancing tumours and Grade 1 gliomas, by extracting patient-level data from many authors, we were able to select participants with the target and alternative conditions only. Thus concerns of applicability with regard to participant selection were low.

Index test

The highest level of risk of bias was observed in the index test domain, with six studies lacking use of a pre-specified threshold. Only one study used a pre-specified rCBV threshold of 1.5 (Cuccarini 2016), which was chosen as a mean between literature values (Law 2003; Zonari 2007). However, this limitation in study design was overcome by using individual patient-level data, which allowed use of a common rCBV threshold of 1.75 for the quantitative analyses. Meanwhile, in one study it was unclear if the index test was interpreted without knowledge of the results of the reference standard (Yang 2002). Concerns for applicability with regard to the index test were low, with good evidence in all included studies to suggest MR perfusion was performed in a way similar to clinical practice.

Reference standard

Reference standard issues were present in two studies, due to uncertainties regarding the blinding of interpretation (Koob 2016; Yang 2002). All studies based tumour grading on histopathological assessment. Concerns for applicability with regard to reference standard domains were generally low, with one study deemed high concern due to an unclear description of the proportions of patients undergoing a resection or biopsy (Koob 2016).

Flow and timing

There were no flow and timing issues. In all studies, patients underwent either biopsy or resection irrespective of the results of the index test. Only patients with an interval period of less than two months between the index test and reference standard were included in the analysis.

Findings

Seven studies were included; one study met inclusion criteria based on published data alone (Yang 2002), while the other six were confirmed to meet inclusion criteria after obtaining patient-level data and/or clarification from authors (Cuccarini 2016; Falk 2014; Guzman de Villoria 2014; Koob 2016; Kudo 2016 Maia 2004). Collectively, the seven studies reported 392 patients with brain tumours/gliomas, however only 124 were confirmed to be primary and untreated solid and non-enhancing WHO grade II-IV

gliomas, and of these, only 115 underwent tissue sampling within 2 months of MR perfusion and were included in the review. The sample size per study was generally small and ranged from 4 to 48 cases, and only 2 studies had sample sizes of more than 20 (Cuccarini 2016; Maia 2004). The limited available evidence restricts the conclusions that can be drawn from the review.

All seven studies reported rCBV, which allowed quantitative analysis for DSC MR perfusion. Meanwhile, only one study reported K^{trans} (Falk 2014,) which precluded quantitative analysis for DCE MR perfusion.

The included studies originated from Europe (Italy, Sweden, Spain and France), Asia (two studies from Japan) and South America (one from Brazil). All avoided case-control design. One study was retrospective (Koob 2016), while the rest were prospectively performed. The studies were mostly conducted in university hospitals save for one study (Cuccarini 2016). The studies recruited mostly adults (only Koob 2016 specifically recruited paediatric participants).

Most patients underwent resection and only a small proportion underwent biopsy for tissue diagnosis. Histologic confirmation was via resection only in three studies (Cuccarini 2016; Kudo 2016; Maia 2004), mix of resection (predominant) and biopsy in three studies (Falk 2014; Guzman de Villoria 2014; Yang 2002), and was unspecified in one study (Koob 2016).

The majority of MRI scans were performed on a 1.5T scanner (Cuccarini 2016; Guzman de Villoria 2014; Koob 2016; Maia 2004; Yang 2002); two studies used a 3T scanner (Falk 2014; Kudo 2016). All studies performed DSC MR perfusion and provided rCBV results. Other DSC MR perfusion-derived quantitative measures such as cerebral blood flow and apparent transfer constant were additionally reported by one study (Falk 2014), which was also the only study that performed DCE MR perfusion and provided K^{trans}. Contrast preloading was used in two studies (Falk 2014; Kudo 2016), but not in four studies (Guzman de Villoria 2014; Koob 2016; Maia 2004; Yang 2002), while it was not reported in one study (Cuccarini 2016). The post-processing algorithm was reported in all studies; four studies used arterial input function (Cuccarini 2016; Falk 2014; Koob 2016; Kudo 2016); two used gamma variate function (Guzman de Villoria 2014; Maia 2004), and one used area under the curve analysis (Yang 2002). All studies employed region of interest (ROI) method to obtain perfusion values in areas showing high perfusion, and one study (Falk 2014) provided histogram results from the ROI's drawn.

Individual perfusion values were published in two studies (Maia 2004; Yang 2002) and were provided by authors in the other five studies (Cuccarini 2016; Falk 2014; Guzman de Villoria 2014; Koob 2016; Kudo 2016). From these published and unpublished data, a total of 124 solid and non-enhancing gliomas were identified, of which 115 (83 LGGs, 32 HGGs) met all inclusion criteria and were selected for the review.

The average rCBV per tumour grade and tumour histology in each included study are summarised in Table 2. Most studies recruited Grade II and III gliomas, with only one case of a solid and non-enhancing Grade IV/glioblastoma with rCBV of 0.3 (Cuccarini 2016). All tumours were graded using the WHO classification, and in this review LGG was classified as disease positive, and HGG as disease negative for the quantitative analysis. Histology was available in all of them except for two of the four included cases from Koob 2016. Diffuse astrocytomas were reported in the remainder of the studies, and other tumour histology types were not always represented per study. Other tumours with solid and non-enhancing appearance on MRI but with histology different from the target and alternative conditions were reported and excluded in two studies (Cuccarini 2016; Falk 2014).

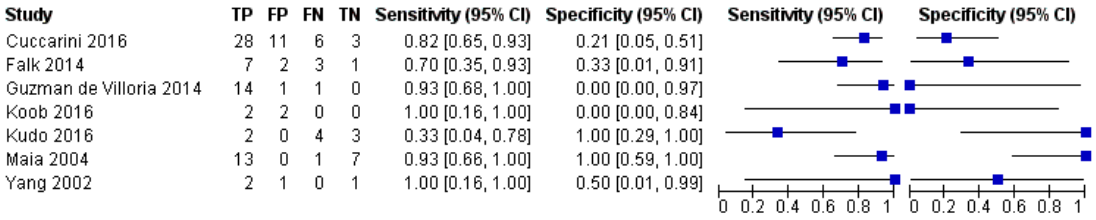
The average rCBV (range) per glioma grade and histology with their numbers are 1.29 (0.01 to 5.10) for LGGs (N = 83), 1.89 (0.30 to 6.51) for HGGs (N = 32). Average rCBV was 1.19 (0.34 to 3.72) for Grade II astrocytomas (N = 40), 1.63 (0.01 to 4.30) for Grade II oligodendrogliomas (N = 19), 1.22 (0.08 to 5.10) for Grade II oligoastrocytomas (N = 23). The rCBV for combined Grade II oligodendroglioma + oligoastrocytoma was 1.41 (0.01 to 5.10) (N = 42); 2.02 (0.65 to 3.79) for Grade III astrocytomas (N = 15), 2.99 (1.70 to 6.51) for Grade III oligodendrogliomas (N = 4); 1.44 (0.60 to 3.34) for Grade III oligoastrocytomas (N = 11) and 1.96 (0.60 to 6.51) for combined Grade III oligodendrogliomas+oligoastrocytomas (N = 15).

Only one study (Cuccarini 2016) used a pre-specified rCBV threshold, and chose 1.5 as a mean between literature threshold values (Law 2003; Zonari 2007). Two studies determined rCBV thresholds for differentiating LGGs and HGGs: 1.29 (Cuccarini 2016) and 5.66 (Kudo 2016). The other five studies did not determine an rCBV threshold (Falk 2014; Guzman de Villoria 2014; Koob 2016; Maia 2004, Yang 2002). Because of the lack or variability of thresholds reported by studies, we adopted the widely accepted rCBV value of 1.75 as common threshold for the quantitative analysis of DSC MR perfusion. In this review, an rCBV $\leq$ 1.75 was classified as test positive and implied a diagnosis of LGG, while an rCBV > 1.75 was classified as test negative and suggested a diagnosis of HGG. Thus in constructing the two-by-two contingency tables, true and false positives represented the number of LGGs correctly and incorrectly diagnosed, respectively, while true and false negatives represented the number of HGGs correctly and incorrectly diagnosed, respectively (Appendix 1).

The sensitivity and specificity of the seven included studies are presented in coupled forest plots in Figure 5. Sensitivity estimates were generally in the upper range and had wide confidence intervals. Mean sensitivities were $\geq$ 0.70 in six out of seven studies (excepting Kudo 2016). Of these, two studies with a mean sensitivity of 1.00 had very wide confidence intervals, and were derived from studies with the smallest sample size of four each (Koob 2016, Yang 2002). In contrast, two studies with the largest sample sizes of 48 and 21 had mean sensitivities of 0.82 and 0.93 (Cuccarini 2016 and Maia 2004, respectively) with moderately wide confi-

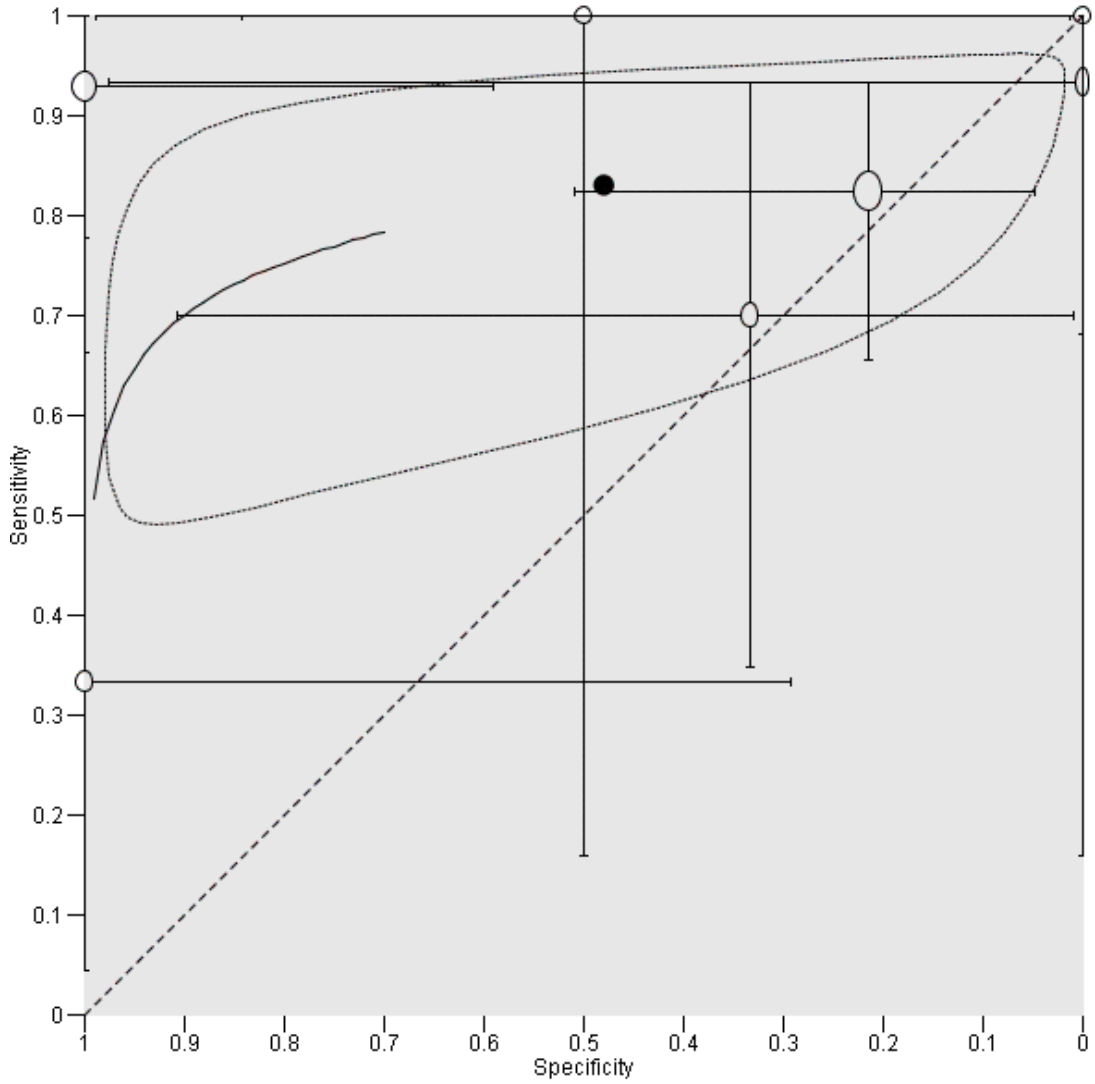
dence intervals. Meanwhile, mean specificities were quite heterogeneous and showed even wider confidence intervals. The two largest studies of Cuccarini 2016 and Maia 2004 had opposing mean specificity values of 0.21 and 1.00, respectively.

Figure 5. Coupled forest plots of included studies using rCBV threshold of < 1.75 for differentiating low grade gliomas from high-grade gliomas.



Meta-analysis of the seven studies using a bivariate model yielded a summary sensitivity and specificity of 0.83 (95% CI 0.66 to 0.93) and 0.48 (95% CI 0.09 to 0.90), respectively (Figure 6). The 95% confidence ellipse of the summary point is quite wide and spans the upper half of the range of sensitivity, and spans nearly the entire range of specificity.

Figure 6. Summary ROC Plot of DSC MR perfusion using rCBV threshold of 1.75 for differentiating low grade gliomas from high-grade gliomas. In this review, a positive test or rCBV < 1.75 implied an LGG diagnosis, while a negative test or rCBV > 1.75 suggested an HGG diagnosis. In the SROC plot, each study is represented by an open circle with emanating lines, representing the sensitivity and specificity with their confidence intervals. The size of the open circle is proportional to the study sample size. The shaded circle represents the pooled sensitivity and specificity surrounded by a 95% confidence ellipse (dotted line), which in this case is 0.830 (95% CI 0.657, 0.926) and 0.479 (95% CI 0.086, 0.900), respectively.



Regression analysis to explore heterogeneity was not performed due to insufficient data.

Subroup analysis on tumour histology types showed summary sensitivities and specificities of 0.92 (95% CI 0.55 to 0.99) and 0.42 (95% CI 0.02 to 0.95) respectively, for astrocytomas using data from six studies (55 participants) (Cuccarini 2016; Falk 2014; Guzman de Villoria 2014; Kudo 2016; Maia 2004; Yang 2002), and 0.77 (95% CI 0.46 to 0.93) and 0.53 (95% CI 0.14 to 0.88), respectively, for combined oligodendrogliomas+oligoastrocytomas using data from six studies (56 participants) (Cuccarini 2016; Falk 2014; Guzman de Villoria 2014; Koob 2016; Kudo 2016; Maia 2004).

Additional subgroup analysis on other variables such as histologic confirmation method, MRI acquisition and post-processing could not be performed due to limited data.

Sensitivity analysis using five good quality studies (107 participants: 79 LGG, 28 HGG) with low risk of bias in the domains of reference standard and flow and timing resulted in summary sensitivity of 0.80 (95% CI 0.61 to 0.91) and summary specificity of 0.67 (95% CI 0.07 to 0.98) (Cuccarini 2016; Falk 2014; Guzman de Villoria 2014; Kudo 2016; Maia 2004).

Overall, the individual studies and meta-analysis yielded variable and/or wide-ranging estimates which are attributed to the small sample sizes. Thus currently, the diagnostic accuracy of MR perfusion cannot be reliably determined based on the available data. Insufficient data also precluded determination of clinical and methodological factors affecting the accuracy of MR perfusion.

Summary of findings

Population	Almost all adults					
Setting	Mostly university hospitals, employing exclusively 1.5T or 3T MRI scanners					
Index test	Dynamic susceptibility contrast MR perfusion (commonly gradient echo rather than spin echo sequence acquisition), usually without contrast preload, typically using arterial input function or gamma variate function post-processing algorithms, and preferentially using region-of-interest method to obtain Max rCBV values (CBV ratio of tumour: contralateral normal appearing white matter)					
Importance	For solid and non-enhancing brain tumours with low rCBV, patients with no or little neurologic deficit may opt for conservative management over surgery to avoid early neurologic disability. Meanwhile, patients with high rCBV could favour early treatment for better tumour control					
Reference standard	All with histologic examinations, majority with resection.					
Studies	Mostly prospective cross sectional studies (no case-control studies)					
Positive Test	Summary accuracy (95%CI) using bivariate model	No. of study participants / selected patients (No. of studies)	Prevalence	Implications	Quality of studies (Based on QUADAS-2 applied on study design and selected patients)	Comments
rCBV threshold <1.75 indicates LGG	Sensitivity (proportion of LGG detected by MR perfusion) 0.83 (0.66, 0.93) Specificity (proportion of HGG detected by MR perfusion) 0.48 (0.09 to 0.90)	392 patients / 115 with solid non-enhancing Grade II-IV gliomas who underwent tissue sampling within 2 months of MR perfusion (7 studies)	In a hypothetical population of solid and non-enhancing Grade II-IV gliomas, the prevalence of LGGs and HGGs is 72% and 28%, respectively	Given 100 patients with solid and non-enhancing infiltrative gliomas, 72 will have LGG and 28 with HGG Of 72 patients with LGG, it is expected 12 patients will be misclassified to have HGG (but this could potentially be between 5 to 24 patients) and may undergo surgery, thus risking early neu-	Generally low risk of bias in the patient selection domain, excepting 2 out of 7 studies with unclear patient sampling and inappropriate exclusion of small tumours High risk of bias in the index test domain, mainly because 6 out of 7 studies did not use a pre-specified threshold. However this did	Low numbers (4 to 48) with target and alternative conditions per study and only 2 studies had >20 patients In general, individual studies had heterogeneous sensitivity and specificity, both with wide confidence intervals Only 1 study had low risk of bias and low concern of applicability

	rologic deterioration. Meanwhile, of 28 patients with HGG, 15 will be misclassified to have LGG (but this could be between 3 to 25 patients), which may lead to a delay in treatment that can potentially adversely affect outcomes	not affect meta-analysis as we used a common rCBV threshold of 1.75. Generally low risk of bias in the reference standard domain, excepting 2 out of 7 studies with unclear method of histologic confirmation and/or presence of blinding. Low risk of bias in the flow and timing domain. Low concerns of applicability for the patient selection, index test and reference standard domains by using patient-level data	across all domains Five studies were considered good quality (i.e., with low risk of bias in the domains of reference standard and flow & timing). Their sensitivity analysis yielded sensitivity 0.80 (95% CI 0.61 to 0.91) and specificity 0.67 (95% CI 0.07 to 0.98) Subgroup analysis showed sensitivity/specificity of [0.92 (95%CI 0.55 to 0.99) / 0.42 (95% CI 0.02 to 0.95) in astrocytomas and 0.77 (95% CI 0.46 to 0.93)/0.53 (95%CI 0.14 to 0.88) in oligodendrogliomas + oligoastrocytomas Data were too sparse to investigate any differences across subgroups

HGG: high-grade glioma, **LGG:** low-grade glioma, **rCBV:** relative cerebral blood volume

DISCUSSION

In this review, we determined the accuracy of magnetic resonance (MR) perfusion for differentiating primary untreated low-grade gliomas (LGGs) from high-grade gliomas (HGGs), when they appear as solid and non-enhancing on standard magnetic resonance imaging (MRI). While MR perfusion is becoming increasingly commonly used in clinical practice and regarded to be an integral technique in current brain tumour imaging (Welker 2015), we found limited evidence regarding its diagnostic performance for grading solid and non-enhancing diffuse gliomas. There were insufficient data to determine the clinical and methodological features that affect the accuracy of this technique. The conclusions that can be drawn from the review are therefore restricted.

Summary of main results

Seven studies were included and all but one were prospectively carried out. All studies reported CBV ratio of tumour (rCBV) and only one reported K^{trans}, limiting this review to DSC MR perfusion only. While most examined the diagnostic accuracy of MR perfusion, pre-specified thresholds were not commonly used, and thresholds were either not determined or varied; thus we applied a common rCBV threshold of 1.75 for the quantitative analysis. The acquisition and post-processing of MR perfusion were moderately heterogeneous, with different scanner magnetic field strengths employed (1.5 and 3T), different pulse sequences (spin echo and gradient echo), use and non-use of contrast preload, and different post-processing algorithms (arterial input function, gamma variate function and area under the curve). This may reflect the difficulties of implementing a single standard in clinical practice, or a lack of evidence for any given protocol, but may also make problematic the use of a single threshold when handling multicentre perfusion data. Subsequent analysis was similar, with predominant use of the region of interest (ROI) method to obtain rCBV, and targeting of tumour regions that show high perfusion. The majority of tumours were resected, allowing a more definitive reference standard.

From published data and unpublished results from authors, we were able to identify 115 solid and non-enhancing gliomas that met all the inclusion criteria and allowed quantitative analysis for dynamic susceptibility (DSC) MR perfusion. The studies generally had small sample sizes (range of 4 to 48). Meta-analysis identified that estimates for both mean sensitivity and specificity were very uncertain so evidence of diagnostic performance is unreliable. This is identified from the wide confidence intervals for the estimates of sensitivity and specificity: sensitivity 0.83 (95% CI 0.66 to 0.93) and specificity of 0.48 (95% CI 0.09 to 0.90). Sensitivity analysis using good quality studies and subgroup analysis on tumour histology produced consistent results; i.e. sensitivity and specificity cannot be reliably estimated based on small number of patients in the included studies. Regression analysis to explore heterogeneity also could not be performed due to insufficient data.

Thus, from the currently reviewed evidence, we cannot reliably estimate specificity from meta-analysis as although the average estimate is 48%, from the 95% CI the value could be as low as 9% or as high as 90%. Sensitivity is also poorly estimated with an average of 83%, but with estimates potentially including values ranging from 66% to 93%.

A precis of these findings, together with the study quality assessment, are presented in the Summary of findings.

Our meta-analysis on 83 LGGs and 32 HGGs suggest that DSC MR perfusion performance cannot be reliably estimated based on current evidence for either sensitivity or specificity for the identification of primary and untreated, solid and non-enhancing WHO grade II gliomas from higher grade gliomas. Additionally, the limited available data also preclude assessment on how other clinical and methodological features affect the accuracy of MR perfusion. Future research would need to include a much larger sample size of patients with both LGG and HGG, preferably using a standardised scanning protocol to reliably estimate performance of MR perfusion. A recent paper demonstrates that standardised acquisition and analysis for MR perfusion in a multicentre clinical setting is feasible, and derived an rCBV threshold of 3.33 to differentiate Grade II from III/IV gliomas (Anzalone 2017).

Strengths and weaknesses of the review

One study (Cuccarini 2016) closely mirrored the patient population and study design considered to be appropriate for studies of diagnostic accuracy. Also, most of the included studies were prospective in design and performed resection, which allowed a more definitive histologic diagnosis to serve as reference standard. The small number of included studies poses a limitation but this is a reflection of strict methodological standards required to remain faithful to the review question. During the screening process, we encountered many studies that performed MR perfusion for glioma grading, however they could not be included because often the MRI appearances of the tumour could not be ascertained or the perfusion values of such solid and non-enhancing gliomas were not specifically reported. Many authors were contacted and invited to share their data by which we were able to include unpublished perfusion values from five studies in the meta-analysis (Cuccarini 2016; Falk 2014; Guzman de Villoria 2014; Koob 2016; Kudo 2016). Overall, performing a meta-analysis has allowed a thorough critique of the methodological quality of studies in the literature, and a substantially larger number of participants to base conclusions upon than any one single study. However, the included number of patients (115) remains small and limits the conclusions that can be drawn from this review.

Applicability of findings to the review question

Based on a small number of participants, the estimated sensitivity suggests that DSC MR perfusion may be able to detect up to 93% of patients with LGG, but sensitivity can be as low as 66%. Thus, between 7% and 34% of patients with LGG may have MR perfusion findings suggestive of HGG, and patients may feel compelled to undergo early intervention. In this instance one option could be to perform an early diagnostic biopsy, which can be performed with little morbidity (Kreth 2001), but risks undersampling and falsely undergrading the tumour (Muragaki 2008). Another option would be to consider aggressive surgical resection as is typically performed in HGG, for example with fluorescence or intra-operative MRI guidance. This could potentially differ from the surgical approach offered in LGG where one might prefer awake craniotomy with functional brain mapping. A further option would be a further standard MRI scan with rCBV after a short time interval, as earlier intervention has not been widely shown yet to extend survival in LGG or asymptomatic transforming LGG and repeat scan may add further weight regarding whether or not to intervene.

Both surgical options will allow histologic confirmation but perhaps more importantly, provide a molecular profile of the tumour. The recent major restructuring of the WHO classification for brain tumours (Louis 2016) now establishes primacy of the incorporation of molecular genetic features with histology in tumour diagnosis, prognostication and therapy guidance. Following suit, the European Association for Neuro-Oncology (EANO) have recently issued treatment guidelines based on this integrated phenotype-genotype classification and recommends diagnostic biopsy at minimum, excepting high-risk cases and those with unfavourable prognosis where treatment is unlikely to be successful (Weller 2017).

Meanwhile the estimated specificity of MR perfusion is more heterogeneous: 9% to 90%. This means that between 10% and 91% of cases of HGGs may be labelled as LGGs and patients may decide for a watch-and-wait approach. This would lead to delay in performing resection, when this would have been the strongly recommended initial treatment approach for people with surgically accessible HGG (Dietrich 2017).

AUTHORS' CONCLUSIONS

Implications for practice

Currently, the limited available evidence neither supports nor refutes the use of MR perfusion for the differentiation of primary and untreated solid and non-enhancing LGGs and HGGs.

Implications for research

There is limited evidence available in the literature and even fewer good quality studies reporting the diagnostic accuracy of MR perfusion for grading solid and non-enhancing astrocytic and oligodendrogial gliomas. More research and larger sample sizes are required, but standardisation of the technique is equally important as variations in MRI acquisition and post-processing are known to affect perfusion values. Current practice recommendations (Essig 2013; Welker 2015) can pave the way for a harmonised approach and should be considered by future studies. Such efforts will facilitate handling of multicentre perfusion data and allow better assessment of the clinical applicability of the technique.

However, the recent nosological shift in the WHO classification of brain tumours (Louis 2016) also poses a foreseeable change in the reference standard that MR perfusion will be compared against in future testing of its accuracy. In this vein, the new integrated genotype-phenotype classification of diffuse gliomas may be more concordant with multimodal imaging rather than MR perfusion alone. Meanwhile, the clinical management of LGGs is also evolving and the watch-and-wait approach may become obsolete in the future (Boissonneau 2017); recent evidence in parallel population-based cohorts suggests clear survival benefit with early surgical resection in unselected patients with LGGs (Jakola 2017). In the future the relevance of MR perfusion identifying primary LGG's may diminish and its role may become limited to characterisation of tumour biologic activity, prognostication, and/or surveillance during the post-treatment period.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cuccarini 2016

Study characteristics			
Patient sampling	Prospective, consecutive		
Patient characteristics and setting	The study reported 89 patients with suspected LGGs with absent or faint enhancement, mean age 39.6 ± 12.6 y.o., in a neurological institute in Italy, between 2006 and 2009. The author provided individual data on 48 patients with solid and non-enhancing gliomas which were selected for the review		
Index tests	DSC MR perfusion (Max rCBV) Pre-specified rCBV threshold: 1.5 Study-determined rCBV threshold: 1.29		
Target condition and reference standard(s)	Resection		
Flow and timing	Interval period between MR perfusion and resection: 1-45 days		
Comparative			
MR perfusion acquisition and analysis	1.5 T MRI scanner Use of contrast preload: N/A Post-processing algorithm: Arterial input function (unpublished information, confirmed by authors) 3 ROI placed on areas of maximal CBV and normalised with an identical ROI positioned on the contralateral healthy white matter		
Notes	The author provided individual patient data and clarification of study method		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		

Did the study avoid inappropriate inclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
If a threshold was used, was it pre-specified?	Yes		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Was tumour grading based on histopathological assessment or WHO criteria only?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Falk 2014

Study characteristics			
Patient sampling	Prospective, consecutive		
Patient characteristics and setting	The study reported 25 adults with non- and minimally enhancing radiologically suspected LGGs, 22-70 y.o., in a university hospital in Sweden from May 2010 and November 2012. The author provided individual data on 20 patients with solid and non-enhancing gliomas. After excluding patients with >2-month interval period between MR perfusion and histology, 13 patients were selected for the review		
Index tests	DSC MR perfusion: single shot gradient-echo EPI (Mean CBV, CBF, kapp) DCE MR perfusion (Mean CBV, CBF, ktrans), performed prior to DSC MR perfusion Pre-specified rCBV/K^{trans} threshold: None Study-determined rCBV/K^{trans} threshold: None		
Target condition and reference standard(s)	Resection (N = 15), Biopsy (N = 5)		
Flow and timing	Interval period between MR perfusion and resection: <1 - 10 months		
Comparative			
MR perfusion acquisition and analysis	3 T MRI scanner Use of contrast preload: Yes (as DCE MR perfusion) Post-processing algorithm: Arterial input function ROI placed in tumour and normal appearing white matter in lobe contralateral to tumour and histogram parameters (mean, median, skewness, etc.) obtained		
Notes	The author provided individual patient data and clarification of study method		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Did the study avoid inappropriate inclusions?	Yes		
		Low	**Low**

Falk 2014 (*Continued*)

DOMAIN 2: Index Test All tests			
If a threshold was used, was it pre-specified?	No		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		High	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Was tumour grading based on histopathological assessment or WHO criteria only?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Guzman de Villoria 2014

Study characteristics			
Patient sampling	Prospective, consecutive		
Patient characteristics and setting	The study reported 129 patients with primary brain tumours, 11-84 y.o., in a university hospital in Spain, from Feb 2004 - April 2009. The author provided individual data on 18 solid and non-enhancing gliomas. After excluding patients with >2-month interval period between MR perfusion and histology, 16 patients were selected for the review		
Index tests	DSC MR perfusion: single shot gradient-echo EPI (Mean rCBV) Pre-specified rCBV threshold: None Study-determined rCBV threshold: None		
Target condition and reference standard(s)	Resection (N = 15), Biopsy (N = 3)		
Flow and timing	Interval period between MR perfusion and biopsy/resection: 5-103 days		
Comparative			
MR perfusion acquisition and analysis	1.5 T MRI scanner Use of contrast preload: No Post-processing algorithm: Gamma variate function ROI centred on highest tumour rCBV value, drawn as large as possible to include all voxels with highest and similar values of rCBV, normalised to contralateral NAWM		
Notes	The author provided individual patient data and clarification of study method		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Did the study avoid inappropriate inclusions?	Yes		
		Low	**Low**

Guzman de Villoria 2014 (*Continued*)

DOMAIN 2: Index Test All tests			
If a threshold was used, was it pre-specified?	No		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		High	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Was tumour grading based on histopathological assessment or WHO criteria only?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Koob 2016

Study characteristics			
Patient sampling	Retrospective, consecutive		
Patient characteristics and setting	The study reported 169 patients with brain tumour, 1-18 y.o., in a university hospital in France, from Oct 2006 to Apr 2013 The author provided individual data on 4 patients with solid and non-enhancing gliomas which were selected for the review		
Index tests	DSC MR perfusion: gradient echo EPI (Max rCBV) Pre-specified rCBV threshold: None Study-determined rCBV threshold: None		
Target condition and reference standard(s)	Resection and biopsy (not specified per case)		
Flow and timing	Interval period between MR perfusion and biopsy/resection: 1 week		
Comparative			
MR perfusion acquisition and analysis	1.5 T MRI scanner Use of contrast preload: No Post-processing algorithm: Arterial input function 5-10 ROIs placed in areas of maximal rCBV normalised to ROI in contralateral NAWM or cerebellar GM for posterior fossa tumours		
Notes	The author provided individual patient data.		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Did the study avoid inappropriate inclusions?	Yes		
		High	**Low**
DOMAIN 2: Index Test All tests			

Koob 2016 (*Continued*)

If a threshold was used, was it pre-specified?	No		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		High	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Was tumour grading based on histopathological assessment or WHO criteria only?	Yes		
		High	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Kudo 2016

Study characteristics	
Patient sampling	Prospective, consecutive

Kudo 2016 (*Continued*)

Patient characteristics and setting	The study reported 35 patients with WHO Grade II-IV gliomas, 8-91y.o., in a university hospital in Japan, from May 2009 to June 2013. The authors provided individual data on 9 patients with solid and non-enhancing gliomas which were selected for the review
Index tests	DSC MR perfusion: gradient echo EPI (Max rCBV) Pre-specified rCBV threshold: None Study-determined rCBV threshold: 5.66
Target condition and reference standard(s)	Resection in majority (unpublished data, confirmed by authors)
Flow and timing	Interval period between MR perfusion and resection: Within 2 weeks (unpublished data, confirmed by authors)
Comparative	
MR perfusion acquisition and analysis	3 T MRI scanner Use of contrast preload: Yes Post-processing algorithm: Arterial input function >2 ROIs (diameter of 2 mm) placed in high CBV area of the tumour, and 10 ROIs of the same diameter in the contralateral, normal white matter
Notes	The author provided individual patient data and clarification of study method

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Did the study avoid inappropriate inclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
If a threshold was used, was it pre-specified?	No		

Kudo 2016 (*Continued*)

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
		High	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Was tumour grading based on histopathological assessment or WHO criteria only?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Maia 2004

Study characteristics	
Patient sampling	Prospective, consecutive
Patient characteristics and setting	The study reported individual data on 21 adults with suspected supratentorial nonenhancing LGG, 23-60 y.o., in a university hospital in Brazil, from Feb 2001-2004. All patients selected for the review.

Maia 2004 (*Continued*)

Index tests	DSC MR perfusion: spin-echo EPI (Mean rCBV for homogeneous tumour, Max rCBV for heterogeneous tumour) Pre-specified rCBV threshold: None Study-determined rCBV threshold: None for LGG vs HGG (1.2 for differentiating diffuse astrocytoma histology subtype)		
Target condition and reference standard(s)	Resection		
Flow and timing	Interval period between MR perfusion and resection: 2 days (unpublished data, confirmed by author)		
Comparative			
MR perfusion acquisition and analysis	1.5 T MRI scanner Use of contrast preload: No Post-processing algorithm: Gamma variate function 6 ROI in tumour and ROI in normal contralateral white matter		
Notes	The author provided clarification of study method.		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Did the study avoid inappropriate inclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
If a threshold was used, was it pre-specified?	No		
Were the index test results interpreted without knowledge of the results of the reference stan-	Yes		

Maia 2004 (*Continued*)

dard?			
		High	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Was tumour grading based on histopathological assessment or WHO criteria only?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Yang 2002

Study characteristics	
Patient sampling	Prospective, patient sampling not reported
Patient characteristics and setting	The study reported individual data on 17 patients with supratentorial gliomas, 14-67 y.o., in a university hospital in Japan. 4 patients were selected for the review.
Index tests	DSC MR perfusion: gradient echo EPI (Max rCBV) Pre-specified rCBV threshold: None Study-determined rCBV threshold: None

Target condition and reference standard(s)	Resection (N = 14), Biopsy (N = 3)		
Flow and timing	Interval period between MR perfusion and biopsy/resection: within 10 days		
Comparative			
MR perfusion acquisition and analysis	1.5 T MRI scanner Use of contrast preload: No Post-processing algorithm: Area under the curve 5 ROI >20 pixels placed in tumour and contralateral white matter		
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Did the study avoid inappropriate inclusions?	Yes		
		High	**Low**
DOMAIN 2: Index Test All tests			
If a threshold was used, was it pre-specified?	No		
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
		High	**Low**
DOMAIN 3: Reference Standard			

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Was tumour grading based on histopathological assessment or WHO criteria only?	Yes		
		High	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

CBF: cerebral blood flow, **CBV:** cerebral blood volume, **DCE:** dynamic contrast-enhanced, **DSC:** dynamic susceptibility, **EPI:** Echo planar images, **HGG:** high-grade gliomas, **LGG:** low-grade gliomas, **MR:** magnetic resonance, **MRI:** magnetic resonance imaging, **rCBV**: CBV ratio of tumour, **ROI:** region of interest, **y.o.:** years old.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Fan 2006	Unclear/long interval period between index test and reference test
Gaudino 2010	Unclear/long interval period between index test and reference test
Law 2003	Unable to select solid and non-enhancing gliomas
Lev 2004	Unclear/long period between index test and reference test

(*Continued*)

Liu 2011	Unclear/long period between index test and reference test
Morita 2010	No 2 x 2 table can be derived
Rollin 2006	Insufficient sample (no solid non-enhancing HGGs)
Romano 2011	Unclear/long interval period between index test and reference test
Sahin 2013	Unclear/long period between index test and reference test
Senturk 2009	Insufficient sample (no solid non-enhancing HGGs)
Sugahara 1998	Unable to select solid and non-enhancing gliomas
Whitmore 2007	Unclear/long interval period between index test and reference test

HGG: high-grade gliomas

DATA

Presented below are all the data for all of the tests entered into the review.

Tests. Data tables by test

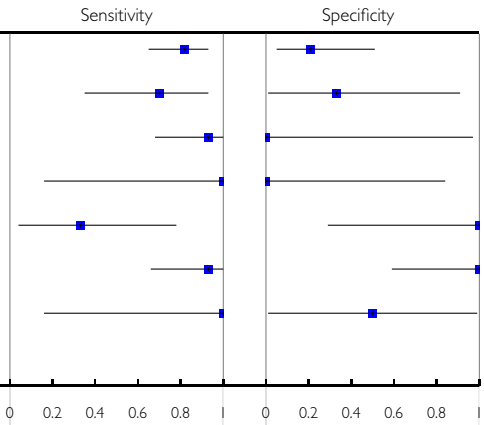
Test	No. of studies	No. of participants
1 rCBV - Law Threshold	7	115

Test 1. rCBV - Law Threshold.

Review: Magnetic resonance perfusion for differentiating low-grade from high-grade gliomas at first presentation

Test: 1 rCBV - Law Threshold

Study	TP	FP	FN	TN	Sensitivity	Specificity
Cuccarini 2016	28	11	6	3	0.82 [0.65, 0.93]	0.21 [0.05, 0.51]
Falk 2014	7	2	3	1	0.70 [0.35, 0.93]	0.33 [0.01, 0.91]
Guzman de Villoria 2014	14	1	1	0	0.93 [0.68, 1.00]	0.0 [0.0, 0.97]
Koob 2016	2	2	0	0	1.00 [0.16, 1.00]	0.0 [0.0, 0.84]
Kudo 2016	2	0	4	3	0.33 [0.04, 0.78]	1.00 [0.29, 1.00]
Maia 2004	13	0	1	7	0.93 [0.66, 1.00]	1.00 [0.59, 1.00]
Yang 2002	2	1	0	1	1.00 [0.16, 1.00]	0.50 [0.01, 0.99]



ADDITIONAL TABLES

Table 1. World Health Organization (WHO) Grading of Brain Tumors*

WHO Grade	Tumour histology
I**	Pilocytic astrocytoma Subependymal giant cell astrocytoma Pleomorphic xanthoastrocytoma Ganglioglioma

Table 1. World Health Organization (WHO) Grading of Brain Tumors* (*Continued*)

	Ependymoma
II	Diffuse astrocytoma Oligodendroglioma Oligoastrocytoma
III	Anaplastic astrocytoma Anaplastic oligodendroglioma Anaplastic oligoastrocytoma
IV	Glioblastoma multiforme Gliomatosis cerebri

* Partial listing and specific to the tumour histology types relevant to this review.
**These tumours are included in this table for reference only and are not part of the review.

Table 2. rCBV per tumour grade and per tumour histology

Included studies	LGG (Grade II)	HGG (Grade III+IV)	DA	OA	OG	AA	AOA	AOG
Cuccarini 2016	1.15 ± 0.95	1.18 + 0.8	1.19 ± 0.76	1.12 ± 1.13	1.22 ± 0.57	1.15 ± 0.53	1.33 ± 0.98	
Falk 2014	1.30 + 0.48	1.76 + 0.93	1.48 + 0.69	1.20 + 0.21	1.19 + 0.32	2.22 + 1.18	0.86	1.76
Guzman de Villoria 2014	1.07 + 0.79	0.75	0.98 + 0.29		1.24 ±1.33	0.75		
Koob 2016	0.8 + 0.04	0.8 + 0.6	[0.77]		0.82	[0.41]	1.28	
Kudo 2016	3.1 ± 1.19	3.83 ± 2.34	2.31 ±1.23		3.88 ±.46			3.8 + 2.3
Maia 2004	1.16 ± 0.63	3.2 ± 0.35	0.9 ±.43	1.98 ± 0.57	1.27	3.24 ± 0.37	2.99	
Yang 2002	1.29 ± 0.17	1.76 ± 0.08	1.29 ± 0.17			1.81		1.7

LGG: Low-grade glioma, **HGG:** high-grade glioma, **DA:** diffuse astrocytoma, **OA:** oligoastrocytoma, **OG:** oligodendroglioma, **AA:** anaplastic astrocytoma, **AOA:** Anaplastic oligoastrocytoma, **AOG:** anaplastic oligodendroglioma.
Nearly all HGGs are Grade III, except for one case of Grade IV/glioblastoma from Cuccarini 2016, with rCBV of 0.3. Bracketed values in Koob 2016 are included for completion but represent unspecified gliomas, with no reported histology.

APPENDICES

Appendix 1. Two-by-two contingency table for extraction of data

	Histologic diagnosis	
MR Perfusion result	LGG (Disease positive)	HGG (Disease negative)
rCBV < 1.75 (Test positive)	True positive	False negative
rCBV > 1.75 (Test negative)	False positive	True negative

Abbreviations: **HGG:** high-grade glioma;**LGG:** low-grade glioma; **rCBV:** relative cerebral blood volume

Appendix 2. MEDLINE search strategy

Medline (OvidSP Epub Ahead of Print, Medline R In-Process & Other Non-Indexed Citations and Ovid Medline R 1946 to present) (searched 10 November 2016)
1. Glioma/
2. Glioma, Subependymal/
3. Astrocytoma/
4. Oligodendroglioma/
5. (glioma*1 or astrocytoma* or astrocytic or subependym* or oligodendroglioma* or oligoastrocytoma* or oligo-astrocytoma* or oligo-dendroglioma* or oligodendroglial* or oligo-dendroglial* or LGG or LGGs).ti,ab.
6. Neoplasms, Neuroepithelial/
7. or/1-6
8. exp Infratentorial Neoplasms/
9. Supratentorial Neoplasms/
10. ((supratentorial or supra-tentorial or infratentorial or infra-tentorial or glial cell*1 or neuroepithelial or neuro-epithelial) adj3 (tumo?r* or neoplas* or anaplas* or cancer* or malignan*)).ti,ab.
11. or/8-10
12. Neoplasm Staging/
13. Neoplasm Grading/
14. Disease Progression/
15. Neoplasm Invasiveness/
16. (grading or grade or grades or staging or stageing or differentiat* or delineat* or distinguish* or correlat* or distinct* or characteri* or diagnos* or detect* or predict* or sensitivit* or specificit*).ti,ab.
17. or/12-16
18. 11 and 17
19. Magnetic Resonance Imaging/ or Magnetic Resonance Angiography/
20. Perfusion Imaging/
21. *Diagnostic Imaging/
22. (perfusion adj3 (MR or MRI or magnetic resonance or imaging)).ti,ab.
23. ("dynamic contrast enhanced" or "dynamic susceptibility" or DCE or DSC).ti,ab.
24. or/19-23
25. (7 or 18) and 24
26. exp animals/ not humans.sh.
27. (veterinary or animal or animals or feline or canine or tierheilkunde).jw.

28. (cat or cats or dog or dogs or beagle or beagles or rat or rats or rodent or rodents or mouse or mice or murine or rabbit or rabbits or pig or pigs or bitch or bitches or feline or canine or swine or porcine or sheep or hamster or hamsters or cattle or bovine or monkey or monkeys or macaque or macaques).ti.
29. or/26-28
30. 25 not 29

Appendix 3. Embase search strategy

Embase (OvidSP 1980 to 2016 Week 45) (searched 10 November 2016)
1. Glioma/ or Oligodendroglioma/ or Subependymoma/
2. exp Astrocytoma/
3. (glioma*1 or astrocytoma* or astrocytic or subependym* or oligodendroglioma* or oligoastrocytoma* or oligo-astrocytoma* or oligo-dendroglioma* or oligodendroglial* or oligo-dendroglial* or LGG or LGGs).ti,ab.
4. or/1-3
5. brain tumor/
6. ((supratentorial or supra-tentorial or infratentorial or infra-tentorial or glial cell*1 or neuroepithelial or neuro-epithelial) adj3 (tumo?r* or neoplas* or anaplas* or cancer* or malignan*)).ti,ab.
7. or/5-6
8. Cancer Staging/ or Cancer Grading/
9. Tumor Invasion/
10. (grading or grade or grades or staging or stageing or differentiat* or delineat* or distinguish* or correlat* or distinct* or characteri* or diagnos* or detect* or predict* or sensitivit* or specificit*).ti,ab.
11. or/8-10
12. 7 and 11
13. Magnetic Resonance Angiography/
14. Nuclear Magnetic Resonance Imaging/
15. Perfusion Weighted Imaging/
16. Susceptibility Weighted Imaging/
17. *Diagnostic Imaging/
18. (perfusion adj3 (MR or MRI or magnetic resonance or imaging)).ti,ab.
19. ("dynamic contrast enhanced" or "dynamic susceptibility" or DCE or DSC).ti,ab.
20. or/13-19
21. (4 or 12) and 20
22. (animal.hw. or nonhuman/) not human/
23. (veterinary or animal or animals or feline or canine or tierheilkunde).jw.
24. (cat or cats or dog or dogs or beagle or beagles or rat or rats or rodent or rodents or mouse or mice or murine or rabbit or rabbits or pig or pigs or bitch or bitches or feline or canine or swine or porcine or sheep or hamster or hamsters or cattle or bovine or monkey or monkeys or macaque or macaques).ti.
25. or/22-24
26. 21 not 25

Appendix 4. Web of Science Core Collection

Web of Science Core Collection (Thomson Reuters: Science Citation Index Expanded and Conference Proceedings Citation Index - Science) (1990 to 2016) (searched 09 November 2016)
#1 TOPIC: (glioma* OR astrocytoma* OR subependym* OR astrocytic OR oligodendroglioma* OR oligoastrocytoma* OR oligo-dendroglial* OR LGG OR LGGs)
Indexes=SCI-EXPANDED, CPCI-S Timespan=1990-2016
#2 TOPIC: ((supratentorial OR infratentorial OR "glial cell*" OR neuroepithelial) NEAR/3 (tumo?r* OR neoplas* OR anaplas* OR cancer* OR malignan*))
Indexes=SCI-EXPANDED, CPCI-S Timespan=1990-2016
#3 TOPIC: (grading OR grade* OR stageing OR staging OR differentiat* OR delineat* OR distinguish* OR correlat* OR distinct* OR characteri* OR diagnos* OR detect* OR predict* OR sensitivit* OR specificit*)

Indexes=SCI-EXPANDED, CPCI-S Timespan=1990-2016
#4 #3 AND #2
Indexes=SCI-EXPANDED, CPCI-S Timespan=1990-2016
#5 #4 OR #1
Indexes=SCI-EXPANDED, CPCI-S Timespan=1990-2016
#6 TOPIC: ((perfusion NEAR/3 MR) OR (perfusion NEAR/3 "magnetic resonance") OR (perfusion NEAR/3 imaging) OR "dynamic contrast enhanced" OR "dynamic susceptibility" OR DCE OR DSC OR "magnetic resonance imaging" OR "magnetic resonance angiography")
Indexes=SCI-EXPANDED, CPCI-S Timespan=1990-2016
#7 #6 and #5
Indexes=SCI-EXPANDED, CPCI-S Timespan=1990-2016

Appendix 5. The QUADAS 2 Tool for assessing methodological quality of included studies

Domain 1: PARTICIPANT SELECTION	
SQ1. Was a consecutive or random sample of patients enrolled?	**Yes**: The study states that a consecutive or random sample of patients was enrolled **No**: The study states that patient sampling was not consecutive or not random **Unclear**: This was not clear from the report.
SQ2. Was a case-control design avoided?	**Yes**: Case control design was avoided. **No**: Case-control design was not avoided. The study will be excluded **Unclear**: This was not clear from the report.
SQ3. Did the study avoid inappropriate inclusions?	**Yes**: The study avoided inappropriate inclusions, i.e. the study only included patients with suspected infiltrative gliomas that appear solid and non-enhancing on a standard contrast-enhanced MRI, which were histologically confirmed to be either low- or high-grade glioma **No**: The study included patients with suspected infiltrative gliomas regardless of their appearance on a standard contrast-enhanced MRI; i.e. tumours may be solid or necrotic, non-enhancing or enhancing; or tumours were histologically confirmed to be non-LGG or non-HGG (e.g. indeterminate grade or non-glioma) ; or the study enrolled patients based on histological results and not based on the findings on the standard MRI **Unclear**: This was not clear from the report.
SQ4. Did the study avoid inappropriate exclusions?	**Yes**: The study avoided inappropriate exclusions such as difficult-to-diagnose cases (e.g. small tumour size), presence or absence of symptoms, additional features on other MRI sequences (e.g. calcification, diffusion restriction) or other imaging modalities (e.g. hyperdensity on a computerised tomography scan) **No**: The study excluded patients inappropriately. **Unclear**: This was not clear from the report.

(*Continued*)

RISK OF BIAS Could the selection of patients have introduced bias?	**Low risk**: 'Yes' for all signalling questions. **High risk**: 'No' or 'unclear' for at least one signalling question.
CONCERNS FOR APPLICABILITY Are there concerns that the included patients and setting do not match the review question?	**Low concern**: The patient cohort is mainly comprised of subjects with the target condition **High concern**: The patient cohort is comprised of a small number or none with the target condition, i.e. patients were initially suspected to have infiltrative gliomas but later confirmed to have a different type of brain tumour
Domain 2: INDEX TEST	
SQ1. Were the index test results interpreted without knowledge of the results of the reference standard? In this review, MR perfusion must be performed before the reference standard, however it may be retrospectively analysed in studies	**Yes**: Index test results were interpreted without knowledge of the results of the reference standard **No**: Index test results were interpreted with knowledge of the results of the reference standard **Unclear**: This was not clear from the report.
SQ2. If a numerical threshold was used, was it pre-specified? (Studies must report quantitative results of rCBV or K^{trans}, or they will be excluded from the analysis).	**Yes**: If a quantitative cut off value was pre-specified. **No**: If a quantitative cut off value was not pre-specified. **Unclear**: This was not clear from the report.
RISK OF BIAS Could the conduct or interpretation of the index test have introduced bias?	**Low risk**: 'Yes' for all signalling questions. **High risk**: 'No' or 'unclear' for at least one of the three signalling questions
CONCERNS FOR APPLICABILITY Are there concerns that the index test, its conduct or its interpretation differ from the review question?	**Low concern**: MR perfusion was performed in a way that it is commonly done in clinical practice **High concern**: MR perfusion was performed in a way that differs from clinical practice (e.g. using an MRI with higher field magnet (greater than 3 Tesla)
Domain 3: REFERENCE STANDARD	
SQ1. Is the reference standard likely to correctly classify the target condition? (i.e. Is histological diagnosis made from appropriately sampled tissue?)	**Yes**: All patients underwent surgical resection which allows appropriate sampling of tumour tissue for diagnosis **No**: All patients underwent biopsy. (Biopsy for histological diagnosis is an acceptable reference standard but with high potential for sampling error.) **Unclear**: It is not stated if the patients underwent biopsy or resection for histological diagnosis
SQ2. Were the reference standard results interpreted without knowledge of the results of the index test?	**Yes**: Reference standard results were interpreted without knowledge of the results of the index test **No**: Reference standard results were interpreted with the knowledge of the results of the index test

(*Continued*)

	Unclear: This was not clear from the report.
SQ3. Was tumour grading based on histopathological assessment or WHO criteria only (i.e., direct observation on tissue sections)?	**Yes**: Tumour grading was based on histopathological assessment or WHO criteria only **No**: Results from cellular proliferation markers and genetic profiling tests were considered in assigning the tumour grade **Unclear**: This was not clear from the report.
RISK OF BIAS Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**: 'Yes' for all signalling questions. **High risk**: 'No' or 'unclear' for at least one of the signalling questions
CONCERNS FOR APPLICABILITY Are there concerns that the target condition as defined by the reference standard does not match the review question?	**Low concern**: All patients underwent resection for histological diagnosis **High concern**: All patients underwent biopsy.
Domain 4: FLOW AND TIMING	
SQ1. Was there an appropriate interval between index test and reference standard?	**Yes**: The interval between index test and reference standard was shorter than or equal to two months **No**: The interval between index test and reference standard was longer than two months **Unclear**: This was not clear from the report.
SQ2. Did all patients receive the same reference standard?	**Yes**: All patients underwent histologic examination (through biopsy or resection) irrespective of the index test results **No**: Patients underwent histologic examination based on the results of the index test **Unclear**: This was not clear from the report.
SQ3. Were all patients included in the analysis?	**Yes**: All patients meeting the selection criteria (selected patients) were included in the analysis, or data on all the selected patients were available so that a 2 x 2 table including all selected patients could be constructed **No**: Not all patients meeting the selection criteria were included in the analysis or the 2 x 2 table could not be constructed using data on all selected patients **Unclear**: This was not clear from the report.
RISK OF BIAS Could the patient flow have introduced bias?	**Low risk**: 'Yes' for all signalling questions. **High risk**: 'No' or 'unclear' for at least one signalling question.

HGG: high-grade glioma;**LGG:** low-grade glioma; **MRI:** magnetic resonance imaging

CONTRIBUTIONS OF AUTHORS

Draft the protocol	All review authors
Develop a search strategy	JM Abrigo, JSW Kwong, Anne Eisinga
Search for trials	JM Abrigo, EKC Law, Anne Eisinga
Select which trials to include	JM Abrigo, D Fountain, EKC Law, MG Hart, JM Provenzale
Extract data from trials	JM Abrigo, D Fountain
Enter data into RevMan	D Fountain, JM Abrigo
Carry out the analysis	WWS Tam
Interpret the analysis	All review authors
Draft the final review	All review authors

DECLARATIONS OF INTEREST

Jill M Abrigo - Has no competing interest to declare

Wilson Wai San Tam - None known

Dan Fountain - None known

Michael G Hart - None Known

Eric Ka Chai Law - None Known

Joey SW Kwong - None known

James M Provenzale - Reports that he holds consultancies, industry-sponsored lectures and grants but avows that they have no relationship to the research topic being studied herein.

SOURCES OF SUPPORT

Internal sources

- none, Other.

External sources

- NIHR Cochrane Incentive Scheme 2016, UK.

Award reference 16/72/23

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

No changes to the inclusion criteria were made. When the review was first conceived we intended to request a search of the Cochrane Register of Diagnostic Test Accuracy Studies, a resource developed and maintained by the Cochrane Renal Group (now Cochrane Kidney & Transplant). By the time the protocol was published and the searches approved to run, this resource had not been updated for several years and was no longer available to be searched. We added a step in the screening process due to the high volume of the database search results (32,338). A single review author performed preliminary screening of titles and abstracts to facilitate exclusion of outright irrelevant references. Potential and equivocal references were then included for screening in the next round by two independent review authors. We had originally intended to handsearch through conference proceedings of targeted radiology and neuroradiology societies, however most are now provided online through their respective websites or journals and were accessed instead. For missing years, we contacted the relevant societies for copies. For meta-analysis, we used R instead of SAS.