

Diagnostic value of non-invasive imaging techniques in the detection of carotid artery stenosis: a systematic review

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Abstract The purpose of the study was to evaluate the diagnostic performance of non-invasive imaging methods of detecting carotid artery stenosis in comparison to digital subtraction angiography (DSA) by undertaking a systematic review of the literature. The non-invasive methods reviewed include multi-slice computed tomography (MSCT) angiography, duplex ultrasound (US) and magnetic resonance (MR) angiography.

A search of medical databases (PubMed, Medline, ScienceDirect, ProQuest) of the English literature was performed and 22 studies with 68 comparisons were found to meet the selection criteria and included in our study. Five studies were performed with MSCT angiography, 11 with duplex US and 13 with MR angiography. Both duplex US and MR angiography were studied in seven out of 24 US and MR studies. The diagnostic value of each imaging modality was reviewed in terms of the sensitivity and specificity compared to DSA, which is regarded as the standard method.

The mean sensitivity and specificity for MSCT angiography, duplex US and MR angiography were 88% (95% CI; 83%–92%) and 90% (95% CI; 85%–94%), 88% (95% CI; 81%–94%) and 89% (95% CI; 85%–94%), 94% (95% CI; 90%–97%) and 89% (95% CI; 85%–92%), respectively based on overall assessment. The evaluation showed that contrast-enhanced MR angiography has high diagnostic value for detection of more than 50% stenosis of carotid artery stenosis with mean sensitivity and specificity being 95% (95% CI; 92%–98%) and 91% (95% CI; 86%–95%). When assessment was based on a combination of MR angiography and duplex US, the sensitivity reached the highest value of 98% (95% CI; 96%–100%). This analysis indicates that MR angiography, especially contrast-enhanced MR angiography could be used as a reliable alternative modality to DSA in the detection of carotid artery stenosis.

Keywords: angiography, carotid artery disease, computed tomography angiography, magnetic resonance angiography, ultrasound.

Introduction

It is estimated that 80% of all strokes that occur annually in Western countries are ischemic, and about 30% of these are caused by thromboemboli arising from atherosclerotic lesions leading to an abnormal narrowing (stenosis) at the carotid artery bifurcation.^{1,2} Therefore, a leading index for assessing stroke risk for patients with symptoms of minor ischemic stroke is the degree of stenosis of the carotid artery. Several studies³⁻⁵ have shown that carotid artery degree of stenosis is a critical parameter in the evaluation of stroke risk because the risk of ischemic stroke distal to the carotid stenosis increases with the degree of stenosis and can be markedly reduced with endarterectomy.

Numerous imaging techniques are used in the evaluation of carotid artery stenosis, such as digital subtraction angiography (DSA), multi-slice computed tomography (MSCT) angiography, magnetic resonance (MR) angiography and duplex ultrasound (US). The gold standard for detecting the degree of stenosis remains intra-arterial DSA,⁶ however it is not only an invasive investigation but is associated with complications. Thus it is important to evaluate the performance of less or non-invasive modalities which could be used as an alternative to DSA in the diagnosis of carotid artery disease.

MSCT angiography, MR angiography and duplex US have been studied in detecting carotid artery stenosis as non-invasive imaging modalities. Although each modality has advantages

and disadvantages, the reported diagnostic value for detection of carotid artery disease is quite variable. With rapid development of medical imaging techniques over the last decade, the diagnostic accuracy of these non-invasive modalities has been greatly improved. Specifically, the development of multi-slice CT technique which allows for acquisition of isotropic volume data improves spatial and temporal resolution.^{7,8} Despite these technical advances, it is still unclear whether these modalities are able to reach the diagnostic accuracy as an alternative to invasive carotid angiography. Therefore, the aim of this study was to undertake a systematic review of the literature and determine whether one or more of the above-mentioned three less-invasive techniques might advantageously replace DSA in the diagnosis of carotid artery disease.

Materials and methods

Reference searching

A search of four databases, PubMed, Medline, ScienceDirect and ProQuest for English language publications after 2000 was performed, as the aim of this study was to focus on MSCT angiography in addition to MR angiography and duplex US with regard to their diagnostic value in the detection of carotid artery disease. The following keywords were used to search for relevant references: duplex ultrasound or ultrasonography; magnetic resonance angiography, multi-slice CT angiography and carotid artery

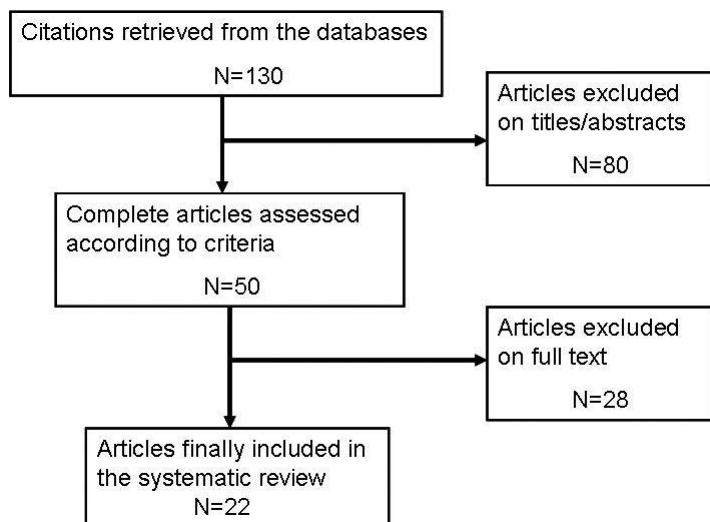


Figure 1: Strategy used in the study to search for eligible references.

disease or stenosis. The search was limited to only human subjects. Exclusion criteria included: studies performed with carotid stenting and angioplasty, case reports, in vitro or phantom studies, conference abstract, review article or a comment to the editor.

The search of literature ranges from 2000 to 2009 (last search August 2009). A statistical appraisal of the literature was performed on the applications of MSCT angiography, duplex US and MR angiography for the assessment of carotid artery stenosis. The reference lists of identified articles were checked to obtain additional articles. Studies were included if they met all of the following criteria:

- Patients undergoing either duplex US, MSCT or MR angiography and invasive carotid angiography examinations
- Studies included at least 10 patients
- The diagnostic value of each above-mentioned imaging modality or combined modalities in terms of sensitivity and specificity was compared to invasive angiography which is regarded as the gold standard technique for diagnosis of carotid artery stenosis or occlusion.

Data extraction

Data were extracted by two reviewers, based on the study design and procedure techniques. Any disagreement was resolved by a third reviewer. The reviewers looked for the following characteristics in each study: year of publication, number of patients, patient age and sex, imaging techniques or protocols used in each study, assessment criterion (> 50% or 70%), and the sensitivity and specificity compared to DSA. The reviewers also assessed the quality of each study in terms of image interpretation (blinded to the results of other modality), number of observers involved in the image interpretation or analysis, and reports of findings of all observers. When articles reported results from multiple observers, data from the observer with the highest reported accuracy was used for further analysis.

For MSCT angiography assessment of carotid artery stenosis, in addition to axial 2D images, multiplanar reformation and 3D reconstructions were generated and used in most of the studies. Thus, analysis of the results was based on a combination of these 2D and 3D visualisations rather than individual 2D or 3D evaluation. For MR angiography, both time of flight (TOF) and 3D contrast-enhanced (CE) MR angiography were analysed and compared with each other regarding the diagnostic value in carotid artery stenosis. When TOF and CE MR angiography

were combined to investigate the diagnostic value, the results were compared with that acquired individual MR angiography technique.

Statistical analysis

All of the sensitivity and specificity data was entered into SPSS V 17.0 (SPSS, Inc., Chicago, IL) for analysis. Sensitivity and specificity estimates for each imaging modality were combined across studies using one sample test. Comparison was performed by Chi-square test using n-1 degree of freedom to test if there is any significant difference regarding the diagnostic value of these modalities in the carotid artery stenosis. Statistical hypotheses (two-tailed) were tested at the 5% level of significance.

Results

General information

Figure 1 shows the searching strategy used in this study to identify the eligible articles. A total of 22 articles (with 68 different comparisons) met the selection criteria and were included for analysis,⁶⁻²⁷ resulting in a total of 2234 patients included in these studies. Male patients represented the majority of study sample size with a mean percentage of 73% (95% CI; 66%–79%), and the mean age was 66 years (95% CI; 65%–68%). There were five studies performed with MSCT angiography, 11 studies with duplex US and 13 with MR angiography, respectively. Seven out of 24 studies investigated the diagnostic value of both duplex US and MR angiography.^{6,12-15,17,18}

Table 1 presents pooled sensitivity and specificity of each imaging modality based on different assessment criteria compared to DSA. Overall, diagnostic value of each imaging modality was analysed, based on the criterion of more than 50% and 70% stenosis. TOF MR angiography and CE MR angiography as well as a combination of duplex US and MR angiography were also analysed to demonstrate whether the diagnostic accuracy was improved with use of different techniques or combined techniques.

Diagnostic accuracy of MSCT angiography

All five studies (with 20 comparisons) which met the selection criteria were performed with 4-slice CT scanners, except in one study,⁸ which involved both 4-slice and 40-slice CT scans. Three studies involved more than one comparison with one study including 10 comparisons based on different criteria of internal carotid artery and external carotid artery lumen size as well as their ratio.⁹ In that study, the highest sensitivity and specificity (92% and 96%) were found in the model that both distal internal carotid artery diameter and distal internal carotid artery ratio (ratio of distal internal carotid artery diameter to that of the contralateral distal internal carotid artery) were combined. Another study¹⁰ had five comparisons based on the criterion of calcium volume to determine the significant stenosis with thresholds of 0.03 cc and 0.06 cc resulting in the highest combination of sensitivity and specificity (94% and 76%, and 88% and 87%, respectively). The remaining study¹¹ compared MSCT angiography with rotation angiography and conventional angiography with high sensitivity and specificity achieved when conventional angiography was regarded as the reference method (90% and 95% v 82% and 88%).

Diagnostic accuracy of duplex US

There were 11 studies performed with duplex US for detection of carotid artery stenosis involving 20 comparisons. Two studies compared the diagnostic accuracy assessed by duplex US

Table 1: Pooled sensitivity and specificity of CT angiography, Duplex US and MR angiography for detection of carotid artery stenosis.

Modalities	Number of studies analysed	Pooled sensitivity	Pooled specificity
MSCT angiography (overall)	5 (20 comparisons)	88% (95% CI; 83%–92%)	90% (95%CI; 85%–94%)
MSCT angiography (> 50% stenosis)	3 (9 comparisons)	87% (95% CI; 76%–97%)	87% (95% CI; 76%–97%)
MSCT angiography (> 70% stenosis)	2 (11 comparisons)	89% (95% CI; 85%–92%)	93% (95% CI; 89%–96%)
Duplex US (overall)	11 (20 comparisons)	88% (95% CI; 81%–94%)	89% (95% CI; 85%–94%)
Duplex US (> 50% stenosis)	3 (4 comparisons)	81% (95% CI; 59%–95%)	84% (95% CI; 68%–99%)
Duplex US (> 70% stenosis)	8 (15 comparisons)	89% (95% CI; 81%–96%)	91% (95% CI; 85%–97%)
MR angiography (overall)	13 (28 comparisons)	94% (95% CI; 90%–97%)	89% (95% CI; 85%–92%)
MR angiography (> 50% stenosis)	6 (12 comparisons)	93% (95% CI; 87%–99%)	92% (95% CI; 87%–97%)
MR angiography (> 70% stenosis)	7 (16 comparisons)	94% (95% CI; 91%–96%)	87% (95% CI; 82%–91%)
MR angiography (TOF)	7 (10 comparisons)	90% (95% CI; 83%–97%)	87% (95% CI; 80%–94%)
MR angiography (CE)	8 (14 comparisons)	95% (95% CI; 92%–98%)	91% (95% CI; 86%–95%)
MR angiography +Duplex US	3 (5 comparisons)	98% (95% CI; 96%–100%)	88% (95% CI; 75%–98%)

alone and combinations of duplex US and TOF MR or duplex US and CE MR angiography,^{12,18} and their results showed that significant improvement was achieved with use of combined techniques (100% sensitivity and specificity reported in one study).¹⁸ Duplex US combined with CT angiography was also analysed in one study,²⁷ in addition to duplex US alone, but no significant improvement of diagnostic value was found in the analysis.

Diagnostic accuracy of MR angiography

Of the studies investigating the diagnostic value of MR angiography, 13 met selection criteria with 28 different comparisons. There are two types of examination techniques used in these studies, namely, TOF and CE MR angiography. All of the 13 MR angiography studies were performed on 1.5 Tesla scanners. Diagnostic value of TOF MR angiography was assessed in 10 studies with 12 comparisons, while CE MR angiography was analysed in eight studies with 14 comparisons. Assessment of a combination of TOF and CE MR angiography was performed in two studies,^{16,18} with higher diagnostic value achieved than that based on an individual assessment. A combination of MR angiography and duplex US was found in three studies,^{12,15,18} and again improved diagnostic value was achieved in combined groups.

Comparison of the diagnostic value among these imaging modalities

The table shows that moderate diagnostic value was found in both MSCT angiography and duplex US for detection of carotid artery stenosis, while high diagnostic value was reached in MR angiography, either assessment was based on >50%, or 70% or TOF or CE MR angiography. Of these assessments, CE MR angiography demonstrates the highest sensitivity and specificity for detection of significant carotid artery stenosis.

There was no significant difference of sensitivity and specificity between MSCT angiography and duplex US ($P = 0.970$ and 0.811) based on overall assessment. However, significant difference was found between MSCT angiography and MR angiography in terms of sensitivity ($P = 0.030$), but no difference in the specificity ($P = 0.612$). A nearly marginal significant difference was noticed between duplex US and MR angiography in sensitivity ($P = 0.059$), but no difference in the specificity ($P = 0.770$).

Similarly, no significant difference was found between MSCT

angiography and duplex US in the sensitivity and specificity ($P = 0.157$ and 0.752) for detection of > 50% stenosis, and > 70% stenosis ($P = 0.611$ and 0.541). A significant difference of sensitivity was reached between MSCT angiography and MR angiography for detection of > 50% stenosis ($P = 0.013$), and > 70% stenosis ($P = 0.017$), and significant difference in specificity for > 70% stenosis ($P < 0.0001$). But there was no difference in specificity for detection of > 50% stenosis ($P = 0.445$).

There was no significant difference of sensitivity and specificity between duplex US and MR angiography for detection of > 50% stenosis ($P = 0.070$ and 0.077), and > 70% stenosis ($P = 0.224$ and 0.284). No significant difference of sensitivity and specificity ($P = 0.213$ and 0.462) was found between TOF and CE MR angiography, although increased diagnostic value was noticed with CE MR angiography. Combined MR angiography and duplex US represented the highest sensitivity, which is significantly different from that acquired with TOF angiography ($P = 0.017$), but no significantly different from that with CE MR angiography ($P = 0.930$).

Observers involved in image interpretation among these studies reviewed

This analysis shows that there is more than one observer involved in the assessment of image quality in the studies reviewed. The observers were blindly to clinical symptoms and the outcome of other studies (such as the standard reference, DSA examination or other imaging modalities) when evaluating images acquired with MSCT angiography, duplex US and MR angiography. The study quality was examined using the reported criteria provided in the literature.²⁸ This indicates that most of the studies analysed in this review were performed and evaluated scientifically.

Discussion

This analysis shows that the less-invasive imaging modalities of duplex US and MSCT angiography have moderate diagnostic accuracy in the detection of carotid artery stenosis, so their value has yet to be determined before they can be recommended as a reliable modality for diagnosis of carotid artery stenosis. In contrast, MR angiography was found to demonstrate high diagnostic value compared to DSA, in terms of both sensitivity (> 90%) and speci-

ficity (> 87%). Thus, MR angiography could be used as an effective alternative to DSA for diagnosis of carotid artery stenosis.

DSA has been considered the gold standard method for evaluating carotid artery stenosis, but its accuracy is restricted to the assessment of lumen changes instead of assessment of plaque morphology.^{29,30} Moreover, it is associated with procedure-related complications such as an increased risk of thromboembolic events.³¹ Consequently, less-invasive imaging techniques such as duplex US, MSCT angiography and MR angiography have been increasingly studied for diagnosis of carotid artery disease with regard to their potential value when compared to DSA.⁶⁻⁹

Despite rapid developments of CT imaging, especially the emergence of multislice CT over the last decade, CT angiography is not as widely used in imaging and diagnosing carotid artery disease as duplex US and MR angiography. This is reflected by the small number of five studies included in this analysis. This is mainly due to the interference of blooming artefacts from severe calcified plaques at the carotid artery which result in inaccurate assessment of the degree of carotid artery stenosis. Moderate diagnostic value of MSCT angiography was shown in this review, and this indicates that MSCT angiography is not accurate enough to be used as an alternative to invasive angiography for detection of carotid stenosis.

Chen, *et al.* reported in their study⁷ that MSCT angiography had 100% accuracy in diagnosing total versus near carotid occlusions and their results correlated very well with those of DSA. The higher diagnostic value acquired in the study by Chen, *et al.* is most likely because of inclusion of patients with severe carotid artery stenosis, while in this analysis, the majority of these MSCT studies involved both 50% and 70% stenosis. Moreover, it is noticed that nearly all of the CT angiography articles analysed in this review were performed with a four-slice CT scanner, which could explain the moderate diagnostic accuracy of CT angiography resulting from this review. It is expected that improved spatial and temporal resolution with 16- and 64-slice CT could lead to increased diagnostic value of MSCT angiography in this aspect.³²⁻³⁴

Borisch, *et al.*⁶ reported that both CE MR angiography and duplex US are accurate modalities for the detection of carotid artery stenosis with the sensitivity of MR angiography and duplex US being similar (94.9% and 92.9%) when identifying a stenosis of 70% or greater. Moreover, their results showed that combined CE MR angiography and duplex US were found to increase diagnostic sensitivity to 100%, indicating the reliability of these non-invasive imaging modalities. Similarly, Back, *et al.*¹⁵ reported in their study that the diagnostic accuracy of MR angiography was comparable to duplex US for identification of > 50% and > 75% stenosis with use of North American Symptomatic Carotid Endarterectomy Trial (NASCET) angiographic criteria for measurement of proximal internal carotid artery stenosis. This analysis supports the findings reported in the literature to some extent. MR angiography is an accurate non-invasive imaging modality for detection of carotid artery stenosis as shows the highest diagnostic value compared with MSCT angiography and duplex US (Table 1). The highest sensitivity and specificity of MR angiography were found in the combined MR angiography and duplex US, with the lowest value noticed in the TOF MR angiography group.

Duplex US is considered as a good tool for establishing a final diagnosis and treatment planning for patients with carotid artery stenosis.³⁵ 2D ultrasound imaging is the first line screening tool for carotid atherosclerotic disease due to its non-invasiveness and

fewer associated complications compared with invasive carotid angiography. The analysis of this review shows that there is moderate diagnostic accuracy of duplex US for diagnosis of carotid artery stenosis. Despite promising results of duplex US achieved with some studies,^{18,19,27} the mainly limitation of ultrasound examination is that is an operator-dependent procedure. Thus, operator's experience influences the final results to a greater extent.

The studies reviewed in this report focused only on the assessment of stenosis rather than carotid plaque morphology. Recently, 3D ultrasound has been reported to be a very useful technique for monitoring the evolution of the plaque and assessing the risk of cerebral ischemia as well as the response to carotid artery atherosclerosis to medical therapies.³⁶ Thus, further studies on 3D ultrasound imaging of carotid plaque are needed to confirm the preliminary reports.

This review has some limitations that should be addressed. First, the publication bias exists and may affect the results as non-English publications were excluded. Although it is apparent that more studies are being performed on this topic (especially with the rapid developments of CT or MR techniques), it was difficult to include all of the potential studies in the analysis, especially those studies currently being undertaken or under review. Second, lack of uniform criteria of assessment is another limitation inherent in most of the studies. Not all of the studies provided complete data, such as scanning protocols, numbers of true positive, true negative cases, which prevented the authors from performing a comprehensive analysis. Last, a limitation of pooled sensitivities and specificities is that different positive criteria used in individual studies are not considered. Evaluation of internal carotid artery stenosis as a criterion to determine disease extent was used in the majority of the studies, while common carotid artery or external carotid artery were also analysed in some studies. Between-study heterogeneity is significant. However, heterogeneity is not necessarily a limitation in meta-analysis,³⁷ and it provides a key opportunity to show the consistent performance of the method.

In conclusion, this analysis shows that MR angiography, especially CE MR angiography has high diagnostic accuracy for detection of carotid artery stenosis, thus it could be recommended as a reliable alternative to invasive carotid angiography. Diagnostic value of MR angiography is maximised when combined with duplex US resulting in the highest sensitivity. In contrast, duplex US and MSCT angiography have moderate diagnostic accuracy for detecting stenosis of carotid artery, and their role in this aspect is yet to be clarified.

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