A Critical Appraisal of the Performance, Reporting, and Interpretation of Studies Comparing Carotid Plaque Imaging With Histology

J.K. Lovett, MRCP; J.N.E. Redgrave, MRCP; P.M. Rothwell, FRCP

Background and Purpose—Carotid plaque instability is an important determinant of stroke risk. There are now a number of different imaging techniques that provide information on carotid plaque morphology. However, it is unclear how they compare with one another or whether they can reliably assess plaque instability. Studies comparing imaging with pathology have shown highly variable results, even for similar imaging techniques. This may be because of variable pathology techniques rather than differences in imaging.

Methods—We performed a systematic review of studies that compared carotid imaging with histology of the excised plaque published between January 1995 and September 2004. We assessed the quality and comparability of these studies. In particular, we determined which histology methods were used and whether observer reproducibility of the histology assessment was reported.

Results—Among 73 eligible studies, histological methods were poorly reported and highly variable; 23% reported reproducibility data for imaging and only 12% reported reproducibility data for histology. Of 29 studies that reported quantitative results of blinded comparisons, there were methodological deficiencies and the results were highly variable. No study considered the extent to which the lack of reproducibility influenced the imaging-pathological correlations reported.

Conclusions—Pathological correlation in studies of carotid plaque imaging cannot be reliably interpreted or compared because of incomparable and poorly reported histology methods. We make recommendations for the performance, reporting, and interpretation of imaging–pathological correlation studies and highlight the need for consensus guidelines. (Stroke. 2005;36:1085-1091.)

Key Words: arteriosclerosis ■ carotid artery plaque ■ cerebral angiography ■ pathology

Carotid artery atherosclerosis is the underlying cause of 10% to 20% of strokes.1 Degree of stenosis at the carotid bifurcation is the most widely used radiological predictor of stroke risk on medical treatment and of likely benefit from carotid endarterectomy.2,3 However, pathological studies have shown that plaque instability, rather than the extent of disease, is the main cause of acute thromboembolic events.4,5 Acute myocardial infarction is associated with a large lipid core, a thin ruptured cap, and adherent thrombus,4,5 and similar features have been found in pathological studies of carotid arteries from patients with recent stroke.6,7 Furthermore, 2 large prospective studies have shown that angiographic carotid plaque ulceration is a strong independent predictor of ipsilateral ischemic stroke on follow-up, and of increased benefit from endarterectomy.8,9 However, ultrasound, magnetic resonance imaging, and computed tomography are now widely used to assess carotid artery disease. Although these techniques have the advantage of being less invasive than intra-arterial angiography, it is important that they are validated against angiography and pathological specimens.

There have been a large number of published studies on the imaging–pathological correlation of unstable carotid plaque. The majority has imaged the carotid arteries of patients awaiting endarterectomy and used the histological assessment of the excised plaque as the “gold standard” for comparison. However, the results have been highly variable, even when similar methods of imaging have been used, for example the Gray–Weale scale of ultrasound echogenicity.10–13 One explanation is that variability arises not from the imaging methods, but from the pathological assessments. Histopathological assessments, such as staging of cervical, prostatic, ovarian, and lung neoplasia, commonly show considerable variability, even between experienced pathologists.14–18 In a study of the reproducibility of a histological assessment of 60 carotid plaques, we found significant intra-observer and inter-observer variability even with simple and well-defined assessments, eg, for presence of rupture, the $\kappa$ values for
intra-observer and inter-observer variability were 0.68 and 0.43, respectively. Moreover, we demonstrated that there is considerable variation between sections taken from different positions in the same plaque. It is important, therefore, that imaging versus pathology agreement within studies and variability in results between studies of the same imaging modality are interpreted in the light of the reproducibility of the histological assessments and any imprecision introduced by the pathology methods, as well as the properties of the imaging technique.

Therefore, we reviewed the literature on studies that compared carotid imaging with histology. In particular, we aimed to determine which histology methods were used and whether the histology methods were described in sufficient detail to make valid comparisons between studies. We also assessed whether observer reproducibility of the imaging and histology assessments was reported, and we used our own data to demonstrate the influence of observer variability on an imaging–pathological comparison.

Materials and Methods
We searched for studies that compared imaging of carotid plaque morphology with histology of plaque excised at endarterectomy or postmortem, published between January 1995 and September 2004. Our search strategy was as follows: (1) we searched Medline using combinations of the search terms “carotid,” “atheroma,” “atherosclerosis,” “plaque,” “histolog*,” “patholog*,” “angiogram*,” “ultrason*,” “Doppler,” “duplex,” “radio*,” and “imaging”; (2) searches were restricted to articles in English using human subjects; (3) we hand-searched the contents pages of the 4 journals from which articles were most frequently found in the electronic search; and (4) we examined reference lists from all articles. For each study we recorded the number of carotid arteries imaged and the modality and method of radiological assessment. We noted the method of pathological specimen preparation frequency, number and plane of sectioning and staining, the method of histological data collection recorded features and system of grading for each feature, and the method of comparison including whether there was blinding. We also noted whether the authors assessed reproducibility of the imaging and histology assessment or whether there was any reference to previously used histological classifications.

Results
We found 73 eligible studies. Articles were most frequently found in the journals Stroke (n=11), Circulation (n=10), European Journal of Vascular and Endovascular Surgery (n=6), and Journal of Vascular Surgery (n=4). All studies used histology of excised carotid plaque, from endarterectomy in 65 studies, from cadavers in 7 studies, and from both sources in 1 study, as the “gold standard.” Nineteen (26%) studies used carotid plaques from patients with a history of ipsilateral ischemic symptoms, 26 (36%) used plaques from both symptomatic and asymptomatic patients, but in 28 (38%) studies the symptomatic status of the patients was not reported. The number of carotid plaques in the studies ranged from 2 to 270 (median, 24; interquartile range, 15 to 52).

Imaging
Thirty-nine studies used carotid ultrasound as the imaging modality, 4 used intra-arterial angiography, and 30 used magnetic resonance imaging. Three studies used other forms of imaging and some studied more than one imaging modality. Only 17 (23%) studies reported observer reproducibility of the imaging technique. Forty-eight (66%) studies imaged the plaques in vivo before endarterectomy but 23 (48%) of these studies did not report the time interval between imaging and surgery.

Histological Methods
There was great variation in the preparation of the plaque for histological assessment. Forty-eight (66%) studies used transverse sections. Three (4%) used longitudinal sections, and 1 used transverse and longitudinal sections, and did not indicate the sectioning plane. The number of sections taken ranged from 2 to 21 per plaque (median 4), but was not stated in 52 (71%) studies. The frequency of sectioning ranged from 0.2 mm to 5 mm (median, 3 mm), but was not stated in 27 (37%) studies. At least 10 different stains were used overall, but the majority of studies used hematoxylin and eosin (61 of 66 studies when stated [92%]). Four studies provided no information on the sectioning, number or staining of histology slides.

Forty-three studies did not state whether the plaques were decalcified before histological analysis, of which 30 studies subsequently drew conclusions about the ability of imaging to detect calcification seen on histology. The histological features that were compared with imaging findings included size of lipid core relative to fibrous tissue (56 studies, 77%), calcification (48 studies, 66%), intraplaque hemorrhage (41 studies, 56%), surface-thrombus (27 studies, 37%), rupture (15 studies, 21%), inflammatory cells (9 studies, 12%), cap thickness (7 studies, 10%), and neovascularization (3 studies, 4%). These features were generally assessed qualitatively, although 20 studies used computer image analysis, or a similar technique, to estimate percentage area or volume of plaque constituents.

Seven studies (10%) graded the plaques according to the American Heart Association classification of atheromatous plaque developed by Stary. However, 47 studies (64%) did not reference previously used techniques for any part of the histological methods and 9 (12%) studies only reported 1 histological feature.

Nine studies (12%) graded the plaques using the reproducibility of histological assessments, of which 3 studies were by the same author. Six of the 9 studies assessed area of histological features as continuous vari-

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1. References 2, 22, 23, 25, 27, 32–36, 38–42, 46, 47, 49, 56, 74, 75, 80–88
2. References 21, 31, 37, 48, 52, 53, 55, 56, 59, 60, 63–65, 68–70, 72, 74, 75, 78–80, 82
5. References 11, 12, 21–24, 26, 28, 31, 34, 36, 43–45, 48, 53, 54, 56, 58, 60, 65, 69, 72, 74, 75, 77, 79
6. **References** 13, 21–23, 27, 30, 31, 38, 43, 45, 46, 51, 52, 54–57, 60, 63–65, 67, 70–72, 74, 75, 86, 87, 89
7. **References** 13, 20, 24, 28, 30, 41, 45, 46, 49, 51, 52, 55, 57, 59, 63, 64, 67, 71, 73, 82
TABLE 1. Summary of the 29 Studies Found in Literature Review That Reported Quantitative Results for Blinded Comparisons Between Imaging and Histology

<table>
<thead>
<tr>
<th>Reference</th>
<th>Plaques, No.</th>
<th>Histology Assessment</th>
<th>Imaging Assessment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnold 1998</td>
<td>60</td>
<td>Lipid/fibrous</td>
<td>US echogenicity: 2 or 4 grades</td>
<td>$\kappa = 0.12, 4 \times 4$</td>
</tr>
<tr>
<td>Schulte 2000</td>
<td>46</td>
<td>Lipid/fibrous, hemorrhage, calcification, thrombus</td>
<td>US echogenicity: 6 grades</td>
<td>Range of sensitivities and specificities for each grade: 35%–97%</td>
</tr>
<tr>
<td>Arnold 2001</td>
<td>50</td>
<td>Lipid/fibrous, hemorrhage, calcification</td>
<td>US echogenicity: 2 grades</td>
<td>$\kappa = 0.49$</td>
</tr>
<tr>
<td>Gronholdt 2001</td>
<td>38</td>
<td>Lipid/fibrous, hemorrhage, calcification, thrombus</td>
<td>US echogenicity: continuous scale; CT: Hounsfield units</td>
<td>CT correlated with calcium, no significant correlations between US and histology</td>
</tr>
<tr>
<td>Drost 1997</td>
<td>29</td>
<td>Lipid/fibrous, hemorrhage, thrombus</td>
<td>US echogenicity: 2 or 4 grades</td>
<td>No significant relationships</td>
</tr>
<tr>
<td>Lamminie 2000</td>
<td>22</td>
<td>Lipid/fibrous, hemorrhage, cap thickness, rupture, thrombus</td>
<td>US echogenicity: 4 grades</td>
<td>$\kappa = 0.53$ for cap thickness, other comparisons $\kappa = 0.1–0.28$</td>
</tr>
<tr>
<td>Kardoulas 1996</td>
<td>36</td>
<td>Lipid/fibrous, hemorrhage, calcification, rupture</td>
<td>US echogenicity: 4 grades</td>
<td>Significant association only with fibrous tissue, $P=0.04.$</td>
</tr>
<tr>
<td>Gaunt 1996</td>
<td>50</td>
<td>Lipid/fibrous, rupture, thrombus</td>
<td>US echogenicity: 4 grade scale and surface morphology</td>
<td>66% agreement with ulceration and thrombus</td>
</tr>
<tr>
<td>Sitter 1996</td>
<td>37</td>
<td>Rupture</td>
<td>US: Surface morphology</td>
<td>Sensitivity 33%, specificity 76%</td>
</tr>
<tr>
<td>Denzel 2003</td>
<td>97</td>
<td>Lipid/fibrous, calcification</td>
<td>US echogenicity 3 grades</td>
<td>Overall agreement 46.7%, $\kappa = 0.168, P=0.013$</td>
</tr>
<tr>
<td>Denzel 2004</td>
<td>10</td>
<td>Hemorrhage, lipid/fibrous, calcification</td>
<td>US echogenicity and calcium score on CT/XR</td>
<td>$\mathrm{GSM} = 0.088, P=0.22$; CT calcium $P&lt;0.001$; $\mathrm{XR} , \text{calcium} = 0.457, P&lt;0.001$</td>
</tr>
<tr>
<td>Tegos 2000</td>
<td>71</td>
<td>Hemorrhage, lipid/fibrous, thrombus</td>
<td>US echogenicity 2 grades</td>
<td>No correlation with lipid core size $P=0.37$, $r=0.1$ or calcification $P=0.65$; low GSM associated with hemorrhage, $P=0.04$</td>
</tr>
<tr>
<td>Rakebrandt 2000</td>
<td>10</td>
<td>Hemorrhage, lipid, elastin, fibrin, calcification</td>
<td>US trained texture classifier: 5 classes</td>
<td>US overestimated calcium content by 45% and lipid by 25%; hemorrhage underestimated by 63%</td>
</tr>
<tr>
<td>Hatsukami 2000</td>
<td>3</td>
<td>Hemorrhage, rupture, thrombus, cap thickness</td>
<td>MRI: cap thickness and rupture</td>
<td>Rupture $=0.85$, thick vs thin cap $=0.83$</td>
</tr>
<tr>
<td>Yuan 2001</td>
<td>18</td>
<td>Lipid/fibrous, hemorrhage, AHA grade</td>
<td>MRI features</td>
<td>Sensitivity 85%, specificity 92%, $\kappa = 0.69$</td>
</tr>
<tr>
<td>Cai 2002</td>
<td>52</td>
<td>AHA grade</td>
<td>MRI: AHA grade equivalents</td>
<td>Agreement 80%</td>
</tr>
<tr>
<td>Serfaty 2001</td>
<td>18</td>
<td>Lipid/fibrous, calcification, AHA grade</td>
<td>MRI: AHA grade equivalents</td>
<td>MRI identified fibrocalcific plaques but otherwise poor results</td>
</tr>
<tr>
<td>Shinmar 1999</td>
<td>22</td>
<td>Lipid/fibrous, thrombus, calcification, AHA grade</td>
<td>MRI features</td>
<td>Sensitivities 84–100%, specificities 95–100%</td>
</tr>
<tr>
<td>Clarke 2003</td>
<td>8</td>
<td>Lipid/fibrous, calcification, loose connective tissue</td>
<td>MRI features</td>
<td>Sensitivity 60–976%, specificity 75–99.9% for detecting plaque constituents</td>
</tr>
<tr>
<td>Mitsumori 2003</td>
<td>18</td>
<td>Unstable cap, rupture, cap thickness</td>
<td>MRI signal intensity</td>
<td>Sensitivity 0.81, specificity 0.90</td>
</tr>
<tr>
<td>Kerwin 2003</td>
<td>16</td>
<td>2 Microvessels—fraction of plaque area</td>
<td>MRI dynamic contrast enhancer fractional blood volume</td>
<td>Correlation coefficient $r=0.80$, $P=0.001$</td>
</tr>
<tr>
<td>Trivedi 2004</td>
<td>23</td>
<td>Hemorrhage, lipid/fibrous, calcification</td>
<td>MRI signal intensity and area of plaque constituents</td>
<td>Mean differences: 2 SD lipid core content $=0.86$, $P=1.76%$; Fibrous cap content $=0.75$, $P=2.86%$</td>
</tr>
<tr>
<td>Chu 2004</td>
<td>24</td>
<td>Hemorrhage age—fresh, recent, old</td>
<td>MRI signal intensity; hemorrhage age: 3 grades</td>
<td>Sensitivity 90%, specificity 74% for hemorrhage detection, $K=0.44$ and 0.86 (2 observers for hemorrhage age)</td>
</tr>
<tr>
<td>Moody 2003</td>
<td>63</td>
<td>AHA grade 6</td>
<td>MRI signal intensity on direct thrombus imaging</td>
<td>Sensitivity 84%, specificity 84%, negative predictive value 70% positive predictive value 93%</td>
</tr>
<tr>
<td>Tearney 2003</td>
<td>26</td>
<td>Macrophages, smooth muscle cells, cap thickness</td>
<td>OCT signal intensity</td>
<td>Macro-CT: $r=0.84$, $P&lt;0.0001$; smooth muscle density $r=0.56$, $P&lt;0.005$</td>
</tr>
<tr>
<td>Yabushita 2002</td>
<td>105</td>
<td>Lipid/fibrous, calcification</td>
<td>OCT</td>
<td>$K = 0.83-0.84$</td>
</tr>
<tr>
<td>Oliver 1999</td>
<td>9</td>
<td>Lipid/fibrous, hemorrhage, rupture, calcification, cap thickness</td>
<td>CT: calcification, surface morphology</td>
<td>Agreements of 52%–91%</td>
</tr>
<tr>
<td>Walker 2002</td>
<td>55</td>
<td>Lipid/fibrous, hemorrhage, rupture</td>
<td>CT: surface morphology</td>
<td>Sensitivity 60%, specificity 74%</td>
</tr>
<tr>
<td>Manca 2001</td>
<td>22</td>
<td>Lipid/fibrous, hemorrhage, rupture thrombus, calcification</td>
<td>Platelet scintigraphy: thrombus and lipid</td>
<td>Detected 6/9 thrombi, but no association with lipid pools</td>
</tr>
</tbody>
</table>

CT indicates computed tomography; GSM, grayscale median; OCT, optical coherence tomography; US, ultrasound; XR, X-ray.
rable and poorly reported methods. One small study assessed the effect of storage temperature and plaque decalcification on the results of imaging–pathologic comparisons, but no study considered the effect of poor reproducibility of histological assessments.

**Discussion**

This review found 73 studies, the majority from journals with a high “impact factor,” that compared carotid plaque imaging with carotid plaque histology. However, the results were highly variable, even between studies that used the same imaging criteria, such as the Gray–Weale scale of ultrasound echogenicity, which has been shown to be reproducible. Direct comparisons between studies were not possible because of incomparable methods, which were often not shown to be reproducible.

We have recently published data on angiographic plaque surface morphology and histological appearance of plaque instability from 128 carotid arteries and demonstrated the influence of intra-observer reproducibility on the results of an imaging–pathologic comparison. The methods have been described in detail previously but briefly, the intra-observer and inter-observer reproducibility for angiographic appearance of irregular or ulcerated plaque versus smooth plaque was assessed on 50 and 1000 angiograms, respectively. Two independent pathologists calculated intra- and inter-observer reproducibility for a well-defined simple histology assessment of plaque instability. Blinded comparisons were made between histology and angiographic plaque surface morphology.

The agreement between presence of irregularity or ulceration on angiogram with unstable plaque on histology was significant ($P=0.01$), but the calculated $\kappa$ was only 0.22 (95% CI, 0.05 to 0.39). The intra-observer reproducibility $\kappa$ values for angiographic assessments were 0.56 (95% CI, 0.2 to 0.9), 0.60 (95% CI, 0.2 to 0.9), and 0.67 (95% CI, 0.3 to 1.0) for 3 observers, and the inter-observer $\kappa$ value was 0.56 (95% CI, 0.53 to 0.59). For histological assessments, the intra-observer $\kappa$ values ranged from 0.35 (95% CI, 0 to 0.7) for presence of rupture to 0.89 (95% CI, 0.8 to 1) for presence of thrombus. The intra-reproducibility and inter-reproducibility $\kappa$ values for the composite histological assessment of “unstable” plaque were 0.69 (95% CI, 0.5 to 0.9) and 0.40 (95% CI, 0.2 to 0.6), respectively.

The calculation of an actual expected maximum $\kappa$ value for angiography–histology comparisons based on observer reproducibility data are highly complex, but can be no greater than the reproducibility of each individual assessment. Therefore, we recommend that studies of this type report intra-observer and inter-observer reproducibility for the histological assessments as well as those for the imaging technique, and the results of the imaging–pathological comparison should be interpreted in the light of these results.

It has consistently been shown in population-based studies that the risk of recurrent stroke after initial ischemic symptoms declines with time. Moreover, the early risk is highest in patients with large artery atherosclerosis compared with the other etiological subtypes. One explanation for this is that unstable plaques heal with time. We have shown previously that plaques from patients with ischemic symptoms within 30 days of endarterectomy are more unstable on histology than from those with less recent symptoms. Thus, in studies comparing in vivo appearances of carotid plaque with histology of the excised specimens, it is essential to state whether the plaques have been symptomatic. Furthermore, the time interval between imaging and histology should ideally be minimized and kept consistent within studies. Twenty-eight (39%) of the studies in this review did not comment on the symptomatic status of their patients; thus, the application of their findings to clinical practice is severely limited.

Several studies in this review reported only 1 or 2 histological features despite the existence of validated grading scales for the severity of atherosclerosis. Although in some cases this may have been deliberate, reflecting the limitations of the imaging modality concerned to detect certain characteristics, it raises the possibility of selective reporting of histological features. Therefore, we recommend that unless the reasons for reporting selective characteristics are clearly justified, the following well-recognized features of unstable plaque should be routinely reported as a minimum: intraplaque hemorrhage, lipid-to-fibrous tissue ratio, and minimum cap thickness; this is to avoid the potential for selective publication.

**TABLE 2. Recommendations for the Performance and Reporting of Studies of Carotid Plaque Imaging vs Histology**

| Sample size calculations should be performed and should take into account the reproducibility of the assessments studied. |
| $\kappa$ values for the intra-observer and inter-observer reproducibility of imaging and histological assessments should be quoted and the results interpreted in the light of these |
| The numbers of symptomatic and asymptomatic plaques should be reported as well as the time since last symptoms |
| The time interval between in vivo plaque imaging and plaque excision should be reported and kept to a minimum; this is particularly important in the study of recently symptomatic plaques |
| Sufficient detail of the plaque processing methods, particularly whether plaques were decalcified before sectioning should be given |
| Histological assessments should be made blind to imaging and clinical characteristics—when necessary using a second observer to colocalize imaging slices with histology |
| There should be detailed reporting of histological methods including position, plane, number, and frequency of sections; as a minimum, we recommend that sections are taken from the bifurcation or point of maximal stenosis, and from 3 mm either side |
| When there is no clear reason to report a specific histological feature, the following features of unstable plaque should be described: hemorrhage, rupture, thrombus, lipid core-to-fibrous tissue ratio, and minimum cap thickness |

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form the histological assessments and the colocalization, each blind to imaging, and to the results of the other observer.

The position, plane, number, and frequency of histology sections taken from each carotid plaque were infrequently reported in this review. We have previously shown that there is considerable variability in histological features between transverse sections taken at 3-mm intervals along the length of a plaque, but that 3 sections taken from the bifurcation point and from 3 mm proximal and 3 mm distal to this point are sufficient to detect almost all features found on a larger number of sections from the same plaque. We therefore recommend that this method be adopted as a minimum, so that important features seen on imaging are not missed by the histology assessment.

The median number of plaques studied in this review was 24 (interquartile range, 15 to 52). In a hypothetical study of this size, with a 33% prevalence of the investigated characteristic and 75% imaging–pathological agreement, the 95% CI of the $k$ statistic would be 0.1 to 0.8 (ranging from poor to very good agreement). Therefore, large sample sizes are required if the degree of imaging–pathological associations are to be demonstrated reliably and differences between imaging techniques are to be detected.

There are several stages in the preparation of carotid plaques for histological analysis. The process of plaque decalcification is frequently performed to remove large calcified nodules before sectioning. We found that few studies reported data on plaque decalcification or other processing methods, even when this could have influenced subsequent imaging–pathological correlations.

Given the shortcomings of published studies and the consequent difficulty in the reliable comparison and interpretation of the results, consensus guidelines on the performance of imaging–pathological correlations.

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