Imaging of the ulcerated carotid atherosclerotic plaque: a review of the literature

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Abstract

Carotid atherosclerotic disease constitutes a major modern health problem whose diagnosis primarily relies on imaging. Grading of stenosis has been long used as the main factor for risk stratification and guiding of management. Nevertheless, increasing evidence has shown that additional plaque characteristics such as plaque composition and surface morphology play an important role in the occurrence of symptoms, justifying the term “vulnerable plaque”. Carotid plaque surface characteristics either in the form of surface irregularities or ulceration represent an important factor of vulnerability and are associated with the occurrence of neurologic symptoms. The delineation of the carotid plaque surface can be performed with virtually all imaging modalities including ultrasound, contrast-enhanced ultrasound, multi-detector computed tomography angiography, magnetic resonance angiography and the traditional reference method of angiography. These techniques have shown varying levels of diagnostic accuracy for the identification of ulcerated carotid plaques or plaque surface irregularities. As a consequence and given its high clinical significance, radiologists should be familiar with the various aspects of this entity, including its definition, classification, imaging findings on different imaging modalities and associations. The purpose of this review is to present the current literature regarding carotid plaque ulcerations and present illustrative images of ulcerated carotid plaques.

Teaching Points

- Plaque surface and ulceration represent risk factors for stroke in carotid disease.
- Characterisation of the plaque surface and ulcerations can be performed with every modality.
- US is the first-line modality for carotid disease and identification of ulcerations.
- The administration of microbubbles increases US accuracy for diagnosis of carotid ulceration.
- MDCTA and MRA are valuable for diagnosing ulceration and evaluating plaque composition.

Keywords Carotid atherosclerosis · Carotid ulcer · Ultrasound imaging · CT angiography · MRI angiography

Introduction

Carotid atherosclerotic disease represents a well-established cause of ischaemic stroke, accounting for up to 20% of strokes or transient ischaemic attacks (TIA) [1]. Stroke constitutes a major cause of acquired disability in adults and the second most frequent cause of mortality in developed nations [2]. The degree of luminal stenosis has long been serving as the primary criterion for risk stratification of patients and treatment decision-making, being a well-known risk factor for the development of neurologic symptoms in patients with carotid disease [3]. Nevertheless, current research has concluded that plaque features other than degree of stenosis contribute to the occurrence of neurologic symptoms, justifying the introduction of the term “vulnerable plaque” [4], responsible for almost half of stroke cases [5]. From a pathogenic point of view, this is explained by the mechanism of arterio-arterial embolism describing the creation and detachment of embolic...
material from a plaque and its subsequent transportation to the intracranial circulation, causing vascular occlusion and occurrence of symptoms [4].

The plaque surface morphology is among those features related to the risk for embolic stroke and characterising vulnerability. Based on this criterion, carotid plaques are typically classified into smooth, irregular or ulcerated [6, 7]. The presence of ulceration itself is a well-known feature of vulnerability with high clinical significance as entailing increased risk for neurologic symptoms. As a consequence its accurate diagnosis is essential and primarily relies on imaging. Ultrasound (US) undoubtedly represents the first-line modality for both screening and initial diagnostic evaluation of carotid disease [8]. Beyond grading of stenosis with widely accepted velocity criteria [9], US is valuable in evaluating the plaque’s echogenicity and surface characteristics [10]. Digital subtractive angiography (DSA) has been deemed to be the gold standard for the evaluation of carotid disease but is interventional and has an associated risk for stroke [11]. On the other hand, the emergence and widespread availability of non-invasive cross-sectional imaging modalities such as multidetector computed tomography angiography (MDCTA) or magnetic resonance angiography (MRA) offered a valuable alternative to DSA, providing excellent spatial resolution and great accuracy for evaluation of plaque fine surface characteristics [12]. Nevertheless, the role of US has been significantly boosted by the introduction of US contrast media and recent evidence concludes that contrast-enhanced ultrasound (CEUS) contributes significantly to the characterisation of carotid plaques, in terms of both surface delineation (ulcer detection and characterisation) and internal structure (visualisation of intraplaque neovascularisation) [13, 14].

The purpose of this review is to deliver an overview of the literature regarding carotid plaque ulceration. Subjects that will be discussed include the ulcer’s definition and classification, clinical significance and imaging. Imaging findings of ulcerated carotid plaques will be illustrated with diagrammatic representations and educational images, correlating US, CEUS, MDCTA and MRA.

**Definitions**

The definition of carotid plaque ulceration varies depending on the modality used or even among different research groups [10, 15]. In terms of histology, the term “ulceration” describes an endothelial defect of at least 1000 μm in width, resulting in the exposure of the plaque’s necrotic core to circulation [7, 16]. From the point of view of imaging, different criteria have been used to define ulceration [10, 15]. In general, a plaque’s surface can be characterised as smooth, irregular or ulcerated [4], with smooth referring to a plaque with regular luminal morphology (Fig. 1). The term irregular can be used for

![Fig. 1](image_url)

**Fig. 1** Diagrammatic representations and MDCTA images illustrating the classification of carotid plaques based on their surface morphology as smooth (a), irregular (b) and ulcerated (c)

**Table 1** Classification of carotid ulcerations based on their morphology

| Type 1 Ulcer projecting perpendicular to the vessel’s lumen with parallel sides (1a) or sides converging to a point (1b) |
|---------------------------------------------------------------|
| Type 2 Narrow-necked ulcer (“mushroom shaped”) or an ulcer with no neck visible |
| Type 3 Ulcer with a proximal neck and its main part pointing distally, parallel to blood flow direction |
| Type 4 Ulcer with distal neck and its main part pointing proximally, opposite to blood flow direction |
plaques whose surface fluctuates from 0.3 mm to 0.9 mm [4], whereas the term ulceration is reserved for cavities measuring at least 1 mm [7, 13] or 2 mm according to different studies and proposed risk stratification systems [17, 18]. Each ulcer is characterised by a neck and a base, both of varying sizes and resulting in various shapes. De Bray et al. introduced the most widely used US criteria, stipulating that ulcerations should (1) be at least 2 mm long and deep, (2) have a well-demarcated posterior wall at its base on B-mode and (3) show internal flow reversal on colour Doppler technique [15]. According to the newer criteria, ulcerations can be diagnosed when there is evidence of a cavity on the plaque surface, irrespective of size, whose surface echogenicity is lower compared to the adjacent intimal plaque’s border on B-mode [10]. On MDCTA, an ulceration can be diagnosed when contrast medium is identified extending beyond the vascular lumen (and within the plaque limits) for at least 1 mm in at least two planes [13]. On CEUS, which is virtually an angiographic technique, the ulcer definition requires the interruption of the plaque-lumen border for at least 1 × 1 mm [13]. When it comes to 3D US, the volume criterion of a cavity measuring at least 1 mm³ has been used [19].

**Frequency/location of ulceration**

Carotid MDCTA studies have shown that 55–62% of plaques are smooth, 15–22% irregular and 16–44% ulcerated [13, 20, 21]. The frequency of carotid ulcerations depends on the presence of symptoms and the modality used. Histological ulcerations have been reported to occur in up to 89% of cases [22]. In a study enrolling more than 3000 patients examined with DSA, the frequency of ulceration was 14% [23]. In MDCTA studies, ulceration was discovered in 10–31% of carotid plaques [7, 21, 24]. There is a documented difference of ulcer frequency between asymptomatic and symptomatic plaques with the former being ulcerated in 14% of cases and the latter...
Clinical significance of ulceration

The association of carotid ulceration and TIA was initially described in a small published group of patients in 1968 where surgical removal of the ulcerated plaque relieved ipsilateral symptoms [27, 28]. It thus became evident that a superficial ulceration may act as a risk factor for neurologic symptoms, on the pathogenic basis of arterio-arterial embolism of thrombotic material [2, 25, 27, 29]. This mechanism was highlighted by a study showing that ulcerated carotid plaques are more common in patients with TIA and that in up to 12.6% of embolic TIAs the emboli originate from such plaques [30]. The arterio-arterial embolism theory was also illustrated in the experimental setting, involving recordings of dye flow inside replicas of ulcerated carotid plaques. The dye could be seen moving in a swirling pattern within the ulcer cavity, explaining how platelet aggregates could be formed and pulled back to circulation and thus the intracranial circulation [31]. This swirling flow pattern observed within the ulcer cavity [31] explains the vortex of colours or “yin-yang” image occasionally observed within ulcers with the colour Doppler technique [32]. This pattern was also observed with CEUS where microbubbles were seen swirling inside the ulcer cavity [33]. This haemodynamic phenomenon in combination with the more frequently observed thrombosis on ulcerated plaques [25] favours the arterio-arterial embolism.

The clinical significance of ulcerated carotid plaques has been documented through numerous studies. For instance, ulceration has been correlated with embolic signals on transcranial Doppler US, regardless of its depth [34, 35], while being recognised as a risk factor for stroke [36, 37]. Namely, the risk for stroke in a patient with ulcerated carotid plaque tends to increase with the degree of stenosis, while it is 1.24 to 3.43 times greater compared to non-ulcerated plaques [37]. However, other studies have correlated ulceration with symptoms even in plaques causing low-grade stenosis (≤50%) [38]. Ulceration is more frequently found in symptomatic carotid plaques [39] and is also associated with the occurrence of new symptoms in asymptomatic patients [40]. Indeed, multiparametric analysis has confirmed the correlation of ipsilateral TIA or stroke with the presence of carotid ulceration in asymptomatic prospectively observed patients [41]. Histologically detected ulceration was found up to 2.32 times

in 36% [25]. Other studies have detected ulcers in 48% of symptomatic plaques and 31% of asymptomatic [26].

Studies have shown that ulcerations are more likely to affect the part of a plaque lying proximally to the point of maximum stenosis (up to 70% of cases) rather than distally. This observation is explained by the higher shear stress applied to the part of the plaque proximal to the point of maximum stenosis [7, 20, 23]. The ulcer frequency is also associated with the degree of stenosis. Namely, ulcer incidence was 16.6% for plaques causing 50–69% stenosis, 22.6% for 70–84% stenosis and 33.4% for stenosis >85% [7]. Other studies have identified a significant percentage of ulcerations in plaques causing <50% stenosis [24].

Table 2  Classification of carotid ulcerations based on their location on the plaque surface

| Classification of carotid ulcerations based on their location on the plaque surface |
|---------------------------------------------------------------|
| Proximal to the point of maximum stenosis                      |
| Distal to the point of maximum stenosis                        |
| Situated at the point of maximum stenosis                      |

Fig. 4 MDCTA images showing carotid plaques with ulcers of type 1a (a), 1b (b), 2 (c), 3 (d) and 4 (e) (arrowheads showing ulcers)
more frequently in symptomatic patients [42]. US studies have shown that ulcerated plaques are related to a seven-fold increase in ipsilateral stroke risk [43] while hypoechoic ulcerated plaques are associated with a nine-fold increase [44]. A higher risk for stroke in patients with ulcerated plaque compared to those without ulceration was also reported in the NASCET study [45]. It was recently concluded that ulceration increases the risk for neurologic symptoms by approximately four times [17]. Similarly to US, MDCTA-detected ulceration is also correlated with symptoms [7].

Even simple irregularity of the plaque surface, without a clear ulceration, has been correlated with an increased risk for stroke [36]. Such plaques have been associated with embolic vascular territory infarcts on brain CT, while smooth plaques were correlated either with normal scans or lacunar infarcts [29]. The plaque surface morphology, specifically the plaque irregularity as assessed with MDCTA, has been identified as an important risk factor for symptoms in patients with 30–69% stenosis [46]. Irregular carotid plaques as evaluated on high-resolution B-mode US have been correlated with higher risk for stroke compared with smooth plaques [47]. Nevertheless, a recent meta-analysis could not confirm these findings showing that US-detected plaque irregularity was not correlated with symptoms [17]. Finally, it was found that irregular stenosis is associated with increased risk for stroke in the long term after an index symptom [48].

**Classification of ulceration**

In an early study carotid plaque ulcers were classified as presented in Table 1 [49] (Figs. 2, 3 and 4).
Alternatively, carotid ulcerations can be classified based on their location on the plaque surface and in relation to the point of maximum stenosis into three types, as presented in Table 2 [23].

Nevertheless, with the introduction of modern sensitive flow visualisation techniques, new types of ulcers can be identified including V-shaped ulcers or ulcers resembling a bucket handle. Moreover, multiple ulcers can be found within the same plaque (Fig. 5).

**Composition of ulcerated carotid plaques**

It is well known that ulcerations are not found in all carotid plaques with the same frequency but rather tend to occur in particular plaque types and are associated with specific histological findings. Namely, it was found that plaques with either ulcerations or simply irregular surfaces, based on DSA, were associated with rupture of the plaque’s fibrous cap, intraplaque haemorrhage, a large lipid core and less fibrous tissue [49]. These initial DSA findings warranted further research of ulcerated plaque’s composition with modern cross-sectional modalities [49]. Based on publications related to US and MDCTA, ulcerations were found to more often affect fatty plaques, less often fibrous and rarely calcified plaques [7]. From a pathogenic point of view, it is expected that ulceration is associated with intraplaque haemorrhage [50]. More precisely, MDCTA-detected ulceration is considered a risk factor for intraplaque haemorrhage [51]. In keeping with these findings, ulceration diagnosed on MDCTA is considered highly sensitive and specific for the presence of intraplaque haemorrhage as identified on MRI [52]. It was also observed that ulcerated plaques tend to be larger in volume and richer in lipid content [24, 53]. On the contrary, ulceration was found to be inversely associated with calcification [24]. Other studies could not confirm the association between ulceration and plaque volume, highlighting the fact that even smaller plaques may be ulcerated [53]. The association between ulceration and fatty hypoechoic plaques has also been reported with US [54]. Finally, it was observed that the plaque’s enhancement on MDCTA is strongly related with the presence of ulceration and neovascularisation [55, 56]. Indeed, studies with CEUS have demonstrated neovessels in close proximity to ulcerations [57] and that ulcerated plaques tend to have significantly more intraplaque neovessels compared to smooth plaques [58] (Figs. 6 and 7). In MRI studies, it was similarly concluded that...
lipid-necrotic content was a strong predictor for a new surface disruption in the form of either ulceration or fibrous cap rupture [59]. MRI studies confirmed the weak association between ulcerations and calcifications [59].

**Do ulcerated carotid plaques heal?**

Once an ulcerated carotid plaque is diagnosed, a reasonable question occurring is how long will it take for it to heal. In general, it remains unknown how long an ulceration takes to heal although there are reports of cases healed after a few months [60]. MRI has been used to monitor the ulceration healing process in a dynamic way, demonstrating the creation of a new fibrous cap covering the ulcer cavity [60]. Other researchers have used 3D US to monitor ulcerated plaques prospectively for more than a year, reporting that the vast majority of plaques (76.5%) remained unchanged, 23.5% of ulcerations regressed while only 5.8% of ulcerations progressed [61]. In accordance with these results, another research group followed up carotid plaques with MDCTA for a period of approximately 2 years, concluding that 88% of plaques remained stable, 8% of plaques showed more surface irregularities while 4% of plaques were smoother. As for the ulcerated plaques, 67% of them showed no change on follow-up, while some of them regressed and only one progressed. This study also identified new ulcerations in previously non-ulcerated plaques [21].

**Imaging of ulceration**

**Ultrasound**

The discussion regarding the optimal imaging modality for diagnosis of carotid ulcerations has been ongoing since 1986 when US was considered superior to angiography for diagnosing ulceration [62]. Given the fact that US is the first-line modality for evaluation of carotid arteries, it is expected that this technique has been extensively investigated with conflicting results regarding the diagnostic accuracy for ulceration [32, 63–67]. Some studies showed high sensitivity and specificity [32, 65], while different researchers concluded that US is inadequate for diagnosing ulcers because of its low sensitivity (23–47%) [66, 68, 69], which was higher in plaques with <50% stenosis [69]. Similarly, correlation of US with histology was poor [70]. Beyond its low accuracy, US has been found to be characterised by low inter-observer agreement for ulceration [71].
Based on the technological advances in the field of US including modern transducers and image optimisation techniques, it is expected that current US devices may provide improved accuracy for diagnosing carotid ulceration [32]. The previously described de Bray criteria are among the most widely used in the literature [61, 71, 73–76]. Nevertheless, a recent study using histology as the reference method has shown that these criteria are only 35.7% sensitive and 75% specific [10]. The size criterion proved inaccurate, with histology detecting ulcers smaller than 2 mm and cavities larger than 2 mm not characterised as ulcers on histology. The newer criteria proposed were 85.7% sensitive and 81.3% specific, outperforming de Bray’s criteria [10]. Although US improved diagnostic accuracy with these new criteria, the acoustic shadow caused by calcified plaques still represents an inherent limitation of US [10]. The low echogenicity of the ulcer base compared to the nearby endothelium reflects the lower acoustic impedance of soft tissues such as thrombus compared to the plaque fibrous cap or normal endothelium. If this echogenicity criterion is not fulfilled, then a concavity on a plaque surface may not truly represent an ulcer but rather a simple cavity or even normal endothelium lying between two juxtapositioned plaques [10]. Other pitfalls in US interpretation potentially leading to false-positive results include mirror image artefact, which refers to the artefactual visualisation of flow within a plaque [76]. Beyond imaging the ulcer itself, modern US studies have evaluated new indirect findings such as a fine trembling motion of echogenic structures inside the plaque, which was found 93% sensitive and 60% specific [77].

**Contrast-enhanced ultrasound**

CEUS has also been introduced in carotid arteries and investigated in plaque surface evaluation and identification of irregularities and ulcerations, showing better results than conventional US [14, 78–84]. A recent study compared US and CEUS in the diagnosis of carotid ulcerations having MDCTA as the reference method. CEUS outperformed US in terms of sensitivity, intra- and inter-reader agreement [13]. Similar subsequent studies have used CEUS for the detection of ulcerations in asymptomatic patients with diabetes [85]. Another recent study confirmed CEUS’s superiority to conventional US for diagnosing histological carotid plaque rupture. Using receiver-operating characteristic (ROC) analysis, the calculated optimal cut-off values of a cavity’s orifice, depth and width for the diagnosis of fibrous cap disruption were 1.4 mm, 1.3 mm and 1.88 mm respectively [86]. The B-flow technique is yet another US technique that can be used as an alternative to the Doppler technique and has been used for detection of carotid ulcers, with greater diagnostic accuracy than the colour Doppler technique [74, 87]. Using this technique, a swirling pattern of blood flow was demonstrated within ulcer cavities, a finding in keeping with previous experimental and US observations [33, 88]. Attempts to overcome ultrasound’s limitation of two-dimensional images are
made with three-dimensional US, which as expected was found to detect more ulcers than conventional US [89, 90].

**Multi-detector computed tomography angiography**

MDCTA constitutes a valuable modality for the evaluation of carotid disease, with accurate grading of stenosis and fewer complications compared to DSA [7, 12]. Early studies have shown good agreement with DSA for the detection of ulcerated plaques [91]. In keeping with these results, MDCTA showed good agreement with histology after endarterectomy [92]. Promising results were also found for MDCTA’s ability to characterise plaque’s composition compared with histology, although with less accuracy for the detection of ulcers according to some authors [93]. In a study comparing MDCTA, MRA and DSA, it was concluded that both MDCTA and MRA may replace DSA for accurate grading of stenosis. However, MDCTA detected luminal surface irregularities more often thanks to its excellent spatial resolution and, along with MRA, they proved superior to DSA for identification of ulcerations [94].

Studies comparing US and MDCTA have shown little agreement between these methods for both the diagnosis of ulcerations and characterisation of plaques as smooth or irregular [95]. With histology as the reference method, MDCTA proved superior to US, with 93% sensitivity and 98% specificity for diagnosing ulceration whereas the latter was only 37% sensitive and 91% specific [7, 96]. Improved accuracy found in this study reflected the use of multidetector technology in comparison with other studies assessing single-detector CT [93, 97, 98]. MDCTA’s ability to readily detect ulcers is partly attributed to the availability of specialised three-dimensional reformatting software such as multiplanar reformation (MPR), maximum intensity projection (MIP) and volume rendering (VR). MDCTA is not free of limitations though, as thorough evaluation may be hindered by artefacts including beam hardening in heavily calcified plaques [7], which may hide small ulcerations [7, 99, 100]. In a study comparing various MDCTA techniques for the detection of ulceration, axial images and VR proved to be the most accurate. The overall accuracy of MDCTA, with all techniques deployed, showed 93.9% sensitivity and 98.7% specificity [101]. When reviewing carotid MDCTA scans, it should be kept in mind that hyperdense material projecting outside the vascular lumen may represent either a focal calcification or a true ulceration. To differentiate these entities, a density threshold of 600 Hounsfield units (HU) has been used [13]. Ideally, though, an unenhanced scan should be performed prior to the intravenous contrast administration (Fig. 8).

Conventional angiography is traditionally considered the reference method for grading carotid stenosis although its accuracy for the detection of ulcerations has been questioned [94, 98, 102–104]. Moreover, it represents an interventional technique associated with a periprocedural risk for thromboembolic events [105]. As a result, modern non-invasive modalities such as MDCTA [97, 98] or MRA [106, 107] are gradually replacing DSA [7]. Anzidei et al. compared US, MDCTA and MRA with DSA, concluding that MDCTA has excellent diagnostic accuracy with a sensitivity, specificity, positive and negative predictive value up to 100% for the diagnosis of ulceration, outperforming MRA [108].

**Magnetic resonance angiography**

Magnetic resonance imaging (MRI) has also been used for the diagnosis of ulcerated carotid plaques with good interobserver agreement [109]. Longitudinal black blood cardiovascular MRA improves the technique’s sensitivity (80%) and specificity (82.3%) for the detection of ulceration in comparison with simple evaluation of axial images [110]. Contrast-enhanced MRA (CEMRA) is considered superior to time-of-flight (TOF) MRA for ulceration, which had more false-negative results (Fig. 9). The main reasons explaining TOF-MRA’s lower accuracy include the ulcer’s orientation and location in relation to the point of maximum stenosis and geometry in the form of neck-to-depth ratio [111]. MRI’s particular strength in detection of ulcerations relies on its ability to image the plaque’s fibrous cap as a black zone lying between the bright lumen and the grey plaque content. Absence of this dark zone represents rupture of the fibrous cap and thus ulceration [111, 112]. If blood pool agents were used, then CEMRA was found superior to MDCTA both for grading of stenosis and characterisation of plaque morphology [113].

**Conclusion**

Carotid plaque surface morphology represents an important feature of plaque vulnerability as both surface irregularity and ulceration have been correlated with stroke. The diagnosis of carotid ulceration relies on imaging and virtually all modalities have been investigated in that respect, showing varying degrees of diagnostic accuracy. US as the first-line imaging modality has the potential to detect ulcerations, especially if microbubbles are used. Nevertheless, cross-sectional modalities such as MDCTA and CEMRA have proved valuable for the delineation of carotid plaque surface and diagnosis of ulceration.

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vessels: a pictorial comparison with cross-sectional imaging (MDCTA or MRA)” (C-0110), which have been accepted for publication by the European Congress of Radiology (ECR) 2017.

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