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Carotid Plaque Analysis: Comparison of Dual-Source Computed Tomography (CT) Findings and Histopathological Correlation

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Abstract *Purpose:* Plaque morphology is an important predictor of stroke risk and may also be a predictor of postoperative outcome after carotid endarterectomy (CEA). Thus, the purpose of our study was to evaluate the findings of preoperative dual-source computed tomography (DSCT) of carotid plaque morphology and correlate these findings with histopathological findings.
Material and methods: Thirty patients undergoing CEA due to neurological events and high-grade carotid artery stenosis were evaluated with DSCT for degree of stenosis following the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria and for non-invasive plaque morphology prior to CEA. CT protocol was as follows (SOMATOM Definition, Siemens Medical Solutions, Forchheim, Germany): A dual-energy protocol was used with tube A (140 kV, 55 mA) and tube B (80 kV, 230 mA) with $2 \times 64 \times 0.6$-mm collimation, pitch 0.65 and rotation time of 0.33 s. Histopathological work-up was performed on the surgically retrieved tissues. The findings from DSCT and histopathology were compared with respect to image quality and plaque composition (fatty plaque, mixed plaque and calcified plaque), were correlated with histological specimens and classified according to the American Heart Association (AHA) classification of atherosclerotic plaque. Pearson correlation and kappa statistics were performed.
Results: The image quality of DSCT was rated as 'excellent' in all the examinations. The mean degree of stenosis was quantified as 82%. The sensitivity of DSCT for the detection of

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calcification was 100% (standard deviation (SD) 0%, confidence interval (CI): 99–100). While the sensitivity for the detection of mixed plaques was 89% (SD 12%, CI: 79–98), it was 85% (SD 10%, CI: 76–92) for the detection of low-density fatty plaques.. The mean degree of agreement was $k = 0.81$.

Conclusion: DSCT angiography of the carotid arteries is feasible and the evaluation of carotid plaque composition allows non-invasive assessment of different plaque components. This may have an impact on the non-invasive differentiation of vulnerable plaques.

The incidence of stroke remains very high with about 780 000 stroke patients per year in the US.[1] As stated in several large trials, the degree of carotid artery stenosis is the most-used predictor of the risk of stroke in a patient. In these trials, patients with high-grade stenosis (>70%) showed the highest benefit from carotid endarterectomy (CEA).[2–5]

Conversely, plaque morphology is increasingly important as it may be an important predictor of postoperative outcome.[6,7] Although plaque morphology is not used in the decision making of whether to perform CEA or not, it plays an important role, as it is directly correlated with the risk of embolism and occlusion, thus resulting in cerebral ischaemia.[8]

'Vulnerable plaque' is relatively a new concept which takes the plaque composition into account. The risk for stroke might increase or decrease depending on the plaque composition. In this respect, plaque ulceration plays the most important role, as nearly 30% of patients with ulcerated plaques develop neurological effects within 2 years, while only 17% of patients without ulceration have an event within a 2-year period.[3]

Thus, it becomes more important to be able to predict the risk of stroke based on the plaque composition. Although digital subtraction angiography (DSA) still functions as the gold standard for the assessment of the degree of stenosis,[9,10] it is unable to make any predictions about plaque composition. Therefore, other non-invasive imaging modalities such as MR imaging, multidetector-row CT and duplex ultrasound are more frequently used and each of them offers some potential for plaque analysis.[11–14] Recent research also indicates that metabolic activity plays an additional role in the assessment of risk.[15]

It was only recently that dual-source computed tomography (DSCT)[16,17] has become available. It facilitates the use of two different X-ray sources, allowing simultaneous use of two different X-ray energies (80 kV and 120 kV) to achieve different Hounsfield numbers in the tissue, for potential tissue differentiation and advanced post-processing .[18] Furthermore, DSCT helps in imaging with high spatial and high temporal resolution and offers easy-to-use bone-removal algorithms for direct visualisation of complex vasculature. The initial results of DSCT angiography imaging, especially of the coronary arteries, have already shown promising results.[16,17,19,20]

Therefore, the purpose of this study was to use the newly introduced DSCT angiography for imaging of the internal carotid artery (ICA) in preoperative plaque analysis and to compare imaging findings with the histopathological specimens.

Material and Methods

Patient population

Ethical approval was given by the clinical ethics committee. Patients included in this prospective study had to give informed consent in order to participate in the study, and they were recruited between April 2007 and July 2008.

A total of 30 carotid arteries were evaluated. The degree of stenosis was assessed according to the North American Carotid Endarterectomy Trial (NASCET) criteria.[2]

DSCT angiography

All patients underwent DSCT imaging (SOMATOM Definition, Siemens Medical Solutions, Forchheim, Germany). A dual-energy protocol was used with tube A (140 kV, 55 mA) and tube B (80 kV, 230 mAs) with $2 \times 64 \times 0.6$-mm collimation, pitch 0.65 and rotation time of 0.33 s. To assess the optimal bolus timing prior to the scan, a test bolus was performed with 20 ml of contrast media (Ultravist 300, Bayer-Schering Healthcare, Berlin, Germany) injected at a flow rate of 6.1 ml s^{-1}, followed by a 40-ml saline chaser. The optimal scan delay was then assessed after graphical presentation of peak enhancement at the aortic arch (DynEva™, Siemens Medical Solutions, Forchheim, Germany). With regard to the main scan, 123 ml of non-ionic contrast media (Ultravist 300, Bayer-Schering Healthcare, Berlin, Germany) were administered through an intravenous 18-gauge line at a flow rate of 6.1 ml s^{-1} (iodine delivery rate was 1.83 g l s^{-1}), followed by a saline chaser of 40 ml at the same flow rate. The scan was performed in caudo-cranial direction from the aortic arch to the mid skull, and the images were reconstructed with 0.6-mm slice thickness and 0.4-mm increment by a smooth D20f Siemens kernel (window 600, centre 200). The average scan time was 11 s and average CTDIvol was 10 mGy.

The images were then displayed on a monitor and multiplanar reformations (MPRs) were used for the optimal orthogonal view of the ICA. The image quality was rated on a three-point scale (1 = excellent, 2 = moderate and 3 = insufficient), especially with respect to contrast enhancement in the vascular lumen.[21]

Plaque analysis

DSCT plaque analysis was performed using three groups as proposed by Schroeder et al.[22] For each patient, a cross section of the ICA was reconstructed on the operated site using the CT images with an orthogonal view of the vessel area at the highest degree of stenosis. For each part of the plaque, the Hounsfield densities were measured using a pixel lens. The three groups consisted of different types of plaque composition, while parts with a density of less than 50 HU were classified as fatty plaques, mixed plaques (50–119 HU) and calcified plaques (>120 HU). Additionally, the plaque composition was measured as the area, and the relative composition of different plaque parts was calculated. The findings were categorised according to the American Heart Association (AHA) classification for carotid plaque as used by Wintermark et al.[23,24] These findings were directly correlated with the plaque appearance in histopathology analysis.

Preparation of plaque specimen for histology

The removed specimens were first fixed in 10% buffered formalin for 24 h. Following which the samples were decalcified for 24 h in 10% ethylenediaminetetraacetic acid (EDTA). After possible calcifications were dissolved, the removed plaques were inked for microscopical positioning and cut into 2-mm-thick slices. Subsequently, following paraffinisation, tissue blocks were prepared for histology by cutting into 3-μm-thick sections. After rehydration, two different standard histochemical stainings were performed: haematoxylin and eosin (H&E) staining and Elastica-van-Gieson (EvG), respectively. The H&E staining gives an overview of the architecture of the vessel and the plaque, including inflammatory cells, while the EvG staining shows a differentiation between collagen, smooth muscle and elastic fibres. All the specimens with respect to plaque consistency were analysed. The composition of plaques was captured by estimation of the percentage of lipids, calcification and fibrotic tissue.

Statistical analysis

The values of the degree of stenosis were summarised with arithmetic means and standard deviations. Furthermore, Pearson correlation coefficient *r* was performed between CT findings and histopathology, and kappa statistics was additionally used for the degree of agreement between the two imaging modalities (kappa < 0.2 = poor, 0.61–0.8 = good, 0.81–1 = very good). All statistics were performed using MedCalc Version 8.1.1.0 (MedCalc Software™, Mariakerke, Belgium).

Results

Thirty patients were included in this prospective study (26 males, four females; mean age: 70 years, minimum age: 52 years and maximum age: 85 years). Seventeen of these patients who had neurological symptoms within 10 days (SD 9 days) before surgery underwent DSCT angiography for evaluation of ICA stenosis prior to CEA.

All the patients could be evaluated with DSCT. The median image quality was rated as excellent (1) (26 were rated as excellent, four were rated as moderate, none were rated insufficient). In computed tomography angiography (CTA), the mean degree of stenosis was 82% (SD 9%, minimum 70 and maximum 100). All patients underwent CEA within 2 days of DSCT angiography. Intra-operatively, the patients underwent CEA with dissection of the carotid bifurcation, and the retrieved histopathological specimen were analysed for all of them. Figs. 1 and 2 show a correlation of the CTA MPR with the histological specimen in two different patients.

Quantitative analysis

The average Hounsfield densities were as follows: fatty plaques 35 HU (SD 25 HU), mixed plaques 51 HU (SD 19 HU) and calcified plaques 290 HU (SD 53 HU).

The sensitivity of DSCT for the detection of calcification was 100% (SD 0%, CI: 99–100). While the sensitivity for the detection of mixed and low-density fatty plaques was 89% (SD 12%, CI: 79–98) and 85% (SD 10%, CI 76–92), respectively. With DSCT, the plaques were classified according to the AHA classification as follows: no type I or II lesions could be detected as these types of lesions are only seen histopathologically and the resolution of the DSCT was not high enough

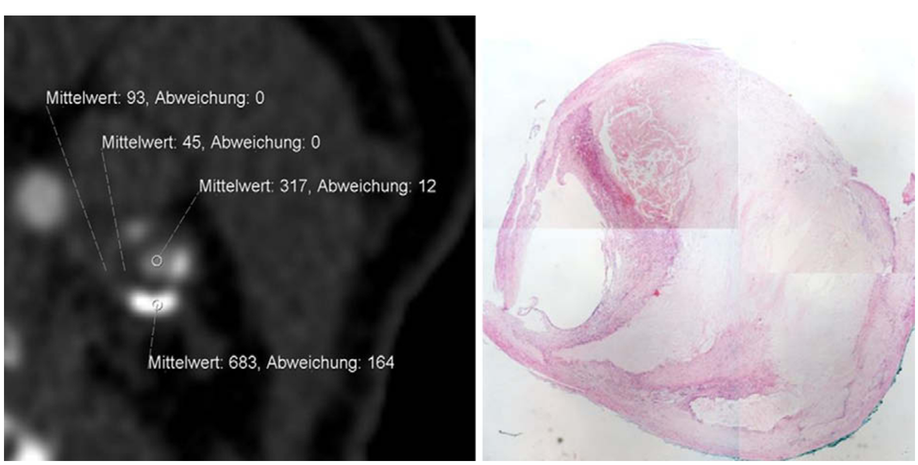

Figure 1 DSCT findings of the ICA in a symptomatic patients and the correlated histopathological specimen after CEA. (Mittelwert = average, Abweichung = standard deviation).

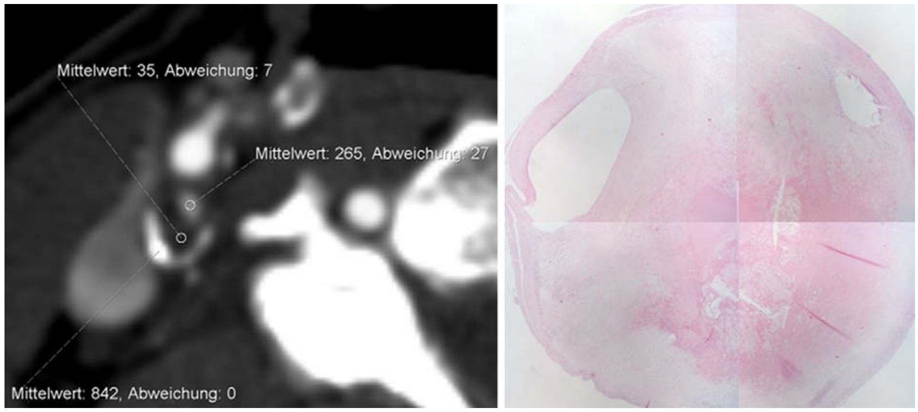

Figure 2 DSCT findings of the ICA in a symptomatic patients and the correlated histopathological specimen after CEA. (Mittelwert = average, Abweichung = standard deviation).

to detect these. Eighteen patients were classified as type IV—V lesions (60%), five patients were classified as type III lesion (16%), two patients were classified as type VIII lesion (7%), three were classified as type VI lesion (10%) and two were classified as type VII lesion (7%). The kappa statistics did show high values in agreement with the histopathological findings (type III $k = 0.82$, type IV—V = 0.86, type VI = 0.81, type VII = 0.88 and type VIII = 0.67). Besides, the density findings correlated very well with the findings from histopathology fatty plaques ($r = 0.91$), mixed plaques ($r = 0.85$) and calcified plaques ($r = 0.95$).

Discussion

The concept of 'vulnerable plaque' is relatively new.[8,25—28] The vulnerable plaque is considered to be a plaque with less calcification, but with a substantial part of fibrous and lipoid composition. It is associated with an increased risk of stroke.[29] As carotid artery imaging has shifted from invasive angiography to non-invasive imaging, the purpose of our study was to evaluate the new technology of DSCT for non-invasive assessment of carotid artery plaque evaluation and compare these results with the histopathology specimens.

As proposed by Schroeder et al.,[22] the plaque composition can be estimated through Hounsfield densities. However, as temporal resolution has increased and post-processing methods — especially high-resolution MPRs — allow optimal visualisation of the vascular orthogonal area, a more precise analysis became possible.[13]

Recently, Wintermark et al. presented a method with automated measurement of plaque morphology using a micro-CT.[23] Consistent with our results, they could show a high correlation between CT findings and histopathology. It would be desirable to use automated classification methods, especially in *in vivo* imaging, as the findings might provide additional information that would benefit patients with CEA. Similar to our study it could be shown that calcifications are less a problem, as calcifications are more often situated in the outer layer of the vessel wall. The uniqueness of our study is situated in the scanner technology, which uses the power of two X-ray tubes to perform faster scan acquisition and higher spatial resolution. Additionally, the use of 2-kV settings allows faster and more efficient post-processing methods, particularly for bone removal. In further studies, we will investigate whether the use of two X-ray tube settings will allow the removal of calcifications in order to focus on the non-calcified plaque components.

Our initial results could demonstrate a very high correlation and agreement between non-invasive imaging findings with DSCT and histopathological specimens. Although DSCT is still beyond the resolution of histology, the main determinants of vulnerable plaque are visible and can be graded visually or quantitatively.

When considering non-invasive imaging of the ICA, one has to compare the results with magnetic resonance imaging (MRI) and ultrasound as well. Several studies have evaluated ultrasound for plaque analysis[3,30—32]; however, ultrasound analysis still remains user dependent. Volumetric analysis would be a desirable option as well, and the initial results are promising. Probably, the most accurate technique would be an intravascular ultrasound (IVUS)[3,33,34]; nevertheless, this would not purport to be the ideal approach as non-invasive imaging is preferable. The developments in MRI are also promising.[35—40] Depending on the imaging protocol and the sequences used, for example, the differentiation of plaques in symptomatic and asymptomatic plaques could be demonstrated.[38] It has been demonstrated that metabolic activity can also be imaged, which will add valuable information to the plaque morphology in the future, and may help to detect vulnerable plaques more precisely. It would be of interest to note which of the non-invasive techniques would be the first-line modality for the evaluation of the ICA in the future.

Limitations

A limitation of our study is the manual quantification of the plaque composition. Automated algorithms would prove beneficial in quantification. This would surely enhance the accuracy of the measurement method. Furthermore, a direct comparison of each value of the CT densities to the corresponding histology is necessary, which was not possible in our study. Secondly, the comparison with histological specimens only works if the histological sections are as precise as the CT sections; however, precise specimen sizes may lead to unexpected results.

Conclusion

Our study results indicate that DSCT angiography of the carotid arteries is feasible and the evaluation of carotid plaque composition allows non-invasive assessment of different plaque components. Although some limitations remain, DSCT offers a high potential to non-invasively assess the patients at a higher risk for stroke.

Conflict of Interest/Funding

None.

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