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Multidetector-Row Computed Tomography in Evaluation of Atherosclerotic Carotid Plaques Complicated with Intraplaque Hemorrhage

Authors: Marko Ajduk, Ladislav Pavić[1], Stela Bulimbašić[2], Mirko Šarlija, Predrag Pavić, Leonardo Patrlj, Boris Brkljačić[1]

Department of Vascular Surgery, University Hospital Dubrava, Zagreb, Croatia

[1]Department of Radiology, University Hospital Dubrava, Zagreb, Croatia

[2]Depatment of Pathology, University Hospital Dubrava, Zagreb, Croatia

Corresponding author: Marko Ajduk, MD, Department of Vascular Surgery, University Hospital Dubrava, Av. Gojka Šuška 6, 10000 Zagreb, Croatia

E-mail: majduk@yahoo.com, Tel.+38591201956

Abstract

Objective: To determine sensitivity and specificity of multidetector-row computed tomography in detecting atherosclerotic carotid plaques complicated with intraplaque hemorrhage.

Material: Carotid plaques from 31 patients operated for carotid artery stenosis.

Methods: Results of preoperative multidetector-row computed tomography analysis of carotid plaques were compared with results of histological analysis of the same plaque areas. Carotid endarterectomy was performed within one week of multidetector-row computed tomography. American Heart Association classification of atherosclerotic plaques was applied for histological classification.

Results: Median tissue density of carotid plaques complicated with intraplaque hemorrhage was 22 Hounsfield units. Median tissue density of noncalcified segments of uncomplicated plaques was 59 Hounsfield units (p=0.0062). The highest tissue density observed for complicated plaques was 31 Hounsfield units. Multidetector-row computed tomography detected plaques complicated with hemorrhage with sensitivity of 100% and specificity of 64.7%, with tissue density of 31 Hounsfield units as a threshold value.

Conclusion: Multidetector-row computed tomography showed high level of sensitivity and moderate level of specificity in detecting atherosclerotic carotid plaques complicated with hemorrhage.

Key words: carotid plaque; hemorrhage; multidetector-row computed tomography

Introduction

Large randomized controlled trials demonstrated benefit of carotid endarterectomy (CEA) in symptomatic patients with high degree carotid artery stenosis.[1,2] Asymptomatic patients benefit less from CEA with absolute risk reduction of only about 1% annually, during the five years follow-up. [3,4] Therefore, large number of asymptomatic patients must be operated to prevent small number of neurological events. The total number of operated asymptomatic patients may be lowered, if subgroups of asymptomatic patients that benefit most from carotid endarterectomy could be identified. Several studies showed higher incidence of neurological incidents in patients with so-called soft plaques (plaques predominantly consisting of lipids, tissue debris and hemorrhage).[5-10] Ultrasound analysis of carotid plaques demonstrated that hypoechoic plaques represent an independent risk factor for stroke incidence in adults aged 65 years or older.[11] Takaya et al. followed asymptomatic patients for 38 months and showed that patients with intraplaque hemorrhage on initial MRI had 5.2 times higher incidence of cerebrovascular events.[12] The American Heart Association (AHA) classification of atherosclerotic plaques defines eight types of plaques, according to histological content (Table I).[13,14] Atherosclerotic carotid plaques complicated with intraplaque hemorrhage (AHA type VIb) are considered as unstable and are associated with a higher incidence of cerebrovascular events.[12,15-17] Computed tomography (CT) angiography demonstrated high accuracy in diagnosing carotid artery stenosis.[18-22] Additional feature of computed tomography is its ability to measure tissue density (expressed as a number of Hounsfield units [HU]). Thus, it can provide some information about the type of analyzed tissue. Atherosclerotic carotid plaques with lower tissue density on multidetector-row CT (MDCT) are associated with lower incidence of cerebrovascular events.[6,7] While single slice computed tomography showed conflicting results in determining carotid plaque composition, MDCT showed good correlation of findings with histological analysis of coronary plaques.[23-27] Histological analysis of coronary plaques showed that remodeling of atherosclerotic plaque changes its histological content. Therefore, the period between imaging and histological analysis should be as short as possible.[28] We compared results of MDCT and histological analysis and calculated sensitivity and specificity of MDCT in detection of AHA type VIb atherosclerotic carotid plaques (plaques complicated with intraplaque hemorrhage, most often containing mixture of lipids, hemorrhage and necrotic debris). Carotid endarterectomy was performed within one week of MDCT.

Material and methods

Carotid plaques from 31 consecutive patients operated for carotid artery stenosis were included in this prospective study. There were 21 male and 10 female patients, age between 51 and 87, median 70 years. There were 6 symptomatic and 25 asymptomatic patients (Table II). Patients who experienced cerebral insult, transient ischemic attack or amaurosis fugax on the side of affected carotid artery within six months of MDCT were considered symptomatic.

Indications for carotid endarterectomy were symptomatic patients with carotid artery stenosis >60% and asymptomatic patients with stenosis >70%. All patients had the same imaging evaluation: color duplex-doppler first, and MDCT in patients with carotid stenosis >60% on doppler.

Endarterectomy was performed within one week of MDCT evaluation. Approval from the institutional ethical committee was obtained.

Two experienced radiologists performed doppler examination, using Logiq 9 scanner, with 7-9 and 9-14 MHz probes (GE-Healthcare, Milwaukee, Wi, U.S.A.).

MDCT analysis

The Siemens (Erlangen, Germany) Somatom Sensation 16-row MDCT scanner was used. One radiologist evaluated collected data on Siemens Leonardo Syngo2004A workstation. The standardized optimized contrast-enhanced protocol was used with intermediate reconstruction: 120 kVp, 120 mAs, collimation 16x0.75 mm, pitch 1, slice thickness 0.75 mm. Iopamidol was used as contrast medium (370 mg iodine/ml, 4 ml/s, 70 mm^3, 325 psi). Transversal multi-planar reconstructions, orthogonal to vessel long axis in both coronal and sagittal planes, were used for plaque analysis. Three measurements of tissue density were performed on visually least dense area of plaque at level of maximal stenosis. Measurements were performed on 2 mm^2 circle area and the smallest value was recorded (Figures 1 and 2). Calcifications are obvious on MDCT and were not further analyzed. Distance between carotid bifurcation and level of maximal stenosis was recorded, in order to help pathologist in finding corresponding level for histological analysis. Percentage of stenosis was calculated applying North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.[14]

Surgical technique

Patients underwent carotid endarterectomy under locoregional or general anesthesia, with selective use of intraluminal shunt in the former group of patients and in all patients in the latter group. Four patients were operated under general anesthesia. Two of them had concomitant cardiac surgery, one had history of epileptic seizures, and one patient with contralateral occlusion had an explicit wish for general anesthesia. Care was taken to preserve the morphologic integrity of plaques as much as possible. There were no verified perioperative insults. The patient with contralateral carotid occlusion had transient postoperative weakness of the contralateral hand without CT evidence of ischemic brain lesion.

Histological analysis

Immediately after carotid endarterectomy, plaques were formalin-fixed (10% buffered formaldehyde) and sent for histological analysis. One pathologist, blinded for MDCT plaque density, performed histological analysis. If calcifications were extensive, plaques were first decalcified using 20% nitric acid. That procedure eliminates calcifications while preserving remaining histological content. Samples were sliced in serial manner, starting from bifurcation, followed by sections 2 mm apart toward internal carotid artery. Performed serial sections technique assured precise measurement of distance between the bifurcation and the level of maximal stenosis.

Plaques sections were embedded in paraffin and cut at 4 µm thin slices, using standard process. Slices were stained with hematoxylin and with Mallory trichrome if necessary (Figures 3 and 4). One pathologist examined all plaques and classified them according to the American Heart Association classification of atherosclerotic plaques. The radiologist that performed MDCT analysis was involved in histological analysis, to make sure that same plaque areas were analysed on MDCT and histology.

Data analysis

Difference of median tissue density between AHA plaques type VIb and other plaque types was calculated using Mann-Whitney U-test. Value of $p<0.05$ were considered statistically significant. To determine cut off value of tissue density, ROC analysis was used.

Results

There were 14 (45%) AHA VIb plaques and 17 (55%) other AHA types (V, VII and VIII). Median MDCT tissue density (TD) of type VIb plaques was 22 HU (range, -17 to 31), and median tissue density of non-calcified segments of non-complicated plaques was 59 HU (range, -6 to 150), (p=0.0062, Mann-Whitney U-test), (Figure 5). ROC analysis showed 100 % sensitivity and 64.7% specificity of MDCT in detecting plaques complicated with intraplaque hemorrhage, with tissue density of 31 HU as a threshold value (i.e., no plaque with MDCT tissue density over 31 HU was complicated with intraplaque hemorrhage), (Figure 6). Four of six plaques from symptomatic patients were AHA type VI b and 10 of 25 plaques from asymptomatic patients were AHA type VIb.

Discussion

This study showed that MDCT could detect atherosclerotic carotid plaque complicated with hemorrhage with 100% sensitivity, with tissue density of 31 HU as a threshold value. Previous studies showed inconclusive results regarding the accuracy of single slice computed tomography in analysing plaque composition.[23,24] De Weert et al. showed good correlation between in vivo MDCT findings and histological findings, however in their analysis of 15 carotid plaques, the period between MDCT evaluation and endarterectomy was up to three months.[29] During that period, remodeling of plaques could change their histological appearance. Histological analysis of coronary plaques performed within one week after infarction showed morphologic features of instability, while plaques taken later were histologicalally similar to those in patients with stable angina.[28] To minimize inaccuracy resulting from this fact, all patients in this study were operated within one week of MDCT analysis.

To our knowledge, among studies comparing in vivo MDCT and histological analysis of carotid plaques and providing the period between MDCT and endarterectomy of less than one week, this study enrolled the largest number of patients.

Our aim was to identify plaques with intraplaque hemorrhage (AHA type VIb) using MDCT. Carotid plaques are most often heterogeneous and small areas of plaque often have mixed histological content. Lipids, hemorrhage and necrotic debris ("soft tissue") have the lowest TD on MDCT and other tissue components (fibrosis or calcifications) increase TD. This can influence MDCT results by giving higher TD values even in predominantly soft areas of plaque due to the partial volume effect. Similar effect is produced by contrast medium in vessel lumen and calcified portions of the plaque. To minimize influence of this effect, we performed three measurements per slice on chosen plaque area (visually least dense area) and recorded only the smallest value, since no plaque component has lower TD than lipids, hemorrhage or necrotic debris.

With 2 mm^2 area on which tissue density was measured and 0.75 mm slice thickness, 1.5 mm^3 of tissue volume was measured by each measurement. Even plaques with such a small MDCT detectable amount of soft tissue (which is most often combination of lipids, hemorrhage and necrotic debris) should probably be regarded as potentially vulnerable, since it is impossible to tell by MDCT whether hemorrhage within plaque is expanding or reducing due to plaque remodeling. To provide the same plaque level for MDCT and histological analysis we measured the distance from bifurcation to level of maximal stenosis on MDCT and that value was used by the pathologist to find corresponding level of specimen for histological analysis. It might have happened that a minor degree of longitudinal plaque shrinkage occured during the histological processing, but it is unlikely to be significant because of the low overall water content of plaques. However, serial slicing and embedding of the whole plaque (including the planes below and above MDCT measured level of maximal stenosis), and possibility of additional slices from deeper levels of paraffin embedded material, assure that the level of the narrowest lumen (maximal stenosis) had been chosen for the analysis.

Current clinical practice in the treatment of asymptomatic patients with carotid artery stenosis differs among different countries and even among different institutions within the same country.[30-43] In general, asymptomatic patients with carotid artery stenosis are treated more conservatively in Europe than in the United States. Asymptomatic patients with carotid artery stenosis comprise 11-52% and 37-92% of all patients operated for carotid artery stenosis in Europe and the United States, respectively.[30-43] Several authors have indicated that operative treatment of asymptomatic patients with carotid artery stenosis should be considered only for medically stable patients with ≥80% stenosis with life expectancy of at least 5 years, and only if a <3% perioperative complication rate can be achieved.[44,45] Asymptomatic patients with complicated plaque and <80% carotid artery stenosis, who would not be treated if the above mentioned recommendations are applied, could benefit from a diagnostic method that is able to detect some features of carotid plaque associated with increased risk of a cerebrovascular event. Asymptomatic patients with carotid artery stenosis of <80% and uncomplicated plaque probably require only the best medical therapy.[44-47] The decision which diagnostic method to use and when to treat asymptomatic patients is affected not only by the results of large trials, but also by diagnostic resources available, medical system funds, and the possibility of treating patients with carotid artery stenosis with low morbidity and mortality at a particular institution. MDCT increases the cost of diagnostic evaluation for each patient if compared to duplex analysis alone, and exposes patient to radiation. However, MDCT is noninvasive and accurate in diagnosing carotid artery stenosis.[18-22] Furthermore, MDCT showed very good interobserver agreement in the evaluation of degree of carotid artery stenosis and can also provide information about the type of analyzed tissue and the presence of intracranial arterial stenosis. [18-22,29,48,49] Studies dealing with doppler examination of carotid artery stenosis showed marked interobserver variabilities.[50-52] Several studies based on measurement of grey scale median of carotid plaques showed conflicting results regarding the correlation of findings with histological content, while studies based on visual evaluation of ultrasound findings showed high variability of intra- and interobserver agreement.[53] In our view, duplex and MDCT are complementary studies. We perform duplex examination first, followed by MDCT, if >60% carotid artery stenosis is found on duplex. We believe that higher cost of diagnostic evaluation that includes MDCT could be in part compensated by the potential reduction of the number of operated asymptomatic patients.

Conclusion

Multidetector-row computed tomography showed very high level of sensitivity and moderate level of specificity in detecting hemorrhage within atherosclerotic carotid plaque. Plaques with TD over 31 HU on MDCT were not complicated with intraplaque hemorrhage. Technical advancements of CT equipment may probably increase the specificity of the method.

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Tables

AHA classification	*Description*
I	Scattered macrophage foam cells
II	Layers of macrophage foam cells and lipid laden smooth muscle cells - fatty streaks
III	Type II with extracellular lipid droplets
IV	Confluent extracellular lipid core
V	Lipid core and thick layer of fibrous connective tissue (previously Va, also called multilayered fibroatheroma)
VI	Types IV or V with disruption of the lesion surface (VIa), hematoma or hemorrhage (VIb) or thrombosis (VIc)
VII	Largely calcified plaque (previously Vb)
VIII	Consisted mainly of fibrous connective tissue and little or no accumulated lipid or calcium (previously Vc)

Table I. American Heart Association classification of atherosclerotic plaques[8,9]

Patient No	Age (years)	Gender	Symptoms	Stenosis % (MDCT)	Tissue density (HU)			AHA plaque type	Stenosis % (duplex)
1	67	M	No	70	59			VII	65
2	74	M	No	95	-11,6			VIb	90
3	65	M	No	95	-17,6			VIb	95
4	56	M	No	95	62,6			V	95
5	87	M	No	90	-23,6			V	90
6	77	M	No	90	63			V	90
7	70	M	No	90	62,8			V	90
8	77	M	No	90	22,2			VIb	90
9	82	F	Yes	80	31,2			VIb	85
10	80	M	No	70	18,2			VIb	70
11	62	M	Yes	80	22,4			V	75
12	81	M	Yes	90	28,5			VIb	90
13	68	M	No	80	62,8			V	70
14	77	M	No	95	25,2			VIb	75
15	68	F	No	70	60,7			V	65
16	79	M	No	90	24,1			VIb	70
17	61	M	No	80	14,7			VIb	65
18	68	M	No	80	21,7			VIb	70
19	77	M	No	80	17,7			V	80
20	72	M	Yes	90	23,3			VIb	80
21	65	M	No	80	42,1			V	95
22	64	M	No	95	26,8			VIb	95
23	61	F	No	90	6,7			V	80
24	76	F	Yes	80	131			VII	70
25	59	F	Yes	95	-3			VIb	80
26	76	F	No	90	150			V	80
27	67	F	No	90	-4,0			VIb	90
28	64	F	No	70	28,6			V	75
29	51	F	No	80	35,8			VIII	70
30	80	F	No	90	11,6			V	95
31	72	M	No	70	59,8			V	75
Summary	Median 70 Range 51-87	M 21 F 10	Yes 6 No 25	Mean 84.8±8.6	Plaque type	Median	Range	VIb 14 Other 17	Mean 80.8±10.3
					VIb	22	-17 to 31		
					Other	59	-6 to 150		

Table II. Patients' characteristics, MDCT, histological and duplex findings. HU-Hounsfield units, MDCT- multidetector-row computed tomography, AHA-American Heart Association

LEGENDS:

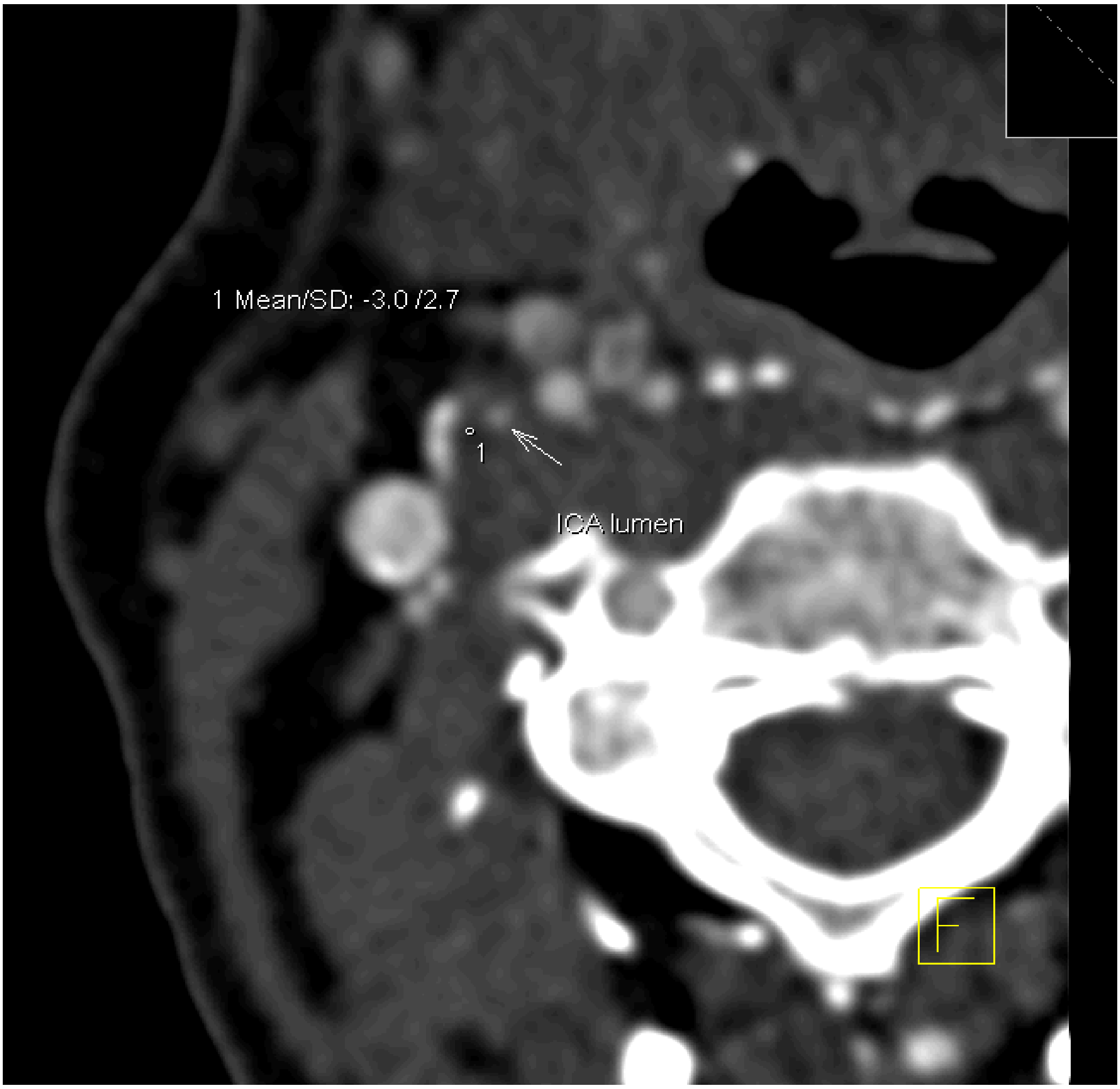

Figure 1. MDCT. Plaque with the least measured tissue density of -3 Hounsfield units (HU). ICA-internal carotid artery, MDCT- multidetector-row computed tomography.

Figure 2. MDCT. Plaque with the least measured tissue density of 59,8 Hounsfield units (HU). ICA-internal carotid artery, MDCT- multidetector-row computed tomography.

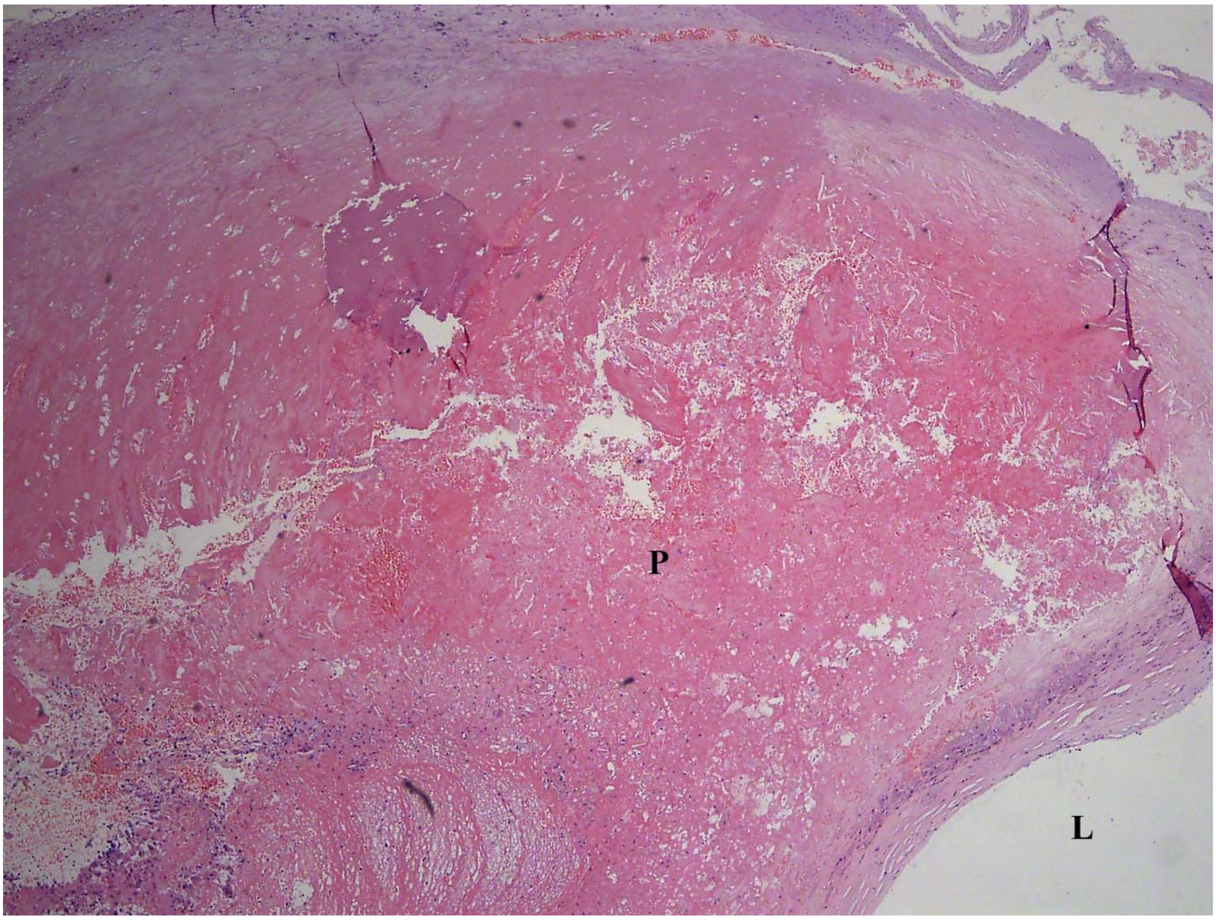

Figure 3. Hemorrhage within plaque (plaque type VIb). Same plaque as on Figure 1. H&E, original magnification x40. P- plaque, L-lumen.

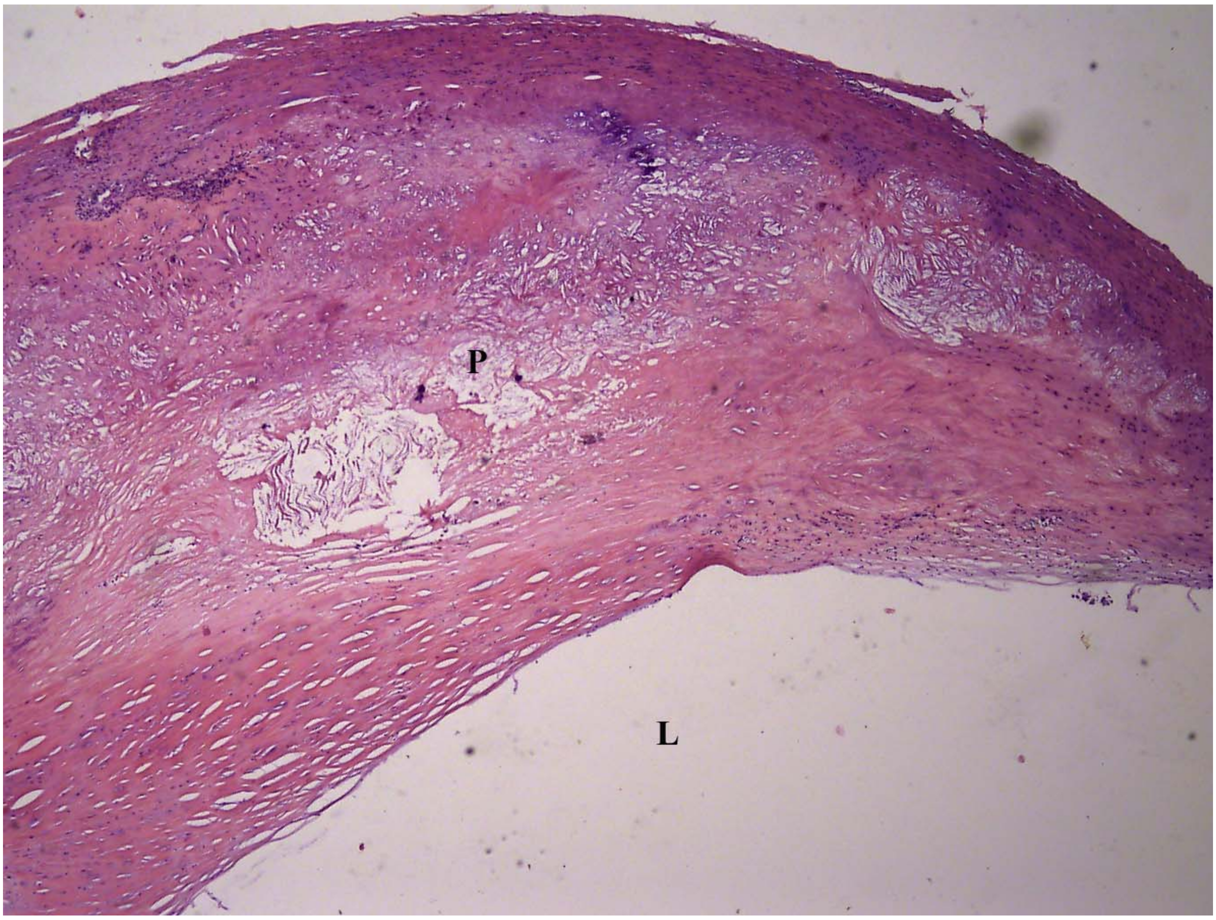

Figure 4. Multilayered fibroatheroma (plaque type V). Same plaque as on Figure 2. H&E, original magnification x40. P- plaque, L-lumen.

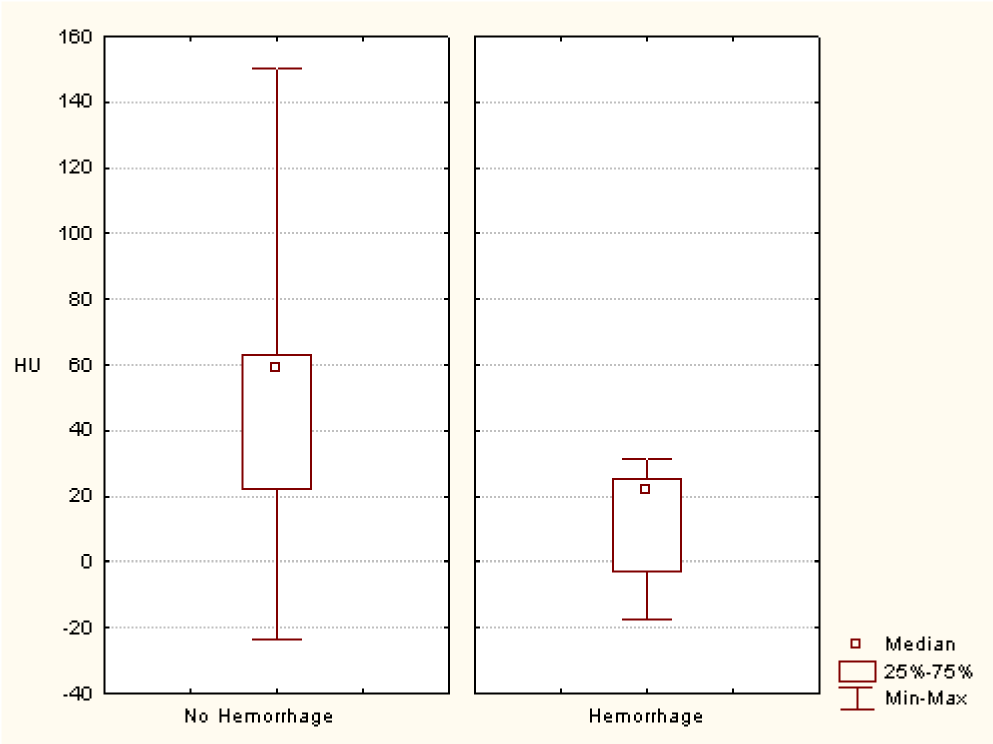

Figure 5. Box-whisker plots of tissue density of plaques without hemorrhage and plaques with hemorrhage. HU-Hounsfield units.

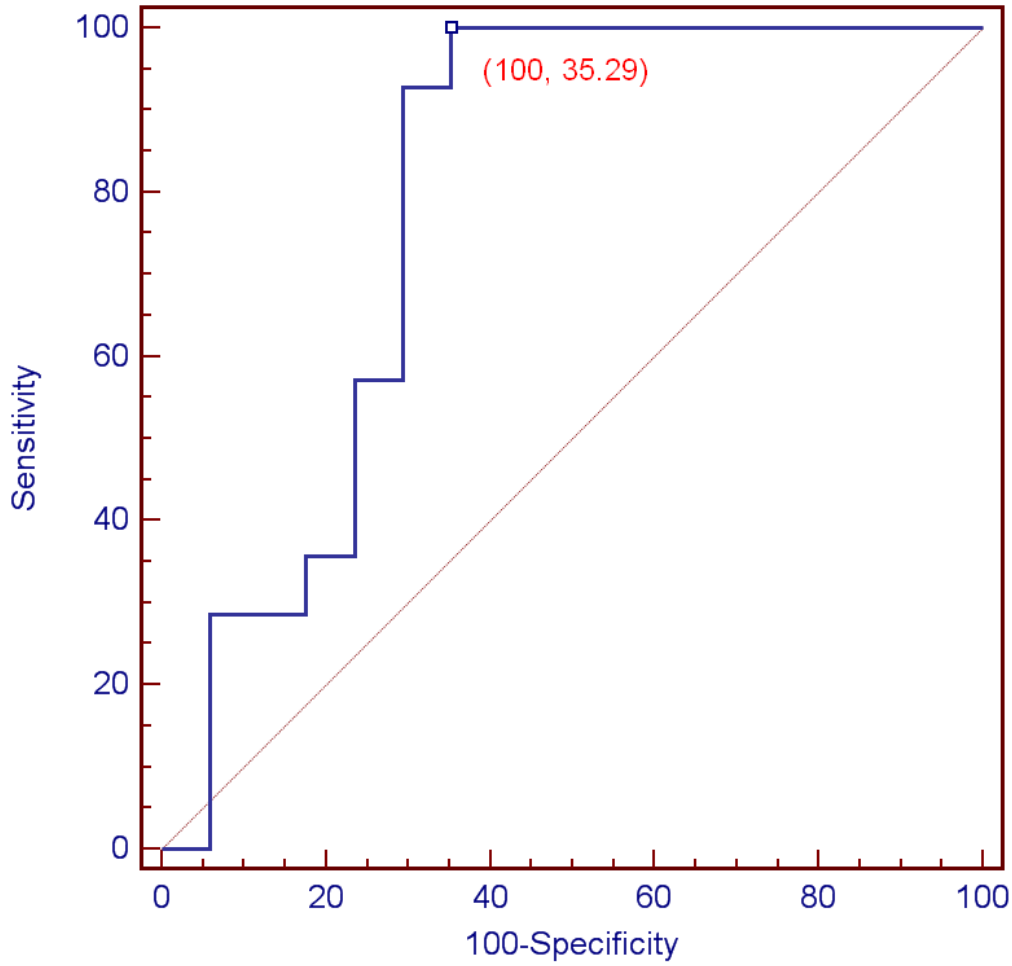

Figure 6. ROC analysis. Cut off value of 31.2 Hounsfield units (HU), sensitivity 100%, specificity 64.71%, area under curve 0.79, p=0.0004.

Table I. American Heart Association classification of atherosclerotic plaques.[8,9]

Table II. Patients' characteristics, MDCT, histological and duplex findings. HU- Hounsfield units, MDCT- multidetector-row computed tomography, AHA- American Heart Association.