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PREOPERATIVE MASSETER AREA IS AN INDEPENDENT PREDICTOR OF LONG TERM SURVIVAL AFTER CAROTID ENDARTERECTOMY

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WHAT THIS PAPER ADDS

Masseter muscle area (MA) can be reliably measured from preoperative computed tomography angiography and is a significant predictor of long-term mortality after carotid endarterectomy independent of other risk factors, anthropometric measures and dental status. To understand its potential in risk stratification and long term mortality, the results need to be validated in independent cohorts and studies powered to stratify for different indication categories.

ABSTRACT

Objectives. Sarcopenia is a predictor of mortality in elderly patients. Masseter area (MA) reflects sarcopenia in trauma patients. We hypothesized that MA and density (MD) could be reliably evaluated from preoperative computed tomography angiography (CTA) scans and that they predict postoperative survival in carotid endarterectomy (CEA) patients. ***Methods.*** Observational registry study. Patients (n=242) were operated due to asymptomatic stenosis (n=32, 13.2%), amaurosis fugax (n=41, 16.9%), transient ischemic attack (TIA) (n=85, 35.1%) or ischemic stroke (n=84, 34.7%). Internal carotid artery (ICA) stenoses were angiographically graded. Intraclass correlation coefficient (ICC) was used to analyze measurement reliability by three independent observers. Cox regression analysis was used to study the effect of MA and MD on survival (hazard ratio, HR). **Results.** The median age was 71.0 years (IQR 13.0) and follow-up time was 68.5 months (range 3-163 months) and at the end of follow-up (1.10.2017) 104 (43.0%) had died according to National Population Register. Average MA (MAavg, mean of left and right MA; median 394.0; IQR 110.1 mm^2) and MD (MDavg, mean of left and right MD; median 53.5 HU; IQR 16.5 HU) could be measured with excellent reliability (ICC>0.865, p<0.001 for all). In multivariable analyses only body surface area (BSA) (p<0.0001) and dental status were associated with MAavg (p=0.021). Increased MAavg predicted lower mortality (HR 0.76, 95% CI 0.61-0.96, p=0.023) independent of age (HR 1.05, 95%CI 1.02-1.07, p=0.001), female gender, BMI, renal insufficiency, ipsilateral stenosis, indication category, and presence of teeth. MDavg did not associate with mortality. In further adjustment BSA (the most significant determinant of MAavg) did not alter the association between MAavg and mortality (0.75, 95% CI 0.58-0.97, p=0.031). **Conclusions**. Average masseter area but not density measured from preoperative CTA-scan provides a reliable estimate of

postoperative long-term survival in CEA patients independent of other risk factors, anthropometric measures and dental status.

INTRODUCTION

The net benefit from carotid endarterectomy (CEA) is critically dependent on length of postoperative survival [1] which in turn is influenced by several factors. Such factors include age, cardiovascular risk factors, chronic obstructive pulmonary disease, renal disease, body mass index (BMI), absence of statin use and contralateral carotid occlusive disease [1–5].

The biological state of reduced physiologic reserve and increased vulnerability associated with age, i.e. frailty, reflects subclinical cardiovascular disease and has been found better than traditional surgical risk scores in estimating postoperative survival [6–10]. Frailty is an independent predictor of postoperative mortality in cardiovascular patients doubling the risk for mortality and morbidity in patients with stable cardiovascular disease, acute coronary syndromes, heart failure and surgical and other interventions [9]. Frailty can be estimated by measuring loss of muscle mass, i.e. sarcopenia, walking speed and daily activity [9].

Paraspinal muscle mass evaluated from computed tomography (CT) images predicted survival in patients undergoing elective open and endovascular AAA repair [11,12] and in general surgery, and vascular patients [13]. Similarly, masseter muscle area measured from CT images predicted mortality and correlated well with psoas muscle area in elderly patients subjected to blunt trauma [14] and traumatic brain injury [15]. In line with this, masseter muscle tension, chewing ability, dental status and physical fitness have previously been shown to be closely associated in elderly care home residents [16].

Sarcopenia related to stroke differs from that related with aging in that it is characterized by rapid loss of muscle mass, structural alterations in the muscle and bilateral difference in physical and functional performance determined by the brain lesion whereas aging-related sarcopenia occurs slowly without structural alterations or bilateral differences [17]. In stroke patients, imbalanced neurovegetative status may also induce a direct catabolic signal to the muscle [17]. Sarcopenia related to stroke is likely unilateral while that related with aging and frailty is reflected bilaterally.

At present, sarcopenia is not preoperatively evaluated nor is the evaluation easy to implement in clinical practice. Furthermore, to the best of our knowledge, no data exists on the effect of sarcopenia on postoperative long-term survival after carotid endarterectomy which is an important factor when considering the net benefit from carotid surgery. We hypothesized that sarcopenia could be easily evaluated from digital preoperative routine CT angiography (CTA) scans by measuring masseter muscle area (MA) and density (MD) and that it is an independent predictor of postoperative survival. The purpose of this study was, firstly, to ascertain the reliability of masseter muscle area and quality measurements from preoperative CTA scans of carotid endarterectomy patients. Secondly, the study sought to determine the association of sarcopenia represented by these parameters with long-term postoperative mortality in a cohort of patients treated for carotid stenosis.

MATERIALS AND METHODS

Consecutive patients from the prospective vascular registry of Tampere University Hospital (TAUH) subjected to carotid endarterectomy during years 2004-2010 (n=382) were retrieved, and those with available digital preoperative computed tomography (CT) and CT angiography (CTA) scans (n=242, 63.4%) comprised the final study population. CTA was implemented in our clinical practice during 2004, therefore the majority of excluded patients were operated during the early years from 2004 to 2006 (n=93). The demographics, risk factors, indications and degrees of carotid stenoses of excluded patients (n=140, 36.7%) did not differ significantly from the included patients (Supplementary table 1). Since patient data were recorded in the prospective register during the operation and no patients died during the operation, the database comprises all the operated patients. Our indications were in line with published guidelines [18]. Cardiovascular risk factors obtained from the vascular registry were defined based on previous diagnoses and current medication as follows: diabetes (DM, diagnosis/insulin or oral hypoglycemic medication), arterial hypertension (HTA, diagnosis/antihypertensive medication), cardiac risk factor (diagnosis of myocardial infarction, coronary intervention, angina pectoris, ischemia on electrocardiography, congestive heart failure), pulmonary risk factor (diagnosis of chronic obstructive pulmonary disease), renal risk factor (diagnosis of renal insufficiency), peripheral arterial disease (PAD, diagnosis/peripheral vascular intervention or amputation) and dyslipidemia (diagnosis/antihyperlipidemic medication). Smoking was defined as smoking within last 5 years or current smoking.

Standard protocol approvals

The study was approved by the Ethics Committee of TAUH and was conducted adhering to the principles of the Helsinki declaration.

Radiological assessment

All study patients were routinely subjected to brain CT and CT angiography. Internal carotid artery (ICA) stenoses were determined (NASCET-criteria) and categorized (<50%, 50-69%, 70-99% and 100%) [19] by a neurointerventional radiologist (JPP). In a pilot analysis of a random set of 30 patients by three independent observes before and after sagittal and coronal tilt adjustment, head tilt was found to have a significant effect on MA measurements. Therefore, tilt alignment of the CTA sections was made according to a tangent along the lower border of arcus zygomaticus in sagittal- and along the lowest point of orbitae in coronal planes and measurements were made 20 ± 2 mm below the arcus by outlining the outer surface of masseter muscle along the fascia after which the image analysis program automatically calculated the area (mm^2) and mean density (Hounsfield Unit, HU) across the region of interest (Figure 1). Thereafter, 30 CTA scans were first randomly selected and the analysis performed in a random and blinded fashion by three independent observers and reliability was assessed by intraclass correlation coefficient analysis (ICC) for both MA and MD measurements. Consequently, after confirmation of excellent repeatability, a single rater proceeded with the rest of the scans. The presence of teeth was scored in three categories: 1) no teeth, 2) any missing teeth and 3) no evidence of missing teeth (Figure 1). Average MA (MAavg, mean of left and right MA) and MD (MDavg, mean of left and right MD) were calculated.

Survival and causes of death

Comprehensive long-term survival data on status of the patient (alive/dead) and date of death was obtained from the TAUH patient record database at 1.10.2017 which is updated in a continuous fashion by the National Population Register. Patients were considered to be alive if there was no date of death available in the register at 1.10.2017, i.e. the last date known to be alive. A possible delay of data transfer from date of death to the National Population Register is within 1-3 weeks. Therefore, the register was reviewed at 1.11.2017 to ensure that all delayed information on deaths until 1.10.2017 was recorded. This database provided full coverage of all the patients included in the study. In Finland, the death certificates are mandatory and the data on deaths is without missing cases. The outcome event was all cause death. The causes of death based on International Statistical Classification of diseases and Related Health Problems (on ICD-9 and ICD-10) classifications were obtained and divided further into cardiac (coronary artery disease, valvular heart disease, arrhythmia and congestive heart disease), cerebral (ischemic or hemorrhagic stroke, cerebral bleeding, vascular dementia), peripheral vascular (peripheral arterial disease, aneurysms) cancer, infection, trauma and other categories (Statistics Finland).

Statistical analysis

The statistical software used for analyses was SPSS 24 for Mac OS X. Continuous variables were analyzed with Mann-Whitney U-test, and Kruskall-Wallis test for independent samples and Wilcoxon signed-rank test for related samples. Intraclass correlation coefficient (ICC) was utilized to analyze reliability, i.e. intra- and interobserver variability of the measured parameters (areas, densities) measured by three independent observers. The two-way random single measurement model was selected and both consistency and absolute agreement were calculated along with 95% confidence intervals. ICC was rated as poor (less than 0.40), fair (0.40-0.59), good (0.60-0.74) and excellent (0.75-1.00). Normal distribution of CT-variables was ascertained by visually and by Levene's test. The association between clinical characteristics and masseter area and density was analyzed with adjusted and unadjusted linear regression analysis. Predictors of survival were analyzed using Cox regression proportional hazards analysis first as univariable analyses. The effect of age, gender, BMI, body surface area (BSA), and tooth loss on CT variables were examined, and included in the multivariable models due to their strong *a priori* association with masseter parameters [20]. Testing of the proportional hazards assumption was based on log-log-plots and the correlation of survival rankings with Schoenfeld residuals. All variables except for age fulfilled this assumption. Consequently all multivariable models using Cox-regression were performed with age as a time-dependent covariate. Kaplan-Meier survival analysis was utilized to plot the overall survival. Multivariable models testing the independent associations of risk factors with mortality were adjusted with factors associating nominally with mortality ($P<.1$) in univariable analysis. Missing values for ipsilateral stenosis (n=32) and dental status (n=33) were replaced by values calculated by multiple imputation (mice package for R) [21]. Subjects with a transient event as an indication (amaurosis fugax and transient ischemic attack) were pooled to a single category because the mortality risk attributable to these events was identical. Age, gender, body surface area (BSA) and dental status were included in the multivariable models due to their strong *a priori* association with masseter parameters [20]. For estimation of BSA (and BMI) body weight and height was available only for a subpopulation (n=158, 65.3%). Due to the large amount of missing data, BSA was included in the analyses separately and without replacing missing values. The reported hazard ratios (HRs) related to main exposure variables (MAavg and MDavg) correspond to one standard deviation increase in exposure variables. Cox regression model with penalized splines were used to evaluate (plot) the relationship between masseter area and mortality (psplines package for R). According to power analysis based on a pilot study of 100 patients, 242 patients were needed (power of 0.9) to detect a significant difference (alpha=0.05) in postoperative survival between different MA and MD categories.

RESULTS

Patient characteristics

The median age of the patients was 71.0 years (IQR 13.0). Less than one third of the patients were women (29.8%) and the majority of patients had hypertension (76.9%), cardiac risk factor (52.9%), dyslipidemia (55.8%), ipsilateral stenosis of 70-99% (85.7%), and contralateral stenosis of <50% (55.3%). The main indications for surgery were TIA (35.1%) and ischemic stroke (34.7%) while a minority of the operations was due to asymptomatic stenosis (13.2%). The side of the operation was left in 55.0% and right in 45.0% of cases (Table 1). A majority of the patients were on beta blockers (62.2%), statins (87.2%), antiaggregatory medication (73.1%), anticoagulants (37.8%), antihypertensives (75.6%) whereas a smaller group received oral antidiabetic medication (25.6%) or insulin (16.0%).

Determinants of masseter area

In univariable analyses the strongest factors associated with with MAavg were BSA, gender, age and dental status ($p<0.001$ for all) (Table 2). In multivariable analyses, the only significant factors linked to MAavg were BSA ($p<0.001$) and dental status ($p=0.021$). For MDavg, the associating factors were gender, dental status and age ($p<0.01$ for all comparisons in univariate analyses as well as in multivariable analysis (Table 2). Overall, BSA showed clearly stronger association with MAavg when compared to BMI. BMI did not correlate significantly with MDavg.

Inter- and intraobserver variability of the CT measurements

MAavg and MDavg demonstrated excellent reliability based on ICC analysis by three independent observers (ICC 0.865-0.971 and p<0.001 for all) (Table 3).

Association of preoperative masseter area and density with long-term mortality

The median follow-up time was 68.5 months (range 3-163 months). During the follow-up, 104 patients (43.0%) of the study population died. No patients were lost during follow-up. A Kaplan-Meier survival plot is presented (Figure 2).

In univariable analysis, MAavg associated significantly with mortality with one SD increase corresponding with a lower risk for death (HR 0.72, with 95% CI 0.59-0.88, p=0.001) (Table 4). MDavg was not significantly connected to mortality (HR 0.92, 95% CI 0.76-1.12, p=0.423) (Table 4).

Factors associated significantly with the measured CT parameters (MAavg and MDavg) and factors nominally connected (p<0.1) to mortality in univariable analyses (age, BMI, BSA, renal risk factor, ipsilateral stenosis, indication category, teeth) (Table 4) were selected for multivariable analysis. In the resulting multivariable Cox regression analysis, increased MAavg remained a predictor of lower mortality (HR 0.76, 95% CI 0.61-0.96, p=0.023) independent of age (HR 1.05, 95%CI 1.02-1.07, p=0.001), female gender, BMI, renal insufficiency, ipsilateral stenosis, indication category, and presence of teeth (Table 4). In a similar analysis, MDavg did not associate with mortality (HR 1.01, 95% CI 0.81-1.26, p=0.942). The development of risk of death across the continuum of MAavg shows an inverse linear relationship between MAavg and mortality with possible tendency for exponential growth in the risk of death when approaching the lowest end of the MAavg range (Figure 3). The risk of death was linearly associated with age (Supplementary Figure 1).

In order to verify that masseter area associates with mortality also independently of BSA, which was the most significant determinant of MAavg, the same multivariable analysis was repeated in a subpopulation with available BSA measurement (n=182, representing 63.6% of the entire study population). Despite the lower sample size, the association persisted (0.75, 95% CI 0.59-0.97, p=0.030).

Causes of death

Of the 104 dead patients, the causes of death were cardiovascular in 29.8% subclassified further into cerebral (13.5%), cardiac (15.3%), and peripheral vascular (1.0%) causes. Remaining deaths were due to cancer (7.7%), infections (1.0%), trauma (1.0%), and other causes (5.8%).

DISCUSSION

According to our results, average masseter muscle area (MAavg) and density (MDavg) can be easily and reliably measured after sagittal and coronal tilt adjustment below the zygomatic arch from routine preoperative CTA images in carotid endarterectomy patients. The independent factors contributing to MAavg are BSA and dental status while for MDavg these are gender, dental status and age. Increased MAavg remains a predictor of lower mortality independent of age, female gender, BMI, renal insufficiency, ipsilateral stenosis, indication category, and presence of teeth whereas MD did not associate with mortality. This effect remains independent of BSA which is the most significant determinant of masseter area.

Our results of an inverse relationship between MAavg and mortality concur with previous studies which found MA to predict mortality in elderly patients subjected to blunt trauma [14] and to traumatic brain injury [15] and this, in turn, suggests that MA could be used as a surrogate for sarcopenia. As in our study, the association has been mostly uninfluenced by age suggesting that despite correlating with age, masseter area provides independent prognostic value when predicting death after trauma or after CEA. In the study by Hu et al. [15], sarcopenia was defined as a decrease in masseter area of one standard deviation or more from the sex-based mean. The mean MA in these sarcopenic patients was 281 mm^2 in men and 224 mm^2 in women and they were at increased risk of 30 day mortality (80.0% vs. 50.6%) compared to those with greater MA [15]. This finding is in line with our analyses showing the inverse association between MA and mortality and suggests that there may be a different threshold for increased mortality according to gender. The present study was not powered to analyze gender differences and the association of MAavg with mortality persisted despite adjustment by gender. In addition to age and gender, other parameters with strong *a priori* association with masseter parameters (BMI, body surface area (BSA), tooth loss) were also examined and included in the multivariable models [20]. In the present study, most of the significant risk factors previously associated with perioperative risk and long term risk among CEA patients in large registry studies and clinical trials [22,23] were also recorded and considered in the analyses. Although some of the previously discovered risk factors were not associated with the risk of long term mortality (contralateral stenosis and BMI) in our study, these factors were recorded to the vascular registry online (i.e. at the time of the operation) by treating surgeons and thus with no information of the future outcomes. The smaller sample size in our study as compared to the previous large trials and registry studies, most likely explains the lack of power to detect significant associations between these factors and mortality. The previous observation on the effect of age, gender and dental status on MA and MD [20] was replicated in the present study which supports our observations and methodology. There were no interactions between age and MA that would suggest the association between MA and mortality would be influenced by age. The age and MA associated significantly but both also independently with death in the same model which confirms that they provide information that is independent regarding survival. Our exploratory analysis showed that there is no clear cut-off for risk across the continuum of masseter area which suggests that categorization of masseter area would lead to better risk stratification results.

The primary shortcoming of our study is that it was conducted retrospectively. However, the prospective vascular registry used is annually audited for data loss and consistency. In addition, all data entries on surgical operations are made already in the operation room to ensure all operated patients are entered. All vascular patients are treated in a single center, and the patient sample in this study was collected from a cohort comprising all consecutive carotid endarterectomy patients with CTA imaging available. No patients died within 30 days from the operation. During the study period, carotid artery stenting was performed only seldom and these cases were excluded from the analysis. We started using CTA for the diagnostics in 2004. Therefore the majority of excluded patients are those treated at the beginning of the study period. We found no differences in demographics, risk factors, indications or degrees of carotid stenosis between those included and excluded in the study which makes availability of CTA an unlikely source of bias. In Finland, determination of cause of death has been based on autopsy in approximately 30% of all deaths in the past two decades (www.tilastokeskus.fi) which is high compared with other European countries. The death certificates of all deceased, whether or not they underwent autopsy, are reviewed by the district forensic physician and therefore the amount of patients with missing date or cause of death is negligible. The potential bias caused by delayed entry of date of death into the National Population Register was eliminated by re-checking the information 1 month after end of follow-up. The official cause of death has been demonstrated to be an accurate means of evaluating disease specific mortality in Finland[24]. This adds to the reliability of the present study. Our study patients were of Caucasian origin and with respect to stroke cases, limited to those with mild-to-moderate strokes, which restricts the generalizability of our results. Finally, as postoperative CTA imaging was not routinely performed, the effect of the operative procedure itself on MA and MD could not be estimated although it is an interesting future research topic.

SUMMARY AND CONCLUSIONS

-After sagittal and coronal tilt correction, MA and MD can be reliably measured from preoperative routine CTA images

- MAavg but not MDavg provides long-term predictive value independent of age, female gender, BMI, renal insufficiency, ipsilateral stenosis, indication category, and presence of teeth independent of BSA, which is the most significant determinant of masseter area.

-Results need to be validated in independent cohorts and studies powered to stratify for different indication categories.

Average masseter area but not density measured from a preoperative CTA-scan provides a reliable estimate of postoperative long-term survival in CEA patients independent of other risk factors, anthropometric measures and dental status.

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CONFLICTS OF INTEREST STATEMENT

No conflicts of interests.

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FIGURE LEGENDS

Figure 1. Representative preoperative images of carotid endarterectomy patients demonstrating the sagittal tilt and coronal tilt measurement (a), the measurement of masseter area and density before and after tilt correction (b) where masseter area (A) and density is shown. The grading of presence of teeth: no teeth any missing teeth, and no evidence of missing teeth (c).

Figure 1.

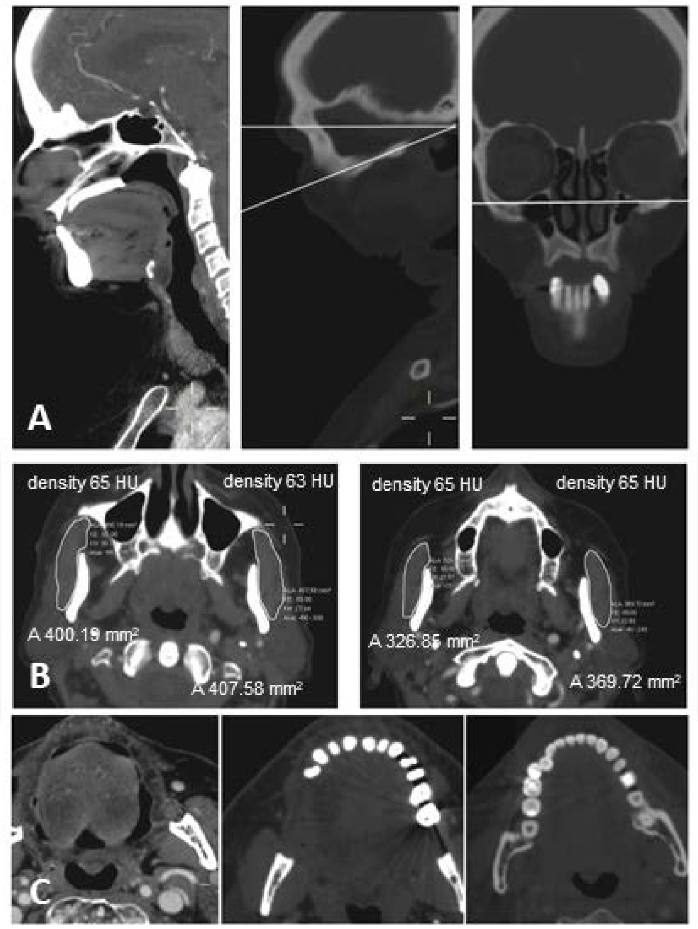


Figure 2. Kaplan-Meier survival plot of carotid endarterectomy patients.

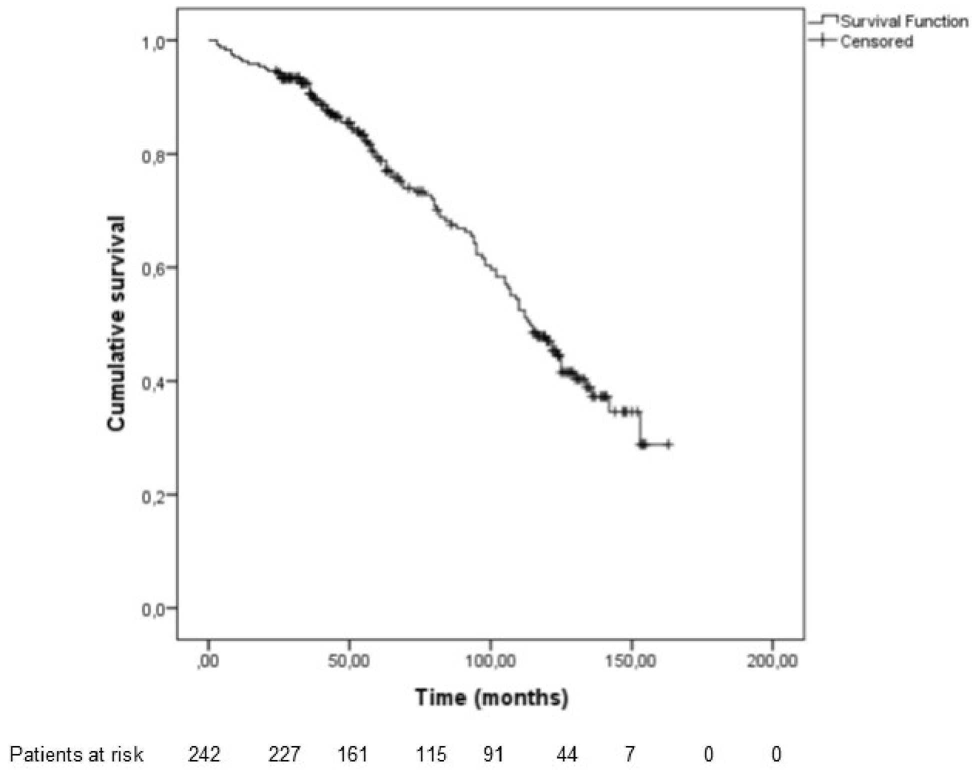
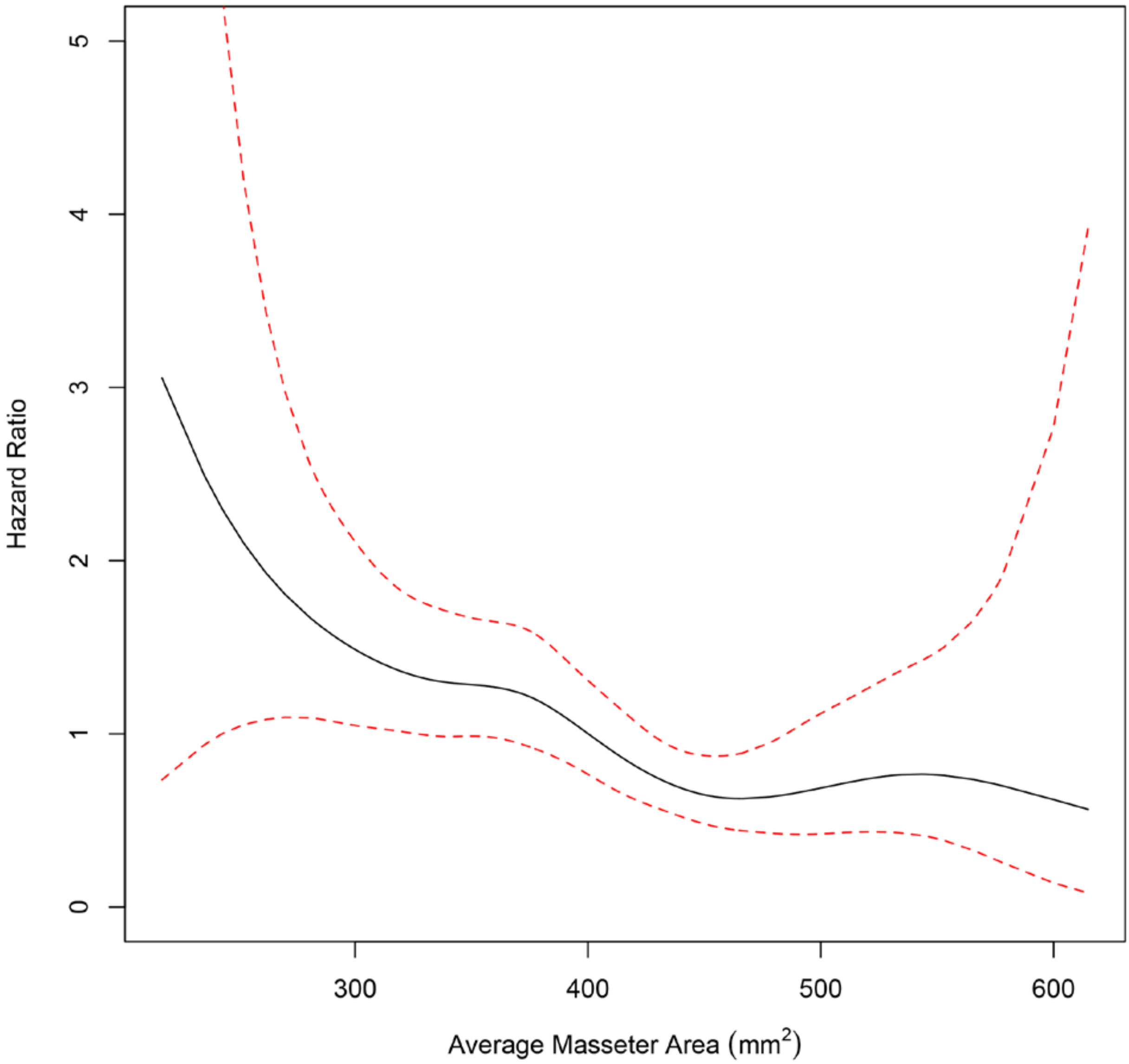


Figure 3. The development of risk of death (hazard rate) across the continuum of average masseter area (mm^2) in carotid endarterectomy patients. The model was adjusted with age, gender, BMI, renal insufficiency, ipsilateral stenosis, indication category and dental status.



TABLES

Table 1. Characteristics of carotid endarterectomy patients.

Risk factor	n=242	
Age, median (IQR)	71.0	(13.0)
BMI, median (IQR)	26.8	(5.6)
BSA, median (IQR)	1.9	(0.3)
Female, n (%)	72	(29.8)
DM, n (%)	71	(29.3)
HTA, n (%)	186	(76.9)
Cardiac, n (%)	128	(52.9)
Dyslipidemia, n (%)	135	(55.8)
Renal, n (%)	5	(2.1)
PAD, n (%)	37	(15.3)
Pulmonary, n (%)	25	(10.3)
Smoking, n (%)	68	(28.1)
IL-stenosis		
<50%, n (%)	2	(0.9)
50-69%, n(%)	28	(14.3)
70-99%, n (%)	180	(85.7)
100%, n (%)	0	(0)
CL-stenosis		
<50%, n (%)	134	(55.3)
50-69%, n (%)	64	(26.4)
70-99%, n (%)	34	(14.0)
100%, n (%)	10	(4.1)
Indication		
Asymptomatic, n (%)	32	(13.2)
Amaurosis, n (%)	41	(16.9)
TIA, n (%)	85	(35.1)
Ischemic stroke, n (%)	84	(34.7)
Side (L/R)		
Right, n (%)	109	(45.0)
Left, n (%)	133	(55.0)

Body mass index (BMI), Body surface area (BSA), Diabetes mellitus (DM), hypertension (HTA), cardiac risk factor (diagnosis of myocardial infarction, coronary intervention, angina pectoris, ischemia on electrocardiography and congestive heart failure), renal risk factor (diagnosis of renal insufficiency), peripheral arterial disease (PAD), ipsilateral (IL), contralateral (CL), transient ischemic attack (TIA). Side (L/R): the side of the index operation.

Table 2. Radiological characteristics of carotid endarterectomy patients.

	All		Age				BSA				Gender			Teeth category			
			T1	T2	T3	p	T1	T2	T3	p	M	F	p	1	2	3	p
MAavg	395.0	(110.1)	423	404	362	<.001	345	389	446	<.001	420	349	<.001	371	394	441	<.001
MDavg	53.5	(16.5)	59	53	49	<.001	55	58	58	NS	55	49	<.010	48	57	59	<.001

Masseter average area (MAavg, mm^2) and masseter average density (MDavg, Hounsfield Units) are presented as medians (interquartile range) in all patients and as medians and tertiles indicated as T1, T2 and T3 according to age, body surface area (BSA), in male (M) and female (F) genders and in different teeth categories (1=no teeth, 2=any missing teeth and 3=no evidence of missing teeth according to computed tomography analysis). P-values are calculated for linear trend using linear regression analysis.

Table 3. Intraclass correlation coefficient (ICC) analysis of preoperative CT-measurements of masseter muscles of carotid endarterectomy patients.

Variable	ICC[a]	p	ICC[b]	p
MAdx	0.785	<.001	0.784	<.001
MDdx	0.940	<.001	0.942	<.001
MAsin	0.880	<.001	0.872	<.001
MDsin	0.974	<.001	0.975	<.001
MAavg	0.870	<.001	0.865	<.001
MDavg	0.970	<.001	0.971	<.001

Masseter area right side (MAdx), masseter density right side (MDdx, masseter area left side (MAsin), masseter density left side (MDsin), average masseter average area (MAavg) and average masseter density (MDavg). [a] Model: Intraclass correlation coefficient (ICC), two-way random consistency. [b] Model: Intraclass correlation coefficient (ICC) two-way random absolute.

Table 4. Univariable Cox regression analysis of the effect of risk factors and preoperative masseter area and teeth measured from CT angiography images on long-term survival in carotid endarterectomy patients.

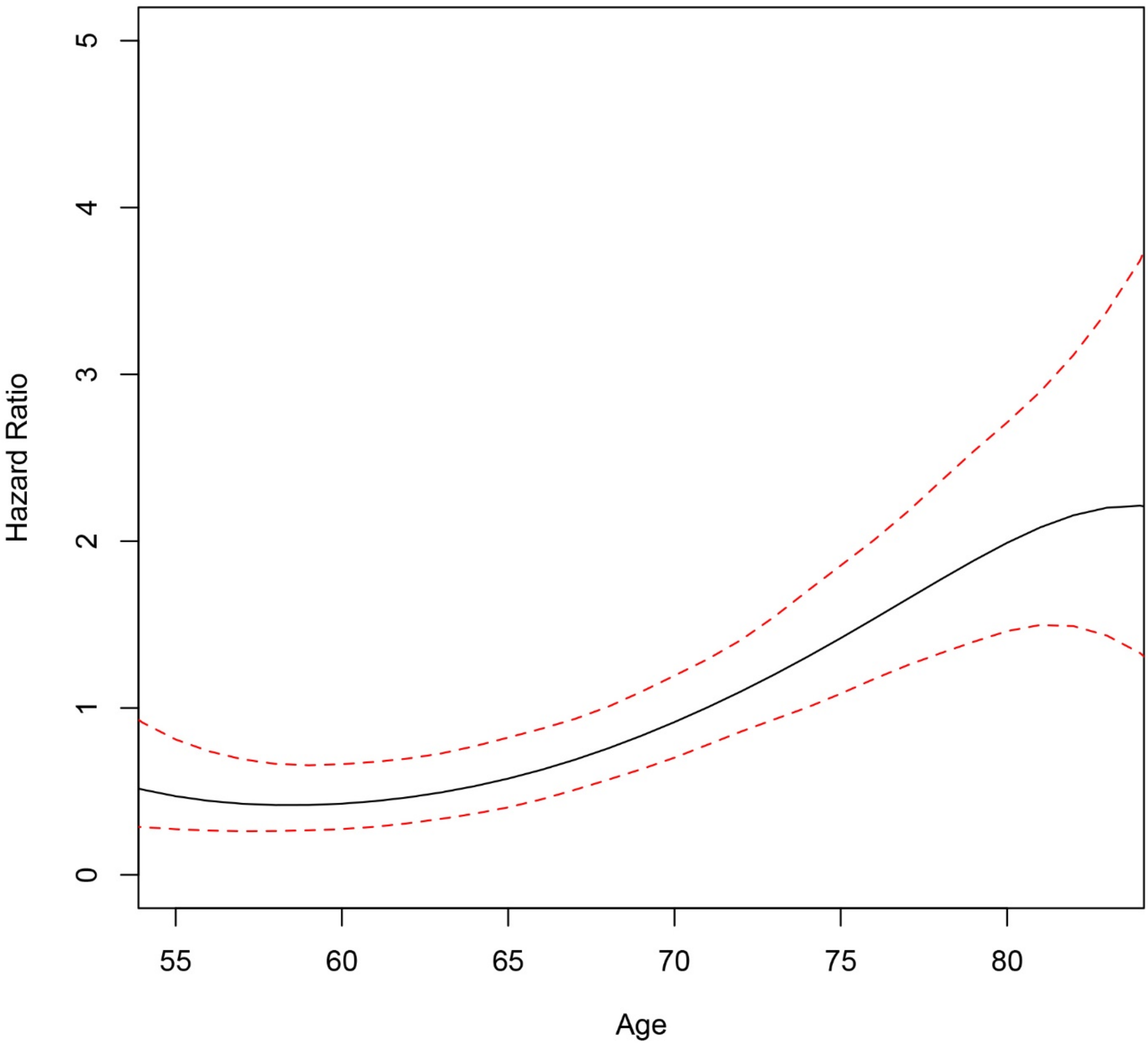
	Univariable		
Risk factor	HR	(95% CI)	p
Age	1.06	(1.03-1.08)	<.001
Female	1.01	(0.65-1.55)	0.978
BMI	0.93	(0.87-1.01)	0.070
BSA	0.65	(0.24-1.78)	0.400
DM	1.15	(0.75-1.75)	0.519
HTA	0.91	(0.57-1.44)	0.676
Cardiac	1.32	(0.89-1.97)	0.170
Dyslipidemia	0.74	(0.50-1.10)	0.137
Pulmonary	1.57	(0.81-3.04)	0.179
Renal	2.60	(0.95-7.09)	0.063
PAD	1.47	(0.89-2.42)	0.133
Smoking	0.85	(0.54-1.34)	0.482
IL-stenosis	2.32	(1.14-4.69)	0.020
CL-stenosis	1.08	(0.86-1.37)	0.505
Indication	1.43	(1.07-1.92)	0.016
Teeth	0.67	(0.49-0.92)	0.012
Side (L/R)	0.70	(0.46-1.10)	0.100
MAavg	0.72	(0.59-0.88)	<.001
MDavg	0.92	(0.76-1.12)	0.423

Cox regression proportional hazards analysis. Hazard Ratio (HR), Confidence Interval (CI), Average masseter area (MAavg), average masseter density (MDavg), female relative to male gender (Female), Body Mass Index (BMI), Body Surface Area (BSA), diabetes mellitus (DM), hypertension (HTA), cardiac risk factor (diagnosis of myocardial infarction, coronary intervention, angina pectoris or ischemia on electrocardiography and congestive heart failure), pulmonary risk factor (Pulmonary), renal risk factor (diagnosed renal insufficiency, peripheral arterial disease (PAD), current smoking (Smoking), ipsilateral (IL), contralateral (CL). Indication category: 1) asymptomatic, 2) amaurosis fugax, 3) TIA, 4) stroke. The reported hazard ratios for masseter area and density parameters correspond to 1 standard deviation increase. The presence of teeth was scored in three categories: 1) no teeth, 2) any missing teeth and 3) no evidence of missing teeth. Operation side left (L), right (R).

Table 5. Multivariable Cox regression analysis of the effect of risk factors and preoperative masseter area and teeth measured from CT angiography images on long-term survival in carotid endarterectomy patients.

Risk factor	HR	(95% CI)	p
Age	1.05	(1.02-1.07)	0.001
Gender	0.72	(0.45-1.15)	0.171
Renal	2.63	(0.91-7.59)	0.073
Indication	1.24	(0.93-1.67)	0.150
IL-stenosis	1.91	(0.95-3.84)	0.070
Teeth	0.74	(0.53-1.05)	0.093
MAavg	0.76	(0.61-0.96)	0.023

Cox regression proportional hazards analysis. Hazard Ratio (HR), Confidence Interval (CI), average masseter area (MAavg), female relative to male gender (Female), Body Mass Index (BMI), renal risk factor (diagnosed renal insufficiency), ipsilateral (IL), Indication category: 1) asymptomatic, 2) amaurosis fugax or TIA, 3) stroke. The reported hazard ratio for masseter area parameter corresponds to 1 standard deviation increase. The presence of teeth was scored in three categories: 1) no teeth, 2) any missing teeth and 3) no evidence of missing teeth.



Hazard Ratio
0
1
2
3
4
5
55
60
65
70
75
80
Age

TABLES

Supplementary table 1. Characteristics of included and excluded carotid endarterectomy patients.

Risk factor	Study patients n=242	Excluded patients n=140	p
Age, median (IQR)	71.0 (13.0)	70 (14.0)	0.100
Female, n (%)	72 (29.8)	35 (24.6)	0.260
DM, n (%)	71 (29.3)	34 (23.9)	0.233
HTA, n (%)	186 (76.9)	105 (73.9)	0.549
Cardiac, n (%)	128 (52.9)	70 (49.3)	0.494
Dyslipidemia, n (%)	135 (55.8)	89 (62.7)	0.165
Renal, n (%)	5 (2.1)	5 (3.5)	0.395
PAD, n (%)	37 (15.3)	20 (14.1)	0.724
Pulmonary, n (%)	25 (10.3)	17 (12.0)	0.639
Smoking, n (%)	68 (28.1)	48 (33.8)	0.226
<u>IL-stenosis</u>			0.915
<50%, n (%)	2 (0.8)	1 (0.9)	
50-69%, n(%)	28 (12.4)	13 (11.8)	
70-99%, n (%)	212 (87.6)	96 (87.3)	
100%, n (%)	0 (0)	0 (0)	
<u>CL-stenosis</u>			0.206
<50%, n (%)	134 (55.3)	69 (62.2)	
50-69%, n (%)	64 (26.4)	20 (18.0)	
70-99%, n (%)	34 (14.0)	21 (18.9)	
100%, n (%)	10 (4.1)	1 (0.9)	
<u>Indication</u>			0.733
Asymptomatic, n (%)	32 (13.2)	20 (14.1)	
Amaurosis, n (%)	41 (16.9)	29 (20.4)	
TIA, n (%)	85 (35.1)	51 (35.8)	
Ischemic stroke, n (%)	84 (34.7)	42 (29.6)	

Diabetes mellitus (DM), hypertension (HTA), cardiac risk factor (diagnosis of myocardial infarction, coronary intervention, angina pectoris, ischemia on electrocardiography and congestive heart failure), renal risk factor (diagnosis of renal insufficiency), peripheral arterial disease (PAD), ipsilateral (IL), contralateral (CL), transient ischemic attack (TIA).

TABLES

Supplementary table 2. Detailed radiological characteristics of carotid endarterectomy patients.

	n	mean	SD	95%CI	median	IQR
MAdx,	242	397.3	79.4	387.2-407.3	389.7	117.7
MAsin	242	397.5	79.1	387.5-407.5	396.5	111.8
MAavg	242	397.4	76.8	387.7-407.1	394.0	110.1
MDdx	242	52.1	11.9	50.6-53.6	53.0	16.3
MDsin	242	52.3	12.8	50.7-53.9	54.0	17.0
MDavg	242	52.2	11.9	50.7-53.7	53.5	16.5

Masseter area right side (MAdx, mm^2), Hounsfield Unit (HU), masseter density right side (MDdx, HU), masseter area left side (MAsin, mm^2), masseter density left side (MDsin, HU), average masseter average area (MAavg, mm^2) and average masseter density (MDavg, HU).

MULTIPLE CHOICE QUESTIONS

1. Masseter area
    - **a. Can be measured from CTA images**
    - b. Can be reliably measured without tilt correction
    - **c. Must be measured after tilt correction**
    - **d. Is associated with body surface area**
    - e. Is not associated with dental status
2. Masseter area
    - a. Is not a predictor of postoperative mortality after carotid endarterectomy
    - **b. Is a predictor of postoperative mortality after carotid endarterectomy**
    - c. Is a predictor of postoperative mortality but not independent of age, gender, BMI, renal insufficiency, ipsilateral stenosis, indication category and presence of teeth
    - **d. Is a predictor of postoperative mortality independent of age, gender, BMI, renal insufficiency, ipsilateral stenosis, indication category and presence of teeth**
    - **e. Age is associated with masseter area**