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**CRITERIA FOR SURGICAL
TREATMENT OF THE INTRACRANIAL
HYPERTENSION CAUSED BY
CEREBRAL INFARCTION**

Summary of the Doctoral Thesis
for obtaining the degree of a Doctor of Medicine

Speciality – Surgery

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LIST OF ABBREVIATIONS

ACA	Anterior cerebral artery
MCA	Middle cerebral artery
PCA	Posterior cerebral artery
UMA	Updated metaanalysis
CI	Cerebral infarct
CIV	Cerebral infarct volume
DCE	Decompressive craniectomy
CT	Computed tomography
GCS	Glasgow Coma Scale
ICH	Intracerebral hemorrhage
ICP	Intracranial pressure
ICU	Intensive Care Unit
MR	Magnetic resonance
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health stroke scale
BMT	Best medical treatment
RCT	Randomized controlled trials
SD	Standart deviation
SOE	Space-occupying edema
CI	Confidence interval
95% CI	Confidence interval of 95%

INTRODUCTION

Literature review and topicality

Despite significant progress in stroke care achieved over the last decades, cerebral infarction (CI) still remains one of the most frequent cause of disability and second largest cause of death worldwide.

The involvement of more than 50% of the middle cerebral artery (MCA) territory produces most devastating, massive hemispheric, space-occupying supratentorial infarct, which is known as malignant MCA stroke. Such massive hemispheric infarctions occur roughly in 10% of all ischaemic strokes. In such a cases, up to 80% of patients die within the first week due to brain herniation caused by infarct-related, space-occupying edema, but survivors remain severely disabled.

Standard management modalities for acute ischaemic stroke according to guidelines and additional measures available at the intensive care unit (ICU) have not proven to reduce mortality or disability as final outcome in randomized controlled trials (RCT).

Due to limitations of medical therapies, decompressive craniectomy (DCE) with duraplasty has been proposed as surgical option. The procedure itself is not new but was performed rarely for MCA stroke before the 1990s, primarily because of concerns that it would result in survival with overwhelming neurological impairment and handicap. However, with improvements in postoperative critical care, there has been a resurgence of interest in hemicraniectomy over the past 20 years.

Until recently, there was no available evidence on potential benefits of DCE from randomised controlled trials. The results of three completed European and one Chinese RCTs have been published recently. Trials clearly

showed that DCE provides increased probability of survival and favorable clinical outcome in part of narrowly selected population. Does the surgery increases survival at the expense of an increased proportion of survivors with very severe disability - remains questionable in up to 60 years old patients, but in older patients there is a tendency of increased amount of very severely disabled survivors observed.

Although published studies provide convincing general information about positive effects of DCE, statistically reliable data and evidence, that would allow to justify the choice of surgery (provide clear indications and contraindications) and predict its effectiveness in every single patient are still lacking.

Statement of the problem and scientific novelty

Surgical treatment of critically ill “malignant” MCA stroke patients is a complex clinical and organizational task that requires combined multi-team approach with involvement of ICU, neurological, neurosurgical and many other services. In order to identify cost effective treatment options and to plan resources that are needed to undertake flow of such a difficult group of patients, there is a great need of estimation of approximate amount of patients per year that would potentially be considered for such a treatment.

To provide maximum benefit of surgery and limit risks - correct patient selection for DCE is a paramount of importance. Identification of demographic and clinical criteria with statistically significant prognostic value on outcome after surgery would allow to define indications and contraindications of DCE more narrowly.

Objectives of the study

- By conducting a retrospective study determine amount of MCA stroke patients, who could be potentially considered as candidates for application of decompressive craniectomy.
- In a prospective study, reaching number of malignant MCA stroke patients which is equivalent to DECIMAL study, identify science-based criteria with prognostic value on outcome after application of the decompressive craniectomy.

Hypotheses

- Decompressive craniectomy is potentially considered in 5-10% of all MCA stroke patients.
- Patient age is a demographic criterion with prognostic value on clinical outcome after application of the decompressive craniectomy.
- Cerebral infarct volume is a clinical criterion with prognostic value on clinical outcome after application of the decompressive craniectomy.
- NIHSS score is a clinical criterion with prognostic value on clinical outcome after application of the decompressive craniectomy.

Tasks of the research

Research tasks derive from problems, objectives and hypotheses discussed in the thesis, they are as follows:

- To investigate the percentage of MCA stroke patients who died from brain stem herniation and could be considered as candidates for application of the decompressive craniectomy.
- To evaluate the prognostic value of patient age on clinical outcome after decompressive craniectomy.
- To evaluate the prognostic value of cerebral infarct volume on clinical outcome after decompressive craniectomy.
- To evaluate the prognostic value of NIHSS score on clinical outcome after decompressive craniectomy.

Ethical concerns

The study was approved by the Committee of Ethics of Latvian Society of Neurosurgeons and Committee of Ethics of Pauls Stradins Clinical University Hospital.

MATERIALS AND METHODS

Retrospective part of the study included all patients with a final clinical diagnosis of MCA stroke, who were admitted to Pauls Stradins Clinical University Hospital during the period from 1st January 2010 until 31st December 2010.

With an aim to assess the epidemiology of MCA stroke, authors estimate frequency of the malignant MCA stroke and number of patients who could potentially be considered as candidates for application of decompressive craniectomy, data from hospital medical records and archive of the digital radiological images were analyzed. The following anthropological, clinical and radiological data were recorded:

- patient age;
- sex;
- severity of symptoms of stroke (classified by NIHSS scale);
- whether there was or there was no evidence of space-occupying edema (SOE) in CT or MRI scans at any time of period of treatment;
- whether there was or there was no observations of clinical signs of intracranial hypertension at any time of period of treatment;
- clinical outcome at discharge (alive/dead);

Depending on severity of symptoms all patients were divided into two groups:

1. severe MCA stroke;
2. mild MCA stroke.

We defined MCA stroke as severe if patient had score of at least 7 in NIH Stroke Scale motor evaluation (plegic in one extremity and with deep

weakness in another on the same side) at presentation. If the motor deficit was milder patient was defined as mild MCA stroke.

Both groups were subdivided by criteria whether there was or there was no radiological evidence of SOE on CT or MRI images at any time. As evidence of SOE we defined compression of lateral ventricles with or without midline shift, with or without compression of basal cisterns.

Overall mortality rate, mortality rates in groups and subgroups were identified. Based on clinical notes and radiological images cause of death was investigated among those who died.

A sequential design-based, **prospective**, randomized, controlled trial was carried out involving all patients meeting the inclusion criteria admitted to Pauls Stradins Clinical University Hospital, Riga Eastern Clinical University Hospital, clinic „Gaiļezers” and „Vidzemes slimnīca” Ltd. during the period of 2008-2012.

The inclusion criteria into the study were as follows:

- age of at least 18 years of both sexes with no other serious prestroke conditions that could affect a clinical course;
- major space-occupying cerebral infarction of at least 50% of the MCA territory as defined by computed tomography (CT) with or without additional infarction in the territory of the anterior or posterior cerebral artery on the same side or CIV of $>145\text{ cm}^3$ as defined by magnetic resonance (MRI) imaging;
- acute onset of corresponding clinical signs and symptoms (NIHSS score ≥ 16);
- no absolute contraindications to perform DCE and possibility to start surgery within 99 hours from onset of symptoms;

The exclusion criteria were as follows:

- the mRS score of 2 or more before stroke or other serious prestroke conditions that could affect a clinical course and outcome;
- Glasgow Come Scale (GCS) score of 5 or less;
- known coagulopathy or systemic bleeding disorder;
- haemorrhagic transformation of the infarct;
- contraindication for anesthesia.

Patients fulfilled the inclusion criteria were randomised (one-by-one randomization) into one of the two groups:

- DCE plus the best medical treatment group;
- best medical treatment alone group (BMT).

After enrolling into the trial the following data were recorded in both groups:

- patient age;
- sex;
- side of the infarct (right/left);
- time in hours from the onset of symptoms until inclusion in the study (BMT group) or until the surgery (DCE group);
- cerebral infarct volume measured on CT or MRI scans (no older than 3 hours before surgery (DCE) or including into the trial (BMT) according to the formula $0.5 \times A \times B \times C$, where A is the largest diameter of the infarct and B is the largest perpendicular diameter. The third vertical diameter (C) was determined by summing the thicknesses of the slices in which the lesion was visible;
- NIHSS score;
- GCS score.

Consent of surgical treatment was obtained according to the standard protocols of the hospital - the patient or his legal representative signing the form.

Medical management (including postoperative) according to current guidelines (at period of study) was conducted in either a stroke unit or an ICU setting. Patient care at posthospital stage took place either at home or in social care institutions.

A parenchymal ICP monitoring gauge was implanted only for those in the DCE group, who had no signs of a cerebral midline shift on scans to avoid performing DCE in case if fatal brain edema is not going to develop. Decompression was performed if there were signs of elevated intracranial pressure on scans and clinically or ICP was more than 25 mm Hg for more than 1 hour despite the maximal conservative treatment.

Ipsilateral to the stroke, DCE of at least 12 cm in anterior-posterior, and 10 cm in vertical diameter was done by removing the parts of the frontal, parietal, temporal, and occipital squama with removal of additional temporal bone so that the floor of the middle cerebral fossa could be reached. The wide durotomy was performed, and a dural patch was placed into the incision to enlarge the intradural space. The infarcted brain tissue was not resected. The position of temporalis muscle was approximated and the skin flap was then sutured.

Clinical outcomes were evaluated at 6 and 12 months after the treatment. The primary outcome measure was overall survival and score of mRS dichotomized between favorable (mRS score 0–4) and unfavorable (mRS score 5–6).

Secondary analysis included a dichotomization of patients in DCE group into subgroups according to following criteria:

- age (dichotomized at 60 years);
- CIV (dichotomized at 390 cm³);

- NIHSS score (dichotomized at 24).

Subgroup analysis was performed to identify impact of every of abovementioned criteria on outcome.

Lifespan in days was determined in those who died.

For the surgical group cranioplasty was not performed before the outcome evaluation to avoid interfering with the outcome measure.

Data processing and statistical analysis was done by using Statistical Package for the Social Sciences (SPSS) program version 20.0 and MS Excel 2010 software. Statistical significance was defined as a p value of less than 0.05.

For the distribution normality testing Shapiro-Wilk W test or Kalmogorov-Smirnov test was used.

Association between age and mortality/clinical outcome was evaluated by logistic regression analysis. For the creation of postoperative mortality and clinical outcome prediction model, coefficients obtained from the logistic regression analysis were used. ROC (Receiver Operating Characteristic) curves were used to identify the threshold values of two comparable groups. In order to characterize the quality of the threshold AUC - area under curve and its 95% confidence interval was used.

The survival analysis was performed with the Kaplan-Meier method. The survival curves were compared by log-rank test.

Comparison of parametric data was made by t-test, while the non-parametric data comparison was made by the Pearson chi-square test (χ^2) or in case of small group (<5) with Fisher's exact test. Mann-Whitney U test was used to compare lifespan of those who died in both groups of prospective part of study.

Levene's test was used to compare age dispersion in the male and female groups of prospective part of study.

RESULTS

Demographics of population in retrospective part of the study

A total of 748 MCA stroke patients were included in the retrospective part of the study. The mean age of the patients was 73.9 years (range from 37 to 97 years), 464 (62%) were women. Gender proportions graphically are shown in Figure 1.

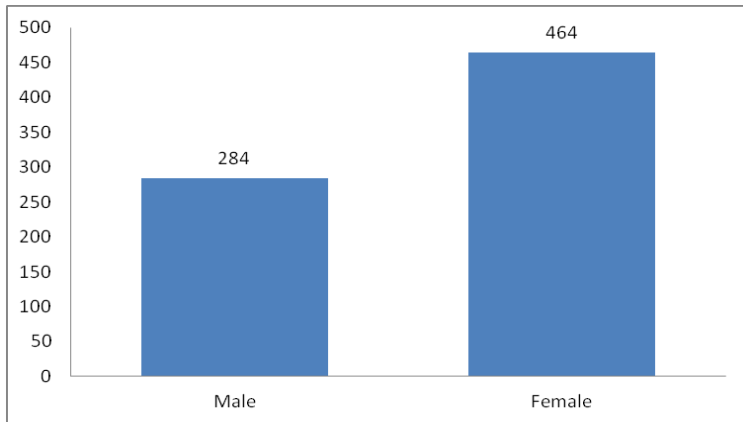


Figure 1. Gender proportions in retrospective part of the study

The proportion of women was statistically significantly higher than in men ($p < 0.05$). Approximate ratio between men and women in a given time period was 1:1,6.

Overall mortality was 12.56%.

Mortality in groups of mild and severe stroke

There were 548 (73.26%) patients in the group of mild stroke with 2.6% (n=14) mortality rate and 200 (26.74%) patients in group of severe stroke with 40.0% (n=80) mortality rate.

Mortality was statistically significantly lower (Fisher's test, $p < 0.05$) in group of mild MCA stroke. Comparison of mortality rates is shown in Table 1 and Figure 2.

Table 1

Comparison of mortality in groups of mild and severe stroke

	Mild MCA stroke	Severe MCA stroke	p value
Alive	97,44%	160%	p=0,0001
Dead	2,56%	40%	
Total	100%	100%	

Amount of survivors in mild MCA stroke group many times exceeds amount of deceased patients, while in group of severe MCA stroke difference between amounts of survivors and deceased patients is much smaller (Figure 2).

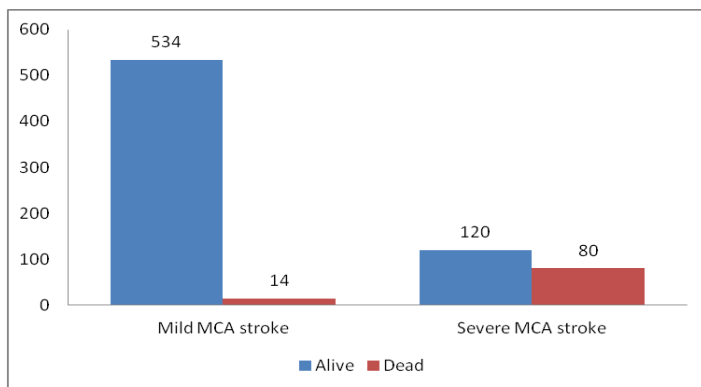


Figure 2. **Mortality proportions in groups of mild and severe MCA stroke**

In the group of mild MCA stroke in 22 cases (4.01%) radiological evidence of space-occupying edema (SOE) was found but none of these patients died. In other 526 (95.99%) cases there was no evidence of SOE, however, 14 (2.56%) of these patients died. Most of the deaths ($n=9$) in this subgroup were related to comorbidities (pulmonary embolism, myocardial infarction etc.) and in other 5 cases the cause of death was not clearly identified.

Overall mortality in the group of severe MCA stroke was 40% ($n=80$). In 97 cases evidence of SOE with 51.6% ($n=50$) mortality was found. In the subgroup of severe MCA stroke patients with radiological evidence of SOE, mortality was significantly higher (Fisher's test, $p<0.05$) comparing to subgroup of severe MCA stroke patients without evidence of SOE.

In the group of severe MCA stroke statistically significant association of evidence of SOE and mortality was found (Fisher's test, $p<0.05$), while, in contrast, in group of mild MCA stroke such correlation was not observed. Mortality distribution depending on whether there was or there was no radiological evidence of SOE is illustrated in Table 2.

Table 2

Mortality distribution depending on radiological evidence of SOE in groups of mild and severe MCA stroke

		SOE evidence	No SOE evidence	p value
Mild MCA stroke	alive	22	512	p=1
	dead	0	14	
Severe MCA stroke	alive	47	73	p=0.0015
	dead	50	30	

Mortality in the group of severe MCA stroke varies significantly depending from fact whether there is or there is no radiological evidence of space-occupying edema. In cases with evidence of edema, the mortality rate exceeds the rate of survival, whereas in cases where edema was not observed, the number of survivors significantly exceeds the number of deceased patients (Figure 3).

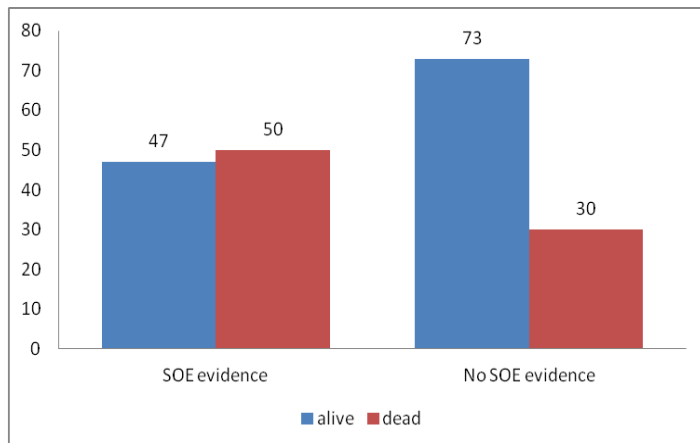


Figure 3. Mortality proportions in severe MCA stroke group depending from fact whether there is or there is no radiological evidence of SOE

Analysis of medical records shows that 49 of 50 patients in group of severe MCA stroke with radiological evidence of SOE died due to brain stem herniation. In the remaining group of 103 severe MCA stroke patients where radiological evidence of SOE were not obtained mortality was 29.1% (n=30). In total there was 49 patients (or 6.6% of all patients) in severe MCA stroke group who died having radiological evidence of SOE and appropriate clinical course.

Demographics of population in prospective part of the study

In total forty-four patients meeting the inclusion criteria were enrolled into trial during the period 2008-2012. The mean age of the patients was 59.6 years (range from 41 to 74 years) the standart deviation of 7.64, age range is 33 years. The modal age is 53 years, the median age is 60 years, therefore there was 50% of the patients between the age of 41 and 60 years. Patient age asymmetry coefficient is -0.33 so the age distribution is with negative or left asymmetry. Shapiro-Wilk test shows that the patient age distribution corresponds to normal distribution ($p=0.67$).

Groups were equal in terms of baseline characteristics as sex, age, infarct side, CIV, NIHSS score. The baseline characteristics of patients are detailed in Table 3.

Table 3

Baseline characteristics of patients

		BMT (n=22)	DCE (n=22)	p value
Sex	male	10	14	p=0.36
	female	12	8	
Age	mean±SD	61.7±7.3	57.5±7.5	p=0.07
	range	49-74	41-68	
Hemisphere	dominant	11	11	p=1
	nondominant	11	11	
CIV, cm ³	mean±SD	381.9±128.2	388±130.7	p=0.88
	range	145-731	150-623	
NIHSS score at surgery (DCE), or at time of enrollment (BMT)				p=0.18
	mean±SD	21±3	22±3.3	
	range	16-29	16-28	
Time from onset to surgery (DCE), h	mean±SD	-	30.8±20.6	
	range	-	8-99	

Clinical outcomes

There was a significant life-saving effect of surgery - overall survival rate in DCE group was 40.9% (n=9) at 6 months and 36.4% (n=8) at 12 months (none of them older than 60y) versus in BMT group 4.5% (n=1) at 6 and 12 months respectively. For detailed mortality of both groups at 6 and 12 months see Table 4.

Table 4

6 and 12 month mortality in BMT and DCE groups

		BMT	DCE	p value
Mortality after 6 months	alive	4.5%	40.9%	p=0.0093
	dead	95.5%	59.1%	
Mortality after 12 months	alive	4.5%	36.4%	p=0.021
	dead	95.5%	63.6%	

The number of survivors with a favorable clinical outcome (mRS 0-4) also statistically significant ($p < 0.05$) differed between the groups in favor of the surgery - 36.4% ($n = 8$) at 6 months and 31.8% ($n = 7$) at 12 months in the surgery group versus 4.5% ($n = 1$) at 6 and 12 months in BMT group. Details of outcomes in both groups at 6 and 12 months shown in Table 5.

Table 5

Clinical outcomes at 6 and 12 months in BMT and DCE groups

		BMT	DCE	p value
Outcome at 6 months	favorable (mRS 0-4)	4.5%	36.4%	p=0.021
	unfavorable (mRS 5-6)	95.5%	63.6%	
Outcome at 12 months	favorable (mRS 0-4)	4.5%	31.8%	p=0.0459
	unfavorable (mRS 5-6)	95.5%	68.2%	

In majority of the survivors in DCE group favorable clinical outcome was observed. The only survivor in BMT group one year after had an mRS score of 4. Details of the clinical outcome in terms of mRS score in both groups shown in Tables 6 and 7.

Table 6

Distribution of outcomes by mRS in both groups at 6 months

	mRS 2	mRS 3	mRS 4	mRS 5	mRS 6	Total
BMT	-	-	1 (4.5%)	-	21 (95.5%)	22
DCE	2 (9.1%)	4 (18.2%)	2 (9.1%)	1 (4.5%)	13 (59.1%)	22

Table 7

Distribution of outcomes by mRS in both groups at 12 months

	mRS 2	mRS 3	mRS 4	mRS 5	mRS 6	Total
BMT	-	-	1 (4.5%)	-	21 (95.5%)	22
DCE	2 (9.1%)	3 (13.6%)	2 (9.1%)	1 (4.5%)	14 (63.6%)	22

In general, the deceased patients in both study groups make up the biggest proportion. However, at six months from the date of illness onset in best medical therapy group only one patient had favorable clinical outcome, whereas in the decompressive craniectomy group eight patients with favorable outcomes were observed.

As can be seen, higher survival rates in surgery group are at least partially generated at the expense of survivors with very severe disability (mRS of 5). Proportional distribution of clinical outcomes by mRS in both groups are shown in Figures 4 and 5.

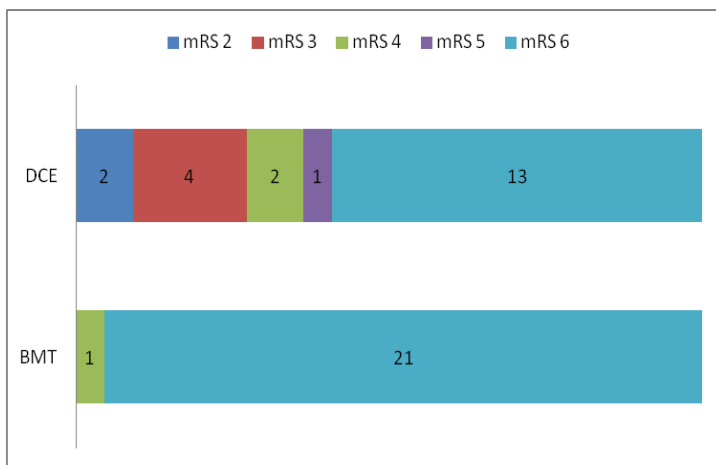


Figure 4. **Proportional distribution of clinical outcomes by mRS in both groups at 6 months**

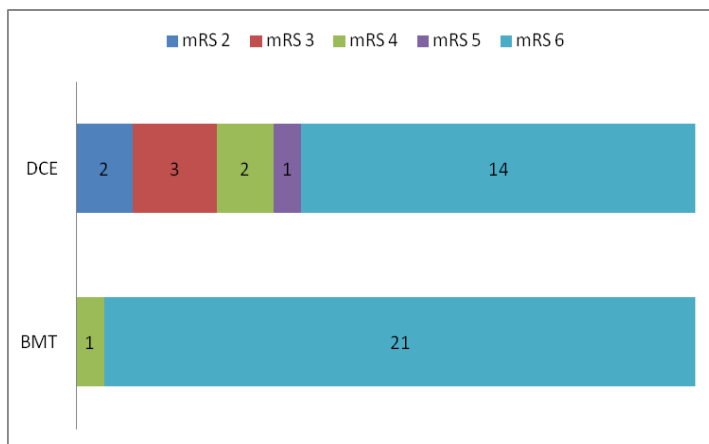


Figure 5. **Proportional distribution of clinical outcomes by mRS in both groups at 12 months**

There were three patients to whom parenchymal ICP monitoring gauge was implanted. In one of them no clinical and radiological signs of herniation or elevated intracranial pressure developed, therefore surgery was not performed on him. Since initially he was included in DCE group, but did not

receive decompression surgery, he was observed separately from both main groups. He survived with favorable outcome of mRS 2 after 1 year.

At the study period there were another 3 patients who underwent decompressive surgery, but they were not included in the study due to the fact that the operation was carried out later than 99 hours from the onset of the disease. None of these patients survived.

Two patients (9.1%) in DCE group developed a symptomatic epidural hematoma which resulted in death in one of them at 16th day, but the second one improved after evacuation of hematoma, nevertheless he died thereafter from additional stroke on day 50th.

Cerebrospinal fluid leak and other surgical complications were not observed.

The mean interval between stroke and death was 6.1 days (95%CI: 2.77 to 9.41) in BMT group and 35.3 (95%CI: 11.77 to 58.80) in DCE group ($p<0.001$). Majority of deaths in BMT group were attributable to brain herniation and brain death, and vice versa in DCE group mainly to secondary complications developed on the background of extremely devastating disease (e.g. pneumonia, fatal pulmonary embolism, bedsores etc.)

Based on the Mann-Whitney test it was found that the average lifespan of the two groups is statistically significantly different ($p<0.001$).

Kaplan-Meier survival analysis shows that the survival curves of the two groups (BMT and DCE) differed statistically significant (log-rank test, $p<0.001$), see Figure 6.

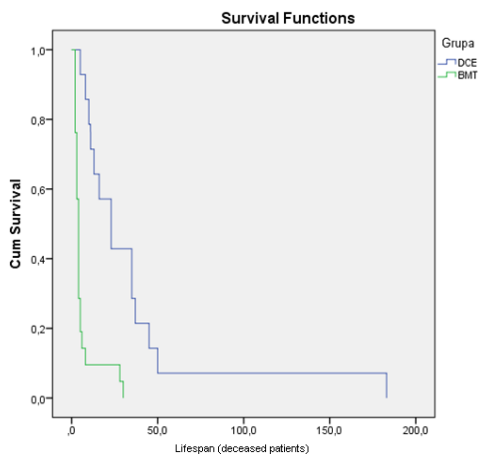


Figure 6. Comparison of lifespan in days of deceased patients in both groups (Log-rank test)

Correlation of demographic and clinical criteria with clinical outcome in DCE subgroups

Three predefined DCE subgroup analyses were performed:

- 1) Patient age impact on clinical outcome;
- 2) CIV impact on clinical outcome;
- 3) NIHSS impact on clinical outcome.

Patient age correlation with clinical outcome

Age of ≤ 60 y is associated with higher survival and favorable outcome achieving statistical significance ($p < 0.05$). Eight of thirteen (61.5%) patients in subgroup of 60y or younger survived at 12 months versus none in subgroup of

61y or older. More detailed mortality depending from age group is shown in Table 8.

Table 8

Mortality depending from age group

		Age≤60g	Age≥61g	p value
Mortality at 6 months	alive	61.5%	11.1%	p=0.03
	dead	38.5%	88.9%	
Mortality at 12 months	alive	61.5%	0%	p=0.006
	dead	38.5%	100%	

Outcome was favorable in 53.8% (n=7) of younger patient subgroup at 6 and 12 months versus 11.1% (n=1) at 6 months and 0% (n=0) at 12 months in older patient subgroup. More detailed characteristics are given in Table 9.

Table 9

Clinical outcome depending from age subgroup

		Age≤60g	Age≥61g	p value
Outcome at 6 months	favorable (mRS 0-4)	53.8%	11.1%	p=0.074
	unfavorable (mRS 5-6)	46.2%	88.9%	
Outcome at 12 months	favorable (mRS 0-4)	53.8%	0%	p=0.017
	unfavorable (mRS 5-6)	46.2%	100%	

Using logistic regression analysis it was found that between mortality and age there exists an equation with variables (see Table 10).

$$mortality\ probability = \frac{e^{-12,31+0,22*age}}{1 + e^{-12,31+0,22*age}}$$

e=2.71

Table 10

Variables in age and mortality equation

	B	Standart error	Wald	df	p value	Exp(B)	95% confidence interval	
							lower	upper
Age	.228	.097	5.489	1	.019	1.256	1.038	1.519
Constant	-12.313	5.479	5.050	1	.025	.000		

So with increase of age for one year the risk of fatal outcome increases 1.26 times (95% CI: 1.03 to 1.51).

With the proposed model at the threshold of 0.5 it is possible to predict mortality after surgery with reliability of 77%. (Nagelkerke $R^2 = 0.45$). See Table 11.

Table 11

Opportunity of prediction with logistic regression analysis at the threshold of 0.5

Observed		Predicted		
		mortality		percentage correct
		alive	dead	
Mortality	alive	5	3	62.5
	dead	2	12	85.7
Overall percentage				77.3

To determine more precise threshold for prediction of mortality analysis of ROC curve analysis was used, with the help of which it was stated that it is 0.7 at the sensitivity of 0.85, specificity of 100 (AUC = 0.9, $p < 0.001$), see Figure 7.

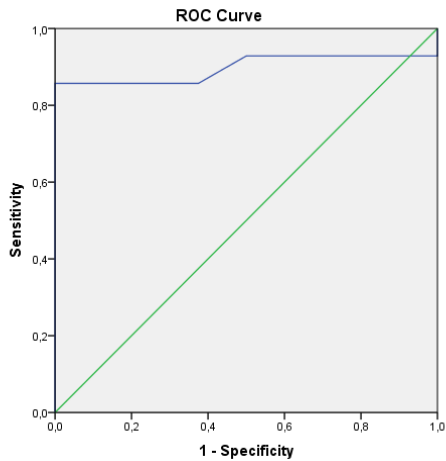


Figure 7. **Threshold detection ROC curve analysis**

As can be seen, the limit value of 0.7 obtained from the ROC curve analysis provides a more accurate prediction of mortality. The proposed model can predict mortality of patients after surgery with 91% reliability (Table 12).

Table 12

Opportunity of prediction with logistic regression analysis at the threshold of 0.7

Observed		Predicted		
		mortality		percentage correct
		alive	dead	
Mortality	alive	8	0	100.0
	dead	2	12	85.7
Overall percentage				90.9

Using logistic regression analysis it was found that between functional outcome and age there exists an equation with variables (see Table 13).

$$\text{probability of unfavorable outcome} = \frac{e^{-12,18+0,23*age}}{1 + e^{-12,18+0,23*age}}$$

$$e=2,71$$

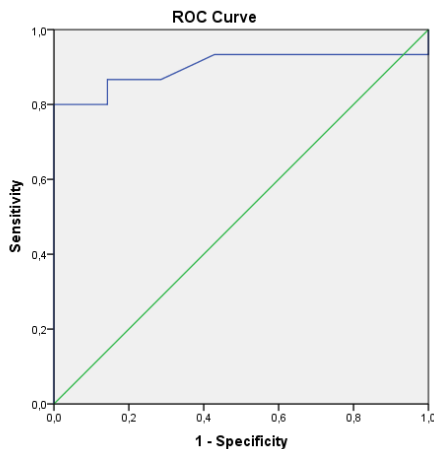
Table 13

Variables in age and functional outcome equation

	B	Standart error	Wald	df	p value	Exp(B)	95% confidence interval	
							lower	upper
Age	.231	.100	5.366	1	.021	1.260	1.036	1.532
Constant	-12.180	5.533	4.846	1	.028	.000		

So with increase of age for one year the risk of unfavorable clinical outcome increases 1.26 times (95% CI: 1.03 to 1.51). With the proposed model at the threshold of 0.5 it is possible to predict unfavorable clinical outcome after surgery with reliability of 82%.

To determine more precise threshold for prediction of unfavorable clinical outcome analysis of ROC curve analysis was used, with the help of which it was stated that it is 0.7 at the sensitivity of 0.80, specificity of 0.86 (AUC = 0.9, $p < 0.001$), see Figure 8.



8. att. Threshold detection ROC curve analysis

CIV correlation with clinical outcome

CIV \leq 390 cm³ is statistically significantly associated with lower mortality ($p<0.05$). In the subgroup of patients with CIV \leq 390 cm³ ($n=12$) after six months 8 (66.7%) and after twelve months 7 (58.3%) of them survived, whereas in the subgroup of patients with CIV \geq 390 cm³ ($n = 10$) after six and twelve months only one patient (10%) survived. He had an unfavorable clinical outcome (mRS 5) after six and twelve months, see Table 14.

Table 14

Mortality depending from CIV

		CIV \leq 390 cm ³	CIV \geq 390 cm ³	p value
Mortality at 6 months	alive	66.7%	10%	p=0.01
	dead	33.3%	90%	
Mortality at 12 months	alive	58.3%	10%	p=0.03
	dead	41.7%	90%	

CIV \leq 390 cm³ is statistically significantly associated with a favorable clinical outcome ($p<0.05$). In subgroup of patients of CIV \leq 390 cm³ ($n = 12$) after six months favorable clinical outcome was observed in 8 (66.7%) and after twelve months in 7 (58.3%) patients, whereas in the subgroup of CIV \geq 390 cm³ ($n=10$) at 6 and 12 months no patients with favorable clinical outcome were observed (Table 15).

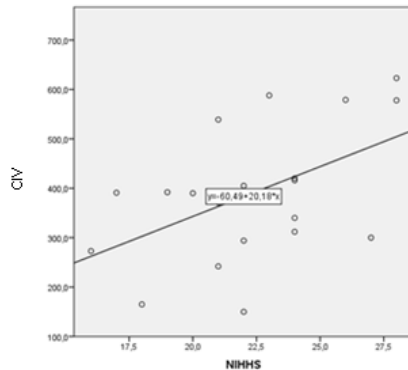
Clinical outcome depending from CIV

		$CIV \leq 390 \text{ cm}^3$	$CIV \geq 390 \text{ cm}^3$	p value
Outcome at 6 months	favorable (mRS 0-4)	66.7%	0%	p=0.0017
	unfavorable (mRS 5-6)	33.3%	100%	
Outcome at 12 months	favorable (mRS 0-4)	58.3%	0%	p=0.0053
	unfavorable (mRS 5-6)	41.7%	100%	

NIHSS score correlation with clinical outcome

Subgroup of patients with NIHSS score ≤ 24 (n=18) compared with the subgroup of patients with NIHSS score ≥ 25 (n=4) did not show a statistically significant difference not in terms of mortality not in terms of clinical outcome after decompression surgery ($p > 0.05$).

Based on the Spearman correlation coefficient analysis it is concluded that between the cerebral infarct volume (CIV) and NIHSS score there is a positive and statistically significant correlation ($r_s = 0.42$, $p < 0.05$). Therefore with an increase in NIHSS score CIV increases (Figure 9).

**Figure 9. Correlation between CIV and NIHSS score**

DISCUSSION

Retrospective part

Data from internationally available literature indicates that mortality rate after “malignant” MCA stroke can be up to 80%. It is known that the distribution of mortality rates is bimodal, with an early peak within the first 3-6 days (due to transtentorial herniation of the brain), followed by a second peak during the 2nd and 3rd weeks after stroke (a result of complications related to both hospitalization, such as pneumonia, as well as medical comorbidities, such as myocardial infarction and hearth failure). It is not precisely specified in literature whether all of “malignant” MCA stroke patients die from brain herniation or there is still a subset of patients who die from secondary complications which are not directly related to herniation, but have developed on the background of extremely devastating disease. Therefore development of secondary complications might also partially explain why decompressive hemicraniectomy performed in case of “malignant” MCA stroke as a life saving procedure still carries roughly 20% mortality. In this retrospective study we did not analyze mortality rate of proven “malignant” MCA stroke, but tried to estimate group of patients who are at high risk of developing fatal brain edema and who would be potential candidates to be considered for decompressive craniectomy. In our study there was 40% (n=80) mortality rate in severe MCA stroke group. Forty-nine of those eighty patients died from brain stem herniation (this finding is supported by radiological evidence of space-occupying edema and corresponding clinical course) which makes 6.6% of all MCA stroke patients.

Thereby our results corresponds well to the international literature indicating that malignant MCA stroke forms about 10% of all MCA strokes with 70-80% mortality.

Between those patients in severe MCA stroke without radiological evidence of space-occupying edema there still were 30 patients who died. According to accepted clinical praxis at Pauls Stradins Clinical University Hospital, CT brain scan is performed for patients with sudden focal neurological symptoms at time of admission to rule out diagnosis of intracerebral hemorrhage (ICH), and if it is ruled out once, repetitive scans are not performed without special need.

Taking into account the fact that most frequently cerebral edema develops 48-72 hours after onset of the disease, but brain CT examination is performed at time admitting to hospital (overwhelming majority of cases are admitted shortly after the onset of the disease) it is easy to explain significant proportion of patients in severe MCA stroke group with no radiological symptoms of cerebral edema who highly probably still died from brain stem herniation with typical clinical course accordingly to analysis of the medical records. It can be concluded that these patients developed fatal cerebral edema later than head CT examination was made. Thereby, it is possible that mortality from fatal brain edema is even higher than it was possible to prove in our study.

Despite the fact that severity of symptoms not always is equivalent to volume of infarction, still it is well known that one of the most consistently identified clinical risk factors for death (due to brain herniation) after MCA infarction is a high initial NIHSS score (if which motor evaluation along with coexisting stroke symptoms makes a big part). All randomised controlled trials focusing on surgical treatment of “malignant” MCA stroke as almost the only one of the clinical inclusion criteria has a clinical deficit suggestive infarction in the territory of the MCA with high initial NIHSS score. Results of our study show that patients with deeper neurological motor deficit on NIHSS scale have statistically significantly higher risk of death. This finding indicates that deeper neurological deficit testifies a broader cerebral infarction area, hence the greater the opportunity for the development of fatal brain edema.

This fact explains the high correlation between the severity of symptoms and mortality in severe MCA stroke group. In the severe MCA stroke group there was also a statistically significant (Fisher's test, $p < 0.05$) association of radiological evidence of SOE with mortality, whereas in group of mild MCA stroke such association was not observed. It reaffirms the connection between deeper neurological deficit, larger cerebral infarct area and higher risk of developing a fatal brain edema.

Prospective part

After decades of uncertainty concerning the question whether decompressive surgery should be performed in patients with malignant MCA stroke, it is now clear, that in some patients it is very effective in terms of survival and favorable outcome. Thanks to evidence from RCTs, the question has changed – it is not about whether to perform surgery or not anymore, it is about whom to perform to achieve maximum benefit and limit the risks - in other words how to distinguish those to whom DCE will provide benefit from those whom will not (i.e. specify narrower indications/contraindications for surgery). Amount of evidence based data available now is still very limited and insufficient for large part of clinical situations and number of questions still remains unanswered. Survival as well as favorable functional outcome are the goals which are aimed to be met through surgery, therefore it is very important to be able to predict, whether surgery, if made, will provide the desired outcome.

The analysis of data from the recently done RCTs and updated meta-analysis of these trials (UMA) suggests that decompressive surgery increases

the probability of survival to nearly 80%, at least if patient is aged 60 years or less, surgery was undertaken within 48 hours from stroke onset and patient had no significant coexisting diseases. However, a considerable proportion of the patients suffering from „malignant” MCA stroke belong to age group of >60 years. In DESTINY II trial (involving patients older than 60 years of age) surgery also showed superiority over medical treatment, but the results (fixed at 12 months after the onset of the disease) were significantly worse than in those studies with patients less than 60 years of age - a satisfactory outcome (mRS 0-4) was observed only in 40.8% of cases versus 74% respectively. On the other hand Chinese study in which patients both younger and older than 60 years of age were included (18-80 years) showed practically the same results regardless of patient age subgroups - survived 87.5% and 83.3% of patients at 6 and 12 months respectively and there was not seen increased amount of survivors in vegetative state (mRS 5) in both age subgroups. A favorable clinical outcome was achieved in 68.8% of cases which is significantly higher than in DESTINY II study. Due to the diversity of the results, age as one of the criteria for outcome prediction after surgery remains unclear.

In our trial, patients older than 60 years were also included. The overall survival rate in the DCE group was 36.4% at 12 months. The benefit of surgery in terms of survival comparing with the BMT (4.5% at 12 months) in our trial showed statistical significance ($p=0.021$). Compared with known RCTs our results are worse which could be due to several reasons. Survival rate in subgroup of patients ≤ 60 y was closer to UMA of RCTs - 61.5% in our study versus 79% in UMA. The difference can be explained by relatively small amount of patients involved in our trial (13 versus 58). Also a small amount of survivors in BMT group compared with results of UMA (4.5% vs 21%) and relatively low compared to UMA amount of patients with favorable clinical outcome in surgical wing of our study (54% versus 67% in UMA) is likely related to the relatively small number of patients involved in the study.

In surgical wing of our study, at subgroup of patients older than 60 years (n=9) at 6 months only one patient survived (11.1%) who had a favorable clinical outcome - mRS 3. This patient died on the seventh month after surgery due to recurrent stroke, therefore at 12 months there were no survivors older than 60 years in surgical wing (all operated patients died due to non-neurological complications). Whereas in DESTINY II study there was 67% survivors and 40.8% of all patients had favorable clinical outcome. Chinese study shows even better results – in subgroup of patients older than 60 years in surgical wing at 12 months there were 81% survivors and 68.7% of patients with a favorable clinical outcome. The reason for such a dramatic difference between the results of our study and DESTINY II/Chinese study is not clearly detectable, but according to the authors, these differences are determined by a combination of factors. Firstly, a significantly smaller number of patients (only 9 patients with age over 60 years in surgical arm). Secondly, one of the deceased patients had surgery at 99 hours from the onset of the disease and, as the HAMLET study demonstrates, the results tend to be better if surgery was made up to 48 hours of onset of the disease (in DESTINY II study and in Chinese study surgeries were performed no later than 48 hours of onset of the disease). DESTINY II study was conducted in Germany and showed a significant increase in the proportion of survivors in a vegetative state, therefore, thirdly, as a hypothetical version, which might partly explain the higher mortality in our study is the difference between countries in care of critically ill patients postoperatively.

As the patient's age issue is still unclear in our study we evaluated the impact of age. At 12 months none of the patients aged over 60 showed favorable outcome. Comparison of DCE subgroups (age \leq 60y (n=13) versus age \geq 60y (n=9)) showed that younger age is statistically significantly associated with survival (p=0.006) and favorable outcome (p=0.017).

Logistic regression analysis indicates the statistically significant adverse trend - with increasing patient age, increasing risk of mortality and poor clinical outcome is observed. The developed model allows to predict mortality with 91% reliability and unfavorable clinical outcome (mRS 5-6) with 82% reliability for the patients meeting inclusion criteria of the study. Although this finding does not define a specific age for when the operation can not be performed anymore but the developed model could be used as part of an overall risk assessment.

Our results tend to agree with the previous findings from uncontrolled series and reviews suggesting that the age of more than 60 years could be one of the most powerful predictors of bad clinical outcome. While there is no doubt that in part of the patients older than 60 years surgery could be very effective, however it can be concluded that the application of surgery for older than 60 years patient population remains uncertain, and it is at least with significantly increased risk. More data from RCTs is needed to address this question in the future.

Data from internationally available literature indicates that the mortality rate after a “malignant” MCA stroke, if treated only medically, is about 80% and in UMA of RCTs it is 70.6%. In our trial, the mortality rate in the BMT group was even higher (95.5%), which actually is not controversial to the international data, but a slightly higher mortality rate in our study can be explained by a relatively small number of the patients included.

In internationally available literature, MCA stroke is defined as “malignant” if CIV is 145 cm³ or more. CIV as an independent criterion whether to perform DCE or not is not widely discussed in literature. Effect of CIV on outcome by now has only been analyzed within subgroup analysis in DECIMAL trial showing not significant trend toward a worse outcome in patients with higher infarct volumes at inclusion to surgical group.

In our trial, we found that in both groups only one patient (DCE) with $CIV > 390 \text{ cm}^3$ survived with poor outcome mRS 5 ($p=0.01$). Subgroup comparison in DCE group ($CIV \leq 390 \text{ cm}^3$ versus $CIV \geq 390 \text{ cm}^3$) showed significantly better survival rate and favorable outcome in lower CIV subgroup. This finding points to a statistically significant trend towards an unfavorable outcome of the operated patients with $CIT > 390 \text{ cm}^3$. According to our results $CIT > 390 \text{ cm}^3$ could be the upper threshold after which a high-risk area begins.

In DECIMAL trial as one of the findings identified was that no patient with infarct volume $> 210 \text{ cm}^3$ survived without craniectomy and in those with volumes between 145 and 210 cm^3 there was still high death rate attributable to brain herniation in absence of surgery. These findings confirm previous data defining stroke as „malignant” if its volume reaches 145 cm^3 and it can be used as lower threshold considering surgery. More data are needed to support these findings.

Two patients who did not underwent DCE survived: 1st - patient initially assigned to the DCE group, but did not develop the clinical signs of elevated intracranial pressure or herniation and to whom ICP monitoring gauge was implanted, but no ICP raise was observed, and 2nd - a 72-year-old woman in the BMT group. Their survival can be easily explained by the fact that not every patient with an MCA infarct develops fatal brain edema (factors contributing to the development of fatal brain edema are poorly understood) and relatively small CIVs (159 and 146 cm^3 respectively), which are just a little above the widely accepted threshold of 145 cm^3 to be considered as a “malignant” MCA stroke.

Higher NIHSS score did not prove to have predictive value on outcome. However, the increase in NIHSS score statistically significantly correlated with the increase in CIV, which again confirms the fact that in most cases, more severe neurological deficits are associated with increased cerebral infarction volumes.

The question of the optimal time of performing surgery is still unclear. Several publications suggest superiority of early (≤ 48 h) decompressive surgery over delayed, but no statistically significant confirmation has made up to date. HAMLET trial included patients up to 96h from onset and subgroup analysis showed trend to better clinical outcome in surgery performed up to 48h, but no statistical significance was achieved. In our trial we included patients up to 99h from onset - a total of three patients later than 48h were included into DCE group with resulting in poor outcomes (two deaths and one survival at mRS 5). Although considering the small number of patients no clear conclusions can be made, it can be agreed that the trend toward better results with early surgery is confirmed in our study as well. This issue certainly needs further investigation to identify the optimal time frame for surgery.

However, most of colleagues agree that mortality alone is not the only important issue. The concern is not only about survival, but also rather about a clinical outcome and quality of life. There is still ongoing discussion about the cutoff of mRS score to be used to distinguish “favorable” outcome from “unfavorable.” The answer to this question becomes even more difficult because our understanding of what patients view as an acceptable outcome may be poor. mRS scale mainly characterizes ability of patient to perform daily activities, but not the quality of life and patient satisfaction in wider meaning. Such factors as aphasia, depression, neuropsychological deficits, family support, caregiver burden etc. are out of the scope of RCTs and those aspects certainly deserve further investigation. However, in most of the literature, a favorable outcome is defined as survival without a disastrous outcome, e.g., complete dependency or permanent vegetative state (mRS score of 5). We also dichotomized outcome as favorable (mRS 0-4) and unfavorable (mRS 5-6) to compare our data to RCTs in which the same dichotomization was used. Our results showed comparatively low favorable clinical outcomes (overall 31.8%

in DCE and 4.5% in BMT group at 12 months) with improved outcomes in DCE subgroups of younger age and lower CIV.

Data from updated pooled analysis of RCTs and DESTINY II trial showed that DCE in the selected patients increases the survival at the expense of increasing the number of survivors with mRS 4 and 5. Our findings support these data. However, in Chinese study in all age groups (18-80 years) there was no increase of survivors in vegetative state observed. It appears that in order to fully address this issue the further research is required.

Lifespan of deceased patients in both groups varied significantly between groups (6.09 days in BMT group versus 35.28 days in DCE group). Majority of deaths in BMT group were related to brain stem herniation, while in DCE group majority of deaths were related to secondary complications. With the help of the surgery in DCE group brain stem herniation was prevented, thereby statistically significantly prolonging the lifespan from onset to death. This finding confirms the previous information on bimodal nature of death after stroke and also invites reflection on the ethical and economic issues while treating this kind of patients. Twelve-month mortality DCE group was 63.2% (n = 14), namely those patients died despite the surgery performed on them. After surgery patients continued to receive treatment in ICU and some of them later in setting of neurosurgical ward. Death of these patients indicates that they were not helped by surgery but on the contrary – surgery caused additional suffering. Taking also into account the ethical and economic considerations, the exact knowledge of benefits and risks of surgery is critically important.

Our study has several shortcomings. The first, the number of patients involved is quite limited. However, it is consistent with numbers reported internationally by RCTs addressing the same issue. The second, blinded evaluation of functional outcome in survivors was not possible due to limited number of investigators involved.

CONCLUSIONS

1. Around 7% of all MCA stroke patients die from brain stem herniation and they are potential candidates to be considered for application of decompressive craniectomy.
2. Patient age is a demographic criterion with statistically significant prognostic value on clinical outcome after decompressive craniectomy. Age over 60 years is associated with an unfavorable clinical outcome after surgery.
3. Cerebral infarct volume is a clinical criterion with statistically significant prognostic value on clinical outcome after decompressive craniectomy. Cerebral infarct volume over 390 cm^3 is associated with an unfavorable clinical outcome after surgery.
4. The initial NIHSS score is not a criterion with statistically significant prognostic value on clinical outcome after decompressive craniectomy.

NOVELTY OF THE RESEARCH AND ITS PRACTICAL SIGNIFICANCE

It has been clarified that around 7% of all MCA stroke patients are potential candidates to be considered for application of decompressive craniectomy.

For the first time in Latvia, clinical effectiveness of decompressive craniectomy has been evaluated in randomized study. Taking into account the results of research, it has become possible to define prognosis after decompressive craniectomy in case of malignant MCA stroke more accurate than previously.

Decompressive craniectomy provides favorable clinical outcome for majority of relatively healthy patients up to 60 years of age with cerebral infarction volume up to 390 cm^3 , thereby it is recommended.

Decompressive craniectomy is not recommended for patients over 60 years of age.

Decompressive craniectomy is not recommended for patients with cerebral infarction volume over 390 cm^3 .

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