



TOPICAL REVIEW

Decompressive Hemicraniectomy for Large Hemispheric Strokes

Jessica Lin, MD and Jennifer A. Frontera, MD

Large hemispheric infarcts occur in up to 10% of all ischemic strokes and can cause devastating disability. Significant research and clinical efforts have been made in hopes of mitigating the morbidity and mortality of this disease. Areas of interest include identifying predictors of malignant edema, optimizing medical and surgical techniques, selecting the patient population that would benefit most from decompressive hemicraniectomy, and studying the impact on quality of life of those who survive. Decompressive surgery can be a life-saving measure, and here we discuss the most up-to-date literature and provide a review on the surgical management of large hemispheric ischemic strokes.

Key Words: brain injury ■ decompressive craniectomy ■ ischemic stroke ■ morbidity ■ quality of life

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Large hemispheric infarctions (LHIs) lead to significant disability and mortality. Harvey Cushing in the early 1900s described primary and secondary brain injury as occurring during immediate (direct injury of vessels), intermediate (during which there is often a lucid period of consciousness), and late (when cerebral edema develops) phases after traumatic brain injury.¹ A similar progression of disease can be seen in LHI, defined as an ischemic stroke affecting all or most of the middle cerebral artery (MCA) territory, with or without involvement of the anterior cerebral or posterior cerebral artery territories.²

The term malignant MCA infarction was coined in 1996, describing a severe hemispheric syndrome with characteristic symptoms and a predictable clinical course including hemiparesis, eye, and head deviation, a progressive decline in consciousness, pupillary dilatation, and increased intracranial pressure.³ Up to 10% of all ischemic strokes are estimated to be large MCA infarcts.³⁻⁵ It has been recognized that mass effect leading to horizontal shift of midline structures, in particular, the pineal gland, leads to a depressed level of awareness.⁶ The space-occupying cerebral edema progresses over the first 2 to 5 days, leading to a high risk of herniation, and is the leading cause of death within the first week after a LHI.³ Without surgical intervention, these strokes have a 40 to 80% mortality rate, and a large number of survivors are severely disabled.^{3,7,8} In addition to the direct damage from neuronal death caused by the infarction itself, there is also secondary brain injury from cytotoxic and vasogenic edema affecting noninfarcted tissue that contributes to the overall morbidity and mortality of large territory strokes.

Studies have shown that decompressive hemicraniectomy in stroke and traumatic brain injury decreases intracranial pressure and improves perfusion and blood flow, not only in ipsilateral

penumbral tissue but in the contralateral hemisphere as well.^{9–11} Naturally, the question that stems from these findings is whether or not these biophysical changes lead to clinically significant improvements in mortality and functional outcome. With regard to traumatic brain injury, there may be a lower mortality with decompressive surgery, but surgery seems to lead to higher rates of poor functional outcomes as was shown in the DECRA (Decompressive Craniectomy) and RESCUEicp (Randomized Evaluation of Surgery With Craniectomy for Uncontrollable Elevation of Intracranial Pressure) trials.^{12,13} These findings in traumatic brain injury suggest there are additional pathophysiological changes that occur with decompressive craniectomy, including but not limited to the morbidity of surgery itself, which may negate the benefits of decreasing intracranial pressure and improving cerebral perfusion. Given that ischemic stroke is a very different disease process, the question remains whether decompressive surgery results in similar trends in clinical outcomes as were found in traumatic brain injury.

Here, we will focus on the utility of decompressive hemicraniectomy in large hemispheric ischemic strokes. A number of randomized controlled trials regarding this topic have been published over the last 2 decades. We will summarize and break down the literature, discuss current guidelines, and describe future directions in the management of LHI in this topical review.

PREDICTORS OF MALIGNANT CEREBRAL EDEMA

There has been much focus on determining the predictors of malignant cerebral edema and identifying those that would most likely need and benefit from surgical decompression. These determinations aid in triage and disposition, especially at medical centers where neurosurgery or neurocritical care services may not be readily available. Predictors that have been studied include clinical, radiographic, and laboratory characteristics. A number of risk scores have been developed that vary in complexity and ease of utility, such as the Kasner risk index, DASH (DWI ASPECTS, ACA territory involvement, M1 susceptibility vessel sign, hyperglycemia), EDEMA (Enhanced Detection of Edema in Malignant Anterior Circulation Stroke), and MBE (Malignant Brain Edema) scores (Table 1).^{14–17} While these risk scores do not purport to identify those who will require surgical decompression, they may potentially complement other factors for surgical risk/benefit stratification. Of note, as expected with any prediction model, those with more variables perform better, but are more difficult to use.

Table 1. Summary of 4 Risk Scores for Predicting the Development of Malignant Cerebral Edema After a Hemispheric Infarct (Table view)

MBE score ¹⁴	Kasner Index ¹⁵	EDEMA score ¹⁶	DASH score ¹⁷
NIHSS	History of hypertension	Basal cistern effacement	DWI ASPECTS
≤8=0	No=0	No=0	>3=0
9–17=1	Yes=1	Yes=3	≤3=1
≥18=2			
ASPECTS	Congestive heart failure	Glucose ≥150 mg/dL	ACA territory involvement
>8=0	No=0	No=0	No=0
≤7=1	Yes=1	Yes=2	Yes=1
Collateral score	White blood cell count	Previous stroke	M1 susceptibility vessel sign
≥2=0	≤10 000/μL=0	Yes=0	No=0

MBE score ¹⁴	Kasner Index ¹⁵	EDEMA score ¹⁶	DASH score ¹⁷
<2=2	>10 000/ μ L=1	No=1	Yes=1
Revascularization failure	CT involvement >50% MCA territory	tPA or thrombectomy	Hyperglycemia (glucose \geq 145 mg/dL)
Success=0	No=0	Yes=0	No=0
Failure=1	Yes=1	No=1	Yes=1
	CT involvement additional territories	Midline shift	
	No=0	0 mm=0	
	Yes=1	0–3 mm=1	
		3–6 mm=2	
		6–9 mm=4	
		>9 mm=7	
Max: 6 points	Max: 5 points	Max: 14 points	Max: 4 points
0: 0.0% rate of MBE	0: 31% rate of fatal brain edema	>7: PPV 93% for potentially fatal malignant edema	0: 9.1% rate of malignant MCA infarction
6: 100.0% rate of MBE \geq 5: PPV 91.7%	5: 100% rate of fatal brain edema		4: 100.0% rate of malignant MCA infarction
C statistic=0.88	C statistic=0.70	C statistic=0.76	C statistic=0.88

ACA indicates anterior cerebral artery; ASPECTS, Alberta Stroke Program Early CT Score; DASH, DWI ASPECTS, ACA territory involvement, M1 susceptibility vessel sign, hyperglycemia; DWI, diffusion-weighted imaging; EDEMA, enhanced detection of edema in malignant anterior circulation stroke; MBE, malignant brain edema; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PPV, positive predictive value; and tPA, tissue-type plasminogen activator.

Certain radiographic features have been found to be associated with the development of malignant edema, based mainly on observational data. For computed tomography (CT), these include early CT hypodensity involving greater than half of the MCA territory, carotid T occlusion on angiography, poor collateral blood flow, infarct volume >220 mL and midline shift >3.7 to 5 mm within 24 to 48 hours after stroke onset.^{18,19} On magnetic resonance imaging, features include apparent diffusion coefficient values <80% compared with the contralateral hemisphere with lesion volume \approx 80 mL within the first 6 hours, and diffusion-weighted imaging infarct volume >145 mL.^{20,21} Transcranial color-coded duplex have also been used in evaluation of cerebral edema and midline shift and may be useful bedside tools if transport to a CT or magnetic resonance imaging scanner is difficult. Assessments of midline shift via transcranial color-coded doppler sonography seem to correlate well with CT examinations.^{22,23} Additionally, elevations in pulsatility index measured by transcranial Doppler have been shown to correlate with increased intracranial pressure and midline shift.²⁴

Serum biomarkers that have been studied and incorporated in some of the abovementioned risk scores include glucose levels, white and red blood cell counts, platelet count, hemoglobin, international normalized ratio, fibrinogen, creatinine, C-reactive protein, and S-100B. None of these have been reliably shown to be associated with malignant cerebral edema.²⁵

SURGICAL TECHNIQUES AND CONSIDERATIONS

In 1956, Scarcella wrote about the clinical similarity of infarction-related mass effect to that of a brain tumor and described 6 cases in which craniotomy with or without resection of necrotic tissue

was performed.²⁶ His work, along with others of his time, paved the way for modern techniques in decompressive hemicraniectomy.

The typical approach for surgical decompression is a frontal-temporal-parietal decompressive hemicraniectomy. An incision is made either from behind or in front of the ear in the figure of a reverse question mark, and the temporalis muscle and scalp flap are pulled back to expose the skull. An anteroposterior length of at least 12 to 13 centimeters and a supero-inferior length of at least 9 centimeters are recommended, and this is achieved by drilling and connecting burr holes (Figure 1).^{27,28} The floor of the middle cranial fossa is then subsequently exposed. After bony decompression has been achieved, a durotomy is performed. The dura is loosely reapproximated with either pericranium or allograft.^{28,29} Those requiring re-operation—such as young patients with large infarcts—may benefit from a temporal lobectomy if bony and dural decompression is not sufficient, although resection of the infarcted tissue itself is not routinely performed with hemicraniectomy.²⁸

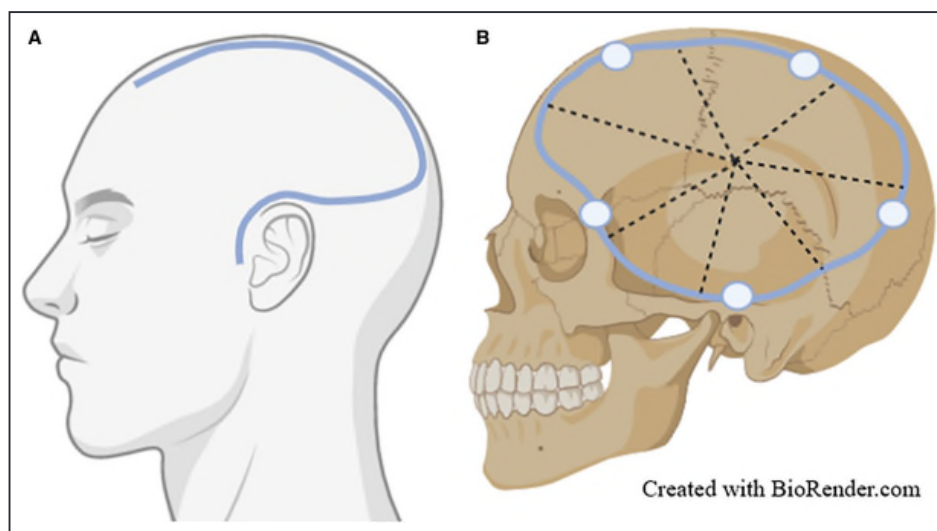


Figure 1. An illustration of a decompressive hemicraniectomy. A, Shows a curved scalp incision; (B) shows the connection of burr holes (circles) for craniectomy, and durotomy in a stellate fashion (dashed lines).

Complications of Hemicraniectomy

There are immediate and late complications that can occur after hemicraniectomy. If a craniectomy is suboptimal in size, there may be external brain herniation and hemorrhages (most often parenchymal) from shear injury and impingement of the cerebral veins at the bony edges.^{27,30} Additional complications include infection (eg, abscess, superficial wound infection, and meningitis), seizures, syndrome of the trephined, and cerebrospinal fluid (CSF) disturbances that may require additional surgical intervention. The prevalence of seizures poststroke has been noted to be 7.5% to 11.5% within the first 5 years; in those with decompressive hemicraniectomy, the prevalence has been noted to be up to 61.1%.^{31–34} Syndrome of the trephined, also known as sunken flap syndrome, is the development of new neurological symptoms (most commonly motor, cognitive and language deficits) associated with sunken skin at the craniectomy site that improve with cranial reconstruction.^{35,36} In some cases, paradoxical herniation (herniation away from the side of the craniectomy) may occur. Immediate therapeutic maneuvers include Trendelenberg positioning and stopping CSF diversion (eg, clamping of the external ventricular drain), with the ultimate treatment being cranioplasty. The pathophysiology behind this syndrome is not completely understood; proposed mechanisms include external atmospheric pressure that is directly

transmitted to brain parenchyma in the absence of a skull, causing decreased blood and CSF flow from a pressure gradient.³⁵ CSF disturbances such as communicating hydrocephalus and fluid collections in the subdural, epidural, and extracranial spaces can generate mass effect and shift, cause wound breakdown and impair healing, increase the risk of infection, and sometimes require permanent CSF shunting.^{27,29} An estimated 5% to 15% of patients with decompressive craniectomy undergo ventriculoperitoneal shunt placement.^{37,38}

Cranioplasty

After a hemicraniectomy, patients require cranial reconstruction after the cerebral edema has subsided. Cranioplasty can be performed with either autologous or alloplastic implants such as with titanium or polymethylmethacrylate. For autologous cranioplasties, the bone flaps are preserved either in a freezer of -80°C or below, or implanted in the patient's abdominal subcutaneous fat.²⁷ Studies have shown that cranioplasty itself has a relatively high complication rate of around 15% to 35%, with up to a quarter of patients requiring revision surgery.^{39–41} The most common reasons for reoperation are infection, bone resorption, and intra- or extra-axial hematomas.³⁹ The optimal timing of cranioplasty after ischemic stroke remains controversial and unknown, and there are no prospective randomized trials on this to date. While some published studies have looked at the effects of early versus late cranioplasty, the definition of early versus late timing has been variable. Early cranioplasty has been mainly defined as within 8 to 12 weeks of surgical decompression, with late cranioplasty defined as occurring after 8 to 12 weeks of decompression.^{42–44} Early cranioplasty seems to be associated with higher rates of complications, especially in those with ventriculoperitoneal shunts, but this requires further study.^{39,42–44} The type of complications after early or late cranioplasty seem to be the same and include subdural or epidural hematomas, infection, and wound healing disturbances.^{42–44}

SUMMARY OF DECOMPRESSIVE HEMICRANIECTOMY RANDOMIZED CONTROLLED TRIALS

A number of studies exploring the utility and benefits of decompressive hemicraniectomy in addition to maximal medical therapy in LHI have been conducted, including 8 randomized controlled trials (RCTs) over the last 2 decades that enrolled 365 patients.^{8,45–51} The trials varied in multiple factors, including time to surgery, age range, standardization of medical management, and definition of a favorable outcome (defined as modified Rankin Scale [mRS] score of 0 to 3 or 0 to 4, depending on the study). The most common outcomes studied included the mortality and functional outcome at 6 or 12 months. **Table 2** lists the 8 RCTs, along with some of their inclusion and exclusion criteria, the primary outcome, and primary findings. Three of the 8 trials only enrolled patients under the age of 60. Six of the 8 trials only enrolled patients with a prestroke mRS score of 0 to 1 (the other 2 trials enrolled those with a prestroke mRS score up to 2). All of the trials were limited by absence of blinding during the hospitalization, and most were also limited by the absence of blinding at follow-up evaluations (with the exception of DECIMAL (Decompressive Craniectomy in Malignant MCA Infarction), HeADDFIRST, and Zhao et al). All of the hemicraniectomy trials had small enrollment numbers, but a number of meta-analyses have been performed in addition to a pooled analysis of DECIMAL, DESTINY (Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery), and HAMLET (Hemicraniectomy After Middle Cerebral Artery Infarction With Life-Threatening Edema Trial).^{52–56}

Table 2. Study Characteristics and Findings of 8 Randomized Controlled Trials of Decompressive Hemicraniectomy vs Medical Management Only (Table view)

Trials	Time criteria, h	Age criteria (y)	NIHSS (or GCS) criteria	Neuroimaging criteria	Prestroke mRS criteria	Primary outcome	Findings
DECIMAL (2007, France) ⁴⁵ ; n=38	<24	18–55	>15; NIHSS 1a≥1	Brain CT ischemia >50% MCA territory; brain MRI DWI infarct volume >145 cm ³	0–1	mRS score 0–3 at 6 mo	No significant difference in favorable functional outcome (mRS score 0–3: 25% of surgical group vs 5.6% of medical group; <i>P</i> =0.18) at 6 mo; significant reduction in mortality (25% vs 78%; <i>P</i> <0.0001) in surgical group at 6 mo
DESTINY (2007, Germany) ⁴⁶ ; n=32	12–36	18–60	>18 for right-sided lesion; >20 for left-sided lesion; NIHSS 1a ≥1	Brain CT ischemia ≥2/3 MCA territory including part of basal ganglia	0–1	mRS at 6 mo (0–3 vs 4–6)	No significant difference in favorable functional outcome (mRS score 0–3) at 6 mo (47% of surgical group vs 27% of medical group; OR 2.44 [95% CI, 0.55–10.83]); significant reduction in mortality (survival rate 88% vs 47%; OR, 6.37 [95% CI, 1.35–29.17]) in surgical group at 30 d

Trials	Time criteria, h	Age criteria (y)	NIHSS (or GCS) criteria	Neuroimaging criteria	Prestroke mRS criteria	Primary outcome	Findings
HAMLET (2009, Netherlands) ⁴⁷ ; n=64	<96	18–60	>15 for right-sided lesion; >20 for left-sided lesion	Brain CT ischemia $\geq 2/3$ MCA territory	0–1	mRS at 12 mo (0–3 vs 4–6)	No significant difference in unfavorable functional outcome (mRS score 4–6: 75% vs 75%, ARR 0% [95% CI, –21 to 21]) at 12 mo; significant reduction in mortality (22% vs 59%, ARR 38% [95% CI, 15–60]) in surgical group at 12 mo
Slezins et al ⁴⁸ (2012, Latvia); n=24	<48	>18	>15	Brain CT or MRI ischemia $\geq 50\%$ MCA territory, or $>145 \text{ cm}^3$ infarct volume	0–1	mRS at 12 mo (0–4 vs 5–6)	Reduction in mortality in surgical group (survival rate 46% vs 8%, $P=0.06$ Fisher exact test)
Zhao et al ⁴⁹ (2012, China); n=47	<48	18–80	(GCS eye and motor score ≤ 9)	Brain CT ischemia $\geq 2/3$ MCA territory and space-occupying edema	0–1	mRS at 6 mo (0–4 vs 5–6)	Significant reduction in unfavorable outcome (mRS score 5–6: 33.3% vs 82.6%; ARR 49.3% [95% CI, 24.9–73.7]) and in mortality (12.5% vs 60.9%; ARR 48.4% [95% CI, 24.4–72.3]) in surgical group at 6 mo

Trials	Time criteria, h	Age criteria (y)	NIHSS (or GCS) criteria	Neuroimaging criteria	Prestroke mRS criteria	Primary outcome	Findings
HeADDFIRST (2014, North America) ⁸ ; n=24	<96	18–75	>17; NIHSS 1a <2	Brain CT ischemia \geq 50% MCA territory within 5 h OR complete MCA territory within 48 h; and anterior septum pellucidum shift from midline of \geq 7.5 mm OR pineal gland shift from midline \geq 4 mm (with deterioration in NIHSS 1a \geq 2)	0–2	Death at 21 d	No significant reduction in mortality at 21 d (21% of surgical group vs 40% of medical group; ARR 19% [90% CI, –13–50])
DESTINY II (2014, Germany) ⁵⁰ ; n=112	<48	>60	>14 for right-sided lesion; >19 for left-sided lesion; NIHSS 1a \geq 1	\geq 2/3 MCA territory including basal ganglia	0–1	mRS score 0–4 at 6 mo	Significant improvement in favorable outcome (mRS score 0–4: 38% vs 18%; OR, 2.91 [95% CI, 1.06–7.49]) and in mortality (33% vs 70%) in surgical group at 6 mo
HeMMI (2015, Philippines) ⁵¹ ; n=24	<72	18–65	(GCS 6–14 for right-sided lesion; 5–9 for left-sided lesion; or, GCS 15 on arrival with subsequent deterioration with NIHSS 1a \geq 1)	Brain CT ischemia >50% MCA territory	0–2	mRS at 6 mo (0–3 vs 4–6)	No significant difference in favorable functional outcome (mRS score 0–3: 23% of surgical group vs 38% of medical group; ARR, 13% [95% CI, –23 to 50]) or mortality (39% of surgical group vs 55% of medical group; ARR –16% [95% CI, –56 to 23]) at 6 mo

ARR indicates absolute risk reduction; CT, computed tomography; DWI, diffusion-weighted imaging; GCS, Glasgow Coma Scale; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

Mortality

Regardless of trial design, the collective results of the RCTs show that decompressive hemicraniectomy reduces mortality in malignant MCA infarctions. Of the studies that provided mortality data at 12 months (all except for HeADDFIRST and HeMMI [Hemicraniectomy for Malignant Middle Cerebral Artery Infarction]), 106/151 (70.2%) patients in the surgical groups were alive at 12 months, compared with 47/163 (28.8%) patients in the medical groups ($P<0.00001$), with an absolute risk reduction of 41.4%, and a number needed to treat (NNT)=2.4.^{45–50} Within the trials individually, the NNTs were small, mostly ≤ 3 , with the exception of the HeMMI trial (NNT=6) and the HeADDFIRST trial (NNT=23).^{8,45–51} Interestingly, HeADDFIRST had the lowest mortality rate in the conservative medical treatment group at 6 months (40.0%, with DESTINY having the second lowest mortality rate at 53.3%, with a range of mortality rates 40.0%–77.8% among the 6 trials that studied mortality rates at 6 months), while the mortality rate in the surgical arm was similar to that in the other studies.^{8,45,46,49–51} It was the most stringent in enforcing a standardized medical protocol, had the strictest neuroimaging criteria (required evidence of midline shift) for enrollment, and was one of only 2 trials with the longest enrollment time (enrolled up to 96 hours) after stroke onset. All 3 of these factors may have reduced the mortality benefit of decompressive hemicraniectomy by optimizing medical therapy, enrolling a cohort with more significant edema and thus worse surgical morbidity and mortality, and performing surgery after significant secondary brain injury had already incurred given the longer time to decompression. This trial raises the question of whether there should be a new focus on optimizing medical treatment in LHI that may ultimately negate the current perceived mortality benefits of surgical decompression; more research is required to make firm conclusions about this.

An important point to mention is that the difference in primary outcome between the medical and surgical arms in all of the studies was largely driven by the difference in mortality rate, which could have been confounded by withholding or withdrawing of life-sustaining therapies either by patient, family, or physician preferences. This is a factor at multiple stages of the trials, including whether eligible patients were ultimately randomized, whether they were withdrawn after randomization, and whether it contributed to the mortality rate after randomization. It is not clearly delineated in the trials whether those in whom decision was made to limit care were withdrawn from the study or were included in the final analysis. As such, a limitation in all the RCTs with regards to mortality outcomes was the effect of withdrawal of care at any time point between enrollment and follow-up. In addition, given the unblinded nature of in-hospital care of study participants (ie, inpatient physicians were aware whether or not a patient underwent hemicraniectomy or received medical care only), there may have been bias in the selection of patients that were approached for discussions about withdrawal or limitation of care.

Functional Outcome

With the exception of one patient in HeADDFIRST (mRS score of 1 at 180 days), no survivor had an mRS score of 0 to 1 in the 7 trials that provided a breakdown of mRS outcomes (HeMMI was the only trial that did not publish the breakdown of the full spectrum of mRS outcomes). A pooled analysis of DESTINY, DECIMAL, and HAMLET showed high absolute risk reductions with decompressive surgery compared with the medical group in functional outcomes at 1 year for both mRS score 0 to 3 (NNT=4, absolute risk reduction 23%) and mRS score 0 to 4 (NNT=2, absolute risk reduction 51%).⁵⁵ For the outcome of mRS score 0 to 4, the benefit was present whether or not there was aphasia. However, the significance of this finding is uncertain as the mRS does not take into account the disabilities encountered with aphasia. Of note, the pooled analysis included

only patients under the age of 60 and those that were treated within 48 hours of stroke onset. If including all the trials that showed the breakdown of mRS outcomes at 12 months (all except for HeADDFIRST and HeMMI), 40/151 (26.5%) patients in the surgical groups obtained a favorable outcome with a mRS of 3 or less, compared with 21/163 (12.9%) in the medical groups. If a favorable outcome is defined as mRS score of 4 or less, 88/151 (58%) patients in the surgical groups obtained a favorable outcome, compared with 36/163 (22%) in the medical groups. As can be seen in **Figure 2**, which pools the mRS outcomes at 12 months between the medical and surgical groups from 6 of the 8 RCTs (DECIMAL, DESTINY, HAMLET, Slezins et al, Zhao et al, DESTINY II), the additional survivors gained in the surgical groups achieved different mRS outcomes across the board, but the majority of survivors had an mRS score of 4 or 5 at 12 months.⁴⁵⁻⁵⁰ It is difficult to generalize the definition of a favorable outcome and thus exists the variability in outcome measures between the studies; however, a multicenter international survey of over 1800 physicians found that while a mRS score of 3 was considered acceptable by 79% of the respondents, only 38% considered a mRS score of 4 to be acceptable.⁵⁷

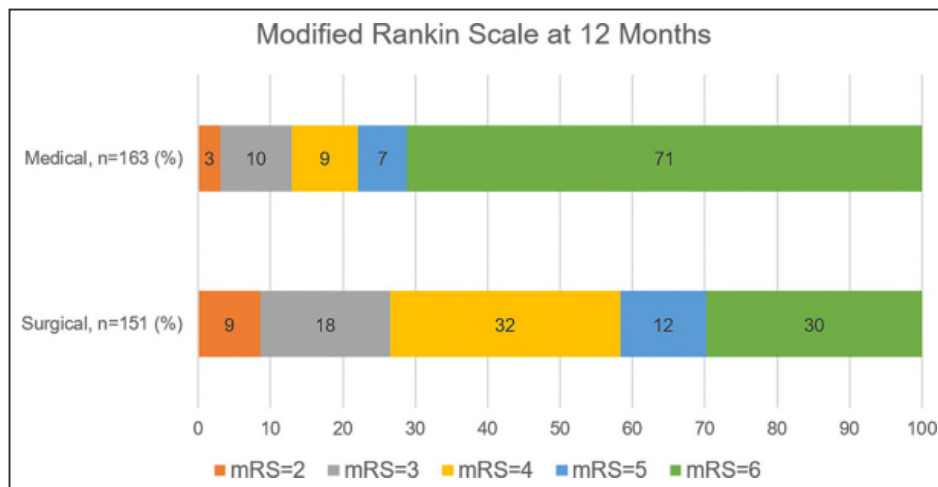


Figure 2. A pooled analysis of functional outcomes as measured by modified Rankin Scale (mRS) at 12 months between the medical management groups and the decompressive hemicraniectomy groups of 6 randomized controlled trials (DECIMAL, DESTINY, HAMLET, Slezins et al,⁴⁸ Zhao et al,⁴⁹ DESTINY II).^{45-47,50}

DECOMPRESSIVE SURGERY IN OLDER PATIENTS

Multiple studies have shown that while there is a mortality benefit with decompressive surgery in older patients, the margin of benefit is lower, and there is a higher likelihood of poor functional outcome compared with younger patients.^{4,58-61} This difference in benefit from surgery is seen even when using an age cutoff as young as age 50, as shown by Uhl et al⁶⁰ and Gupta et al,⁴ which both showed a higher incidence of severe disability or death in those over the age of 50.

While 5 of the 8 RCTs enrolled patients over the age of 60, the mean or median ages in the trials were all under the age of 65, with the exception of DESTINY II, which specifically studied patients over the age of 60 years (median age of 70). In fact, the mean age in DECIMAL, DESTINY, and HAMLET was under 50.⁴⁵⁻⁴⁷ The trials that enrolled patients older than the age of 60 were: Slezins et al,⁴⁸ Zhao et al,⁴⁹ HeADDFIRST, DESTINY II, and HeMMI.^{8,50,51} Slezins et al⁴⁸ and DESTINY II were the only 2 that did not have an upper limit to the age criteria.⁵⁰ HeADDFIRST and HeMMI did not specify what proportion of their study survivors were over the age of 60 (8/24 randomized patients in HeADDFIRST were over age 60).^{8,51} Slezins et al did not

have any survivors over the age of 60 from the surgical group; the sole survivor in the medical group was age 72.⁴⁸

The majority of survivors in Zhao et al⁴⁹ and DESTINY II from the surgical groups compared with the medical groups essentially shifted from a mRS score of 5 to 4.⁵⁰ Indeed, if the primary outcome of DESTINY II had been a mRS dichotomized as 0 to 3 versus 4 to 6 (rather than 0–4 versus 5–6), this would have been a negative trial. Furthermore, none of the patients over the age of 60 in Zhao et al⁴⁹ or in DESTINY II achieved a mRS score of 0 to 2 at 6- or 12-month follow-up.⁵⁰ While an individualized approach to family and patient counseling is generally recommended, it is important to note that the chances of obtaining a functional outcome after surgical decompression in patients over age 60 to 65 years in which the patient would be able to ambulate independently are slim and that most likely the patient would require significant assistance with many routine daily activities.

Age may also play a role in the level of satisfaction post-hemicraniectomy. Some studies have found that patients over the age of 70 would accept only favorable mRS scores post-surgery as compared with those under the age of 60, while others have found that older patients had higher indicators of quality of life (QOL) and a higher rate of retrospective consent for surgery.^{62,63}

DOMINANT VERSUS NONDOMINANT HEMISPHERIC INFARCTS

There is a lingering trepidation among some practitioners about decompressive surgery in patients with dominant hemispheric strokes. This bias is largely tied to the perception of worse functional outcome and quality of life related to aphasia. While one retrospective analysis by Kastrau et al⁶⁴ found that over 90% of their patients with aphasia demonstrated improvement at follow-up with formal aphasia testing, all of the patients in this cohort were age 50 or under. What is notable is that the recovery time frame from aphasia seems to be a protracted one, with reports of significant recovery occurring >1 year poststroke, including a case report of language improvement progressing even up to 25 years poststroke.^{65,66}

A systematic review of case reports and case series performed by Gupta et al⁴ in 2004 in addition to the pooled analysis of DECIMAL, DESTINY, and HAMLET found that functional outcome was not worse in those who underwent decompressive surgery for a dominant hemispheric infarct.⁵⁵ However, scales commonly used to measure functional outcomes such as the mRS, Barthel Index, Glasgow Outcome Scale, and Glasgow Outcome Scale—Extended do not adequately reflect the extent of disability attributable to aphasia from a dominant hemispheric stroke. Conversely, the extent to which neglect and abulia related to nondominant hemispheric strokes hinder rehabilitative efforts is likely underestimated.

Of the RCTs, HeADDFIRST was the only one that reported the lateralization of the infarct per survivor.⁸ For either hemisphere, whether in the surgical or medical group, the majority of survivors had an mRS score of 4 or greater. However, the numbers in each cohort were too small to make any firm conclusions about this. Of the 8 trials, 6 published data either on stroke lateralization or presence of aphasia in their patients (all except for DECIMAL and Slezins et al; in HAMLET, patients were characterized as having aphasia or not, whereas the other trials reported stroke lateralization).^{8,46,47,49–51} From these 6 trials, 126/303 (41.6%) patients had dominant hemisphere infarcts, with no significant difference in distribution between the surgical and medical treatment only groups (59/126 in the surgical group, 67/126 in the medical group).

Overall, we do not have enough evidence to suggest that patients with dominant hemisphere strokes have worse outcomes than those with nondominant hemisphere strokes, and it is difficult

as health care providers to determine what deficits would be more acceptable to patients. While decompressive surgery is often not offered in dominant hemisphere strokes due to a perceived unacceptable quality of life, one study suggests that patients may actually find motor impairment to be associated with a worse quality of life than global aphasia.⁶⁷

TIMING OF SURGERY

The pooled analysis of DECIMAL, DESTINY, and HAMLET showed benefit in obtaining a mRS score of 3 or less, as well as a reduced mortality, when patients were treated within 48 hours of stroke onset, and this benefit was present whether patients were treated under 24 hours or between 24 and 48 hours.⁵⁵ Of the 3 trials, HAMLET was the only one that allowed for randomization after 48 hours.⁴⁷ A subgroup analysis in HAMLET found that those randomized within 48 hours of stroke onset had significant benefit from decompressive surgery for achieving a mRS score of 4 or less as well as in case fatality; no such benefit was found in the subgroup randomized after 48 hours. HeADDFIRST and HeMMI were the only other RCTs that allowed for randomization after 48 hours.^{8,51} The mean time to surgery in HeADDFIRST was 57.1 hours and in HeMMI was 36.6 hours; neither studies performed a subgroup analysis based on time to surgery. In HeADDFIRST, 8/14 (57.1%) patients underwent surgery after 48 hours of stroke onset; however, the numbers were too small to make any meaningful interpretation with regards to timing of surgery and functional outcome.

A large retrospective analysis by Dasenbrock et al⁶⁸ explored the optimal timing of decompressive hemicraniectomy using the Nationwide Inpatient Sample. From 2002 to 2011, 1301 admissions for ischemic stroke underwent decompressive surgery. They found that later surgery was associated with more discharges to institutional care as well as a higher rate of poor outcome. In dichotomized analyses, these associations were not found at 48 hours but were found when surgery was performed after 72 hours.⁶⁸ Notably, the associations found between surgery timing and outcomes were present only when cerebral herniation was present. This study raises the possibility that the timing of surgery may not matter if there is no clinical progression to herniation. Gupta et al⁴ also did not find a difference in outcomes in their retrospective analysis of 138 patients when timing of surgery was dichotomized to within 24 hours versus after 48 hours.

QUALITY OF LIFE AND PATIENT SATISFACTION AFTER LARGE HEMISPHERIC STROKES

Ultimately, the value of decompressive hemicraniectomy in LHI depends on whether or not it was worth it to the patient. While QOL was not a primary outcome in any of the RCTs, a few of them did include it as a secondary outcome. DECIMAL, DESTINY, DESTINY II, and HAMLET reported the results of questionnaires administered to patients or to their caregivers.^{45–47,50} Different assessments were utilized, such as the Stroke Impact Scale, the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), and the EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D) visual analogue scale. Surveys about depression symptoms were conducted for DESTINY II and HAMLET.^{47,50} In DESTINY II, the majority of patients in both the surgical and medical treatment groups did not report severe depressive symptoms; however, it is not clear what proportion had minor depression.⁵⁰ In HAMLET, the majority of patients in both arms reported mild symptoms of depression, with no significant difference in incidence between

the 2 groups.⁴⁷ In the RCTs that assessed for retrospective consent to treatment, the majority of patients or their caregivers in the surgical groups retrospectively agreed to the treatment they received.

Rahme et al⁶⁹ performed a systematic review of the literature and found 16 studies—including DECIMAL, DESTINY, and HAMLET—reporting on QOL and level of satisfaction post-hemicraniectomy for malignant MCA stroke. They found that the mean overall reduction of QOL was 45%, that depression affected over half of the respondents, but that the majority of patients and/or caregivers (77% of those interviewed) were satisfied and would give retrospective consent for surgery. Of note, most of the studies included were nonrandomized, and only a quarter of the patients among all the studies reviewed had a dominant hemisphere stroke. The findings of this review have to be interpreted cautiously, as the majority of those who did not respond to the assessments were unable to because of significant neurological deficit and/or aphasia, and thus there is possibly a selection bias to these patient/caregiver-reported results.

CURRENT GUIDELINES

The American Heart Association/American Stroke Association published guidelines on the management of acute ischemic stroke in 2018 that were endorsed by the Neurocritical Care Society, the American Association of Neurological Surgeons, and the Congress of Neurological Surgeons.^{70,71} It provided 2 class I recommendations: one regarding early discussion of care options and possible outcomes with patients and caregivers for shared decision-making, the other recommending that patients be transferred early to an institution with neurosurgical expertise if at risk for malignant brain edema. There are 2 class IIa recommendations with corresponding level A evidence: that it is reasonable to use a decrease in level of consciousness as a selection criteria for decompressive surgery (although the optimal trigger remains unknown), and that it is reasonable to perform decompressive surgery in those ≤ 60 years of age who deteriorate within 48 hours from cerebral edema associated with unilateral MCA infarctions despite medical therapy. In patients over the age of 60, there is a class IIb recommendation with level B evidence that surgical decompression can be considered if there is deterioration within 48 hours from edema associated with unilateral MCA infarction despite medical therapy. Guidelines were also published by the American Heart Association/American Stroke Association in 2014 specifically on the management of cerebral and cerebellar infarctions with swelling.⁷² Class I recommendations about neuroimaging were published on CT and magnetic resonance imaging findings that may be useful in predicting a severe extent of cerebral edema; these findings include hypodensity on head CT within the first 6 hours of stroke onset involving one-third or more of the MCA territory, early midline shift, and magnetic resonance imaging diffusion-weighted imaging volume within 6 hours ≥ 80 mL.

The Neurocritical Care Society and the German Society for Neuro-Intensive Care and Emergency Medicine jointly published guidelines regarding the management of LHI in 2015.² The recommendations are similar to those of the American Heart Association/American Stroke Association but include the following 2 additional points: that the evidence is currently insufficient to recommend against surgery based on stroke laterality alone, and that a minimum incision length of 12 cm should be performed for surgical decompression.²

CONCLUSIONS AND FUTURE DIRECTIONS

While significant progress has been made about the role of decompressive hemicraniectomy in LHI, there is still much left to learn. What studies have shown thus far is that decompressive hemicraniectomy improves survival and functional outcome, but the majority of survivors live with at least a moderately severe disability. The proportion of survivors with moderately severe to severe disability increases in the elderly.

Predictors of who will ultimately require surgical decompression and the optimal timing of surgery remain to be parsed out. Better understanding of the pathophysiology of edema development and secondary brain injury may not only help form better prediction models but also improve medical therapies in cerebral swelling. Optimization of medical and neurocritical care may potentially reduce the need for surgery. It should also be noted that advancement in other therapies of acute ischemic stroke such as thrombolytics and thrombectomy may further mitigate the need for hemicraniectomy. Another aspect of medical care to consider that requires further evaluation is the optimal provider setting in which these patients should be cared for. While most of the RCTs admitted enrolled patients to intensive care units, there was a higher proportion of surgical patients in an ICU setting, compared with medical patients. The differences in level of care alone could have confounded the outcomes.

Continued research into QOL and patient-centered outcomes are needed, including novel evaluation methods that can more adequately assess those with significant neurological deficits and/or aphasia. Last but not least, further work is needed to enhance shared decision-making with the patient and caregiver, including reconciliation of differences that may exist between the preferences of the patient and that of the health care provider.

ARTICLE INFORMATION

For Sources of Funding and Disclosures, see page 1508.

Correspondence

Correspondence to: Jennifer A. Frontera, NYU Grossman School of Medicine Department of Neurology, 150 55th St, Brooklyn, NY 11220. Email jennifer.frontera@nyulangone.org

Affiliations

Division of Neurocritical Care, Department of Neurology, New York University Langone Health (J.L., J.A.F.), New York, NY. Department of Neurology, Bellevue Hospital Center (J.L.), New York, NY.

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