Large ischemic strokes presenting as malignant cerebral edema account for 1%–10% of all ischemic strokes. Mortality rates have been reported to be as high as 80%, and most of the survivors are left severely disabled. An MCA infarction is the usual culprit, but the anterior and posterior cerebral arteries may additionally be affected. Early death is a result of transtorial herniation while delayed death is typically due to the medical complications of prolonged hospitalization including pneumonia and pulmonary emboli. Although decompressive craniectomy has been shown to significantly decrease mortality, high morbidity rates among survivors have tempered enthusiasm for this procedure. This reluctance has been most pronounced in elderly patients and those with dominant hemisphere infarcts. The span of the optimal operative time window when surgical decompression is superior to medical management alone is also subject to debate.

Predictors of Malignant Cerebral Edema

Severely compressive brain edema is associated with significant mortality and morbidity. From a pathophysiological standpoint, early intervention could minimize secondary ischemia of viable tissue around the infarcted core and possibly prevent herniation. Optimal utility of this procedure would require identifying the population that is most likely to benefit in a way that meets patients’ a priori expectations as well as those of their families and caretakers.

With that objective in mind and by using diffusion-weighted MR imaging, Oppenheim et al. reported that a stroke volume greater than 145 cm³ within 14 hours of onset of stroke symptoms has 100% sensitivity and 94% specificity for predicting the progression to malignant edema. Additionally, in a retrospective multicenter case-control study of 201 patients who suffered a massive MCA stroke, Kasner et al. identified stroke volume greater than 50% of the MCA territory, high white blood cell count, additional involvement of the anterior or posterior cerebral artery, systolic blood pressure higher than 180 mm Hg within 12 hours of stroke onset, and a history...
of hypertension or heart failure as additional risk factors for the progression toward malignant edema. Similarly, Krieger et al.15 found that patients with an NIHSS score of 20 or greater on admission or who present with nausea or emesis are at high risk for developing malignant cerebral edema.

In addition to clinical and radiographic risk factors, serum levels of the astroglial protein S100B have been shown to be predictive of malignant cerebral edema with 94% sensitivity and 83% specificity (for a value of 1.03 μg/L at 24 hours from the ischemic event).2 This may become a useful monitoring tool at crucial clinical time points at which the development of cerebral edema is believed to be an imminent possibility, once a commercially available bedside kit is available.

Best Medical Treatment

Optimal medical management for malignant edema due to stroke has not been standardized. In the HAMLET (Hemicraniectomy After Middle cerebral artery infarction With Life-Threatening Edema Trial), recommendations for medical management of stroke-related malignant edema included admission to the intensive care unit, osmotherapy with mannitol or glycerol, invasive monitoring of intracranial pressure, blood pressure control, elevation of the head to 30°, and maintenance of normothermia, normoglycemia, and normovolemia. Morbidity and mortality rates are high for this disease entity despite such aggressive measures.

Evidence for Decompressive Craniectomy

Craniectomy for the relief of cerebral edema associated with ischemic stroke was first described in the 1970s8,14 and is intended to prevent life-threatening herniation. Although the impact on mortality appeared unequivocal in most studies, several controversies lingered and led to recent randomized trials, which are discussed below.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Year</th>
<th>No. of Pts</th>
<th>Inclusion Criteria</th>
<th>Time to Tx (hrs)</th>
<th>Primary Outcome Measure</th>
<th>Mortality (%)</th>
<th>Good Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DESTINY</td>
<td>2007</td>
<td>32</td>
<td>age 18–60 yrs, NIHSS &gt;18–20, &gt;2/3 MCA territory</td>
<td>36</td>
<td>death at 30 days, mRS score &lt;4 at 6 mos</td>
<td>17.6</td>
<td>53.0</td>
</tr>
<tr>
<td>DECIMAL</td>
<td>2007</td>
<td>38</td>
<td>age 18–55 yrs</td>
<td>24</td>
<td>mRS score &lt;4 at 6 mos</td>
<td>25.0</td>
<td>77.8</td>
</tr>
<tr>
<td>HAMLET</td>
<td>2009</td>
<td>64</td>
<td>age 18–60 yrs</td>
<td>96</td>
<td>mRS score &lt;4 at 12 mos</td>
<td>22.0</td>
<td>59.0</td>
</tr>
<tr>
<td>HeADDFIRST</td>
<td>NA</td>
<td>26</td>
<td>acute unilat MCA territory ischemia</td>
<td>96</td>
<td>death, functional outcome, quality of life, pt perceptions, acute health care use after 21, 90, &amp; 180 days</td>
<td>recruiting patients</td>
<td>recruiting patients</td>
</tr>
<tr>
<td>HeMMI</td>
<td>NA</td>
<td>NA</td>
<td>ischemic MCA stroke, GCS Score 6–14/5–9</td>
<td>GCS, NIHSS, mRS, &amp; Barthel Index; functional outcome at 6 mos</td>
<td>recruiting patients</td>
<td>recruiting patients</td>
<td></td>
</tr>
<tr>
<td>DESTINY II</td>
<td>NA</td>
<td>NA</td>
<td>age ≥61 yrs, MCA malignant infarct</td>
<td>48</td>
<td>mRS score &lt;5 at 6 mos</td>
<td>recruiting patients</td>
<td>recruiting patients</td>
</tr>
</tbody>
</table>

* GCS = Glasgow Coma Scale; NA = not available; Pt = patient.
Decompressive craniectomy after malignant MCA infarction

Table 2: Modified Rankin Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>asymptomatic</td>
</tr>
<tr>
<td>1</td>
<td>no significant disability; able to carry out all usual activities, despite some symptoms</td>
</tr>
<tr>
<td>2</td>
<td>slight disability; able to look after own affairs w/o assistance, but unable to carry out all previous activities</td>
</tr>
<tr>
<td>3</td>
<td>moderate disability; requires some help, but able to walk unassisted</td>
</tr>
<tr>
<td>4</td>
<td>moderately severe disability; unable to attend to own bodily needs w/o assistance, unable to walk unassisted</td>
</tr>
<tr>
<td>5</td>
<td>severe disability; requires constant nursing care &amp; attention, bedridden, incontinent</td>
</tr>
<tr>
<td>6</td>
<td>dead</td>
</tr>
</tbody>
</table>

months for DESTINY and DECIMAL and 1 year for the HAMLET (Table 2). The primary outcome was dichotomized between an mRS score of 0–3, defined as good outcome, and 4–6, defined as poor outcome. The crucial difference between a score of 3 and a score of 4 is that in the former, individuals still possess the ability to walk and attend to their bodily needs unassisted. A major difference in trial design was the time window for craniectomy. Surgical decompression was initiated within 24 hours of symptom onset in DECIMAL, between 12 and 36 hours in DESTINY, and within 96 hours in HAMLET.

After the completion of the HAMLET, the authors published pooled data from the 3 randomized trials.\(^7\) The meta-analysis only included individuals treated within 48 hours of symptom onset from the HAMLET, thus excluding 11 patients and totaling 109 patients. Fifty-eight patients had been assigned to hemicraniectomy and 51 to medical treatment alone. The primary outcome was changed to include an mRS score of 4 in the good outcome category. The dichotomization was thus made between an mRS score of 1–4 for good outcome and an mRS of 5 or 6 for bad outcome.

Results of the RCTs

**Effect on Mortality.** The DECIMAL and DESTINY trials were stopped early in 2006 as ongoing data analysis demonstrated significant mortality reduction in the surgical group compared with those receiving medical treatment. All 3 of the European trials showed a significant reduction in mortality in patients belonging to the surgical arm, with an absolute risk reduction of 53% at 6 months in DECIMAL, and 38% at 1 year in HAMLET. DESTINY also showed a 12% mortality rate in surgically treated patients at 30 days, versus 53% in the medical treatment arm. In the meta-analysis, the absolute risk reduction in mortality with surgery was found to be 49.9% (95% CI 33.9%–65.9%), which meant that the number needed to treat to prevent death equaled 2. The authors concluded that surgical decompression within 48 hours of stroke onset reduced the risk of death.

**Effect on Severe Disability (mRS Score 5).** The DECIMAL, DESTINY, and HAMLET studies showed a statistically significant reduction in severely disabled, bedridden patients (mRS score > 4). In the pooled analysis of the 3 pooled studies, the absolute reduction in risk for a bad functional outcome was 41.9% (95% CI 25.2%–58.6%). As a result, the authors concluded that surgical decompression within 48 hours of stroke onset reduced the risk of significant morbidity.

**Effect on Moderately Severe Disability (mRS Score 4).** The primary outcome measure in the 3 RCTs defined a good outcome as an mRS score of 3 or less. The goal was to prove a significant reduction in the number of patients unable to attend to their bodily needs or walk unassisted (mRS score of 4). Unfortunately, none of the 3 trials reached statistically significant conclusions favoring a good functional outcome after craniectomy as defined by their primary outcome measure, although there was a trend in this direction in DESTINY and DECIMAL studies. This conclusion may not have reached statistical significance because of the small number of patients included in both trials, since they were prematurely terminated. Additional studies with larger patient groups are needed before drawing definite conclusions.

**Disability in Survivors.** Separate and pooled analyses of the DECIMAL, DESTINY, and HAMLET trials, while demonstrating an undeniable increase in the number of survivors among surgical patients, also showed an increase in the number of survivors with moderately severe disability (mRS score of 4). This fact necessitates careful discussion with the patient’s family and/or power of attorney to be sure that outcomes associated with craniectomy are in keeping with patient wishes. Quality of life issues are difficult to put in proper perspective, but the randomized studies discussed above help clarify some facets of this important subject. Future studies will need to focus more rigorously on the long-term quality of life in survivors. There exists a difficult balance between increasing survival and poor neurological outcome, which inherently includes the subjective assessment of outcome along a continuum. Further investigations regarding the neurological outcome of patients after decompression, as well as better standardization of functional outcome measures in larger series, is certainly warranted.

**Dominant Hemisphere Involvement**

While the fear of complete aphasia was classically the reason behind the refusal to operate on large dominant hemispheric strokes, recent data have suggested that nondominant hemispheric injuries leading to serious depression and neglect can be as disabling as aphasia during the rehabilitation process.\(^27\) Additionally a subset analysis in the DECIMAL trial showed no difference in the mRS scores of survivors with or without aphasia at 1 year; in addition, all surgical survivors agreed with the decisions to undergo surgery when asked retrospectively, including patients still experiencing aphasia.\(^16\) Stroke laterality and its correlation with outcome\(^14,17,21\) have also been the subject of subgroup analysis in the other European trials,\(^5,10,24,25\) and controlled and uncontrolled studies have
shown no predicative value for outcome related to laterality. Clearly this issue will continue to warrant debate and should be further studied.

**Surgical Technique and Craniectomy Size**

Wagner et al.\(^2^6\) retrospectively reviewed 60 patients who were admitted with malignant MCA infarcts. They studied the impact of craniectomy size, shape, and location on parenchymal hemorrhagic and ischemic lesions, postoperative bleeding, and mortality. Interestingly, they found a 70% rate of hemicraniectomy-associated infarcts and hemorrhage. Bleeding was associated with a small craniectomy size and sharp bone defects. Parenchymal hemorrhage was the only factor that statistically affected mortality rate, with only 55% of patients surviving compared with 80% in the absence of hemorrhage. Their recommendation for craniectomy size was a diameter larger than 12 cm. This conclusion was validated by the fact that some studies suggest that doubling the diameter from 6 cm to 12 cm potentially increases the decompressive volume from 9 to 86 mL.\(^2^6^,2^9\) Ideally, hemicraniectomy should be performed in the frontotemporoparietal region and reach the floor of the middle cranial fossa. The midline should be spared to avoid injury to the superior sagittal sinus.

**Surgical Complications**

The outcomes of patients undergoing decompressive craniectomy may be impacted by the complications of the procedure.\(^2^5\) Reported complications include inadequate decompression,\(^2^6\) infection,\(^2\) hemorrhage, and the development of contralateral fluid collections.\(^1^3\) Furthermore, delayed sinking flap syndrome may result in headaches, seizure and focal neurological deficits and is typically cured by replacement of the bone flap.\(^1^\) Similarly, hydrocephalus may develop in a delayed fashion.\(^2^8\)

**Time Window for Surgery**

The question of the optimal time window for intervention has not yet been completely elucidated. Although the pooled data from the European trials seem to show benefit from early surgery, only a small number of patients (11) was included in the late group in the HAMLET, and definite conclusions cannot be drawn at this time.\(^2^3\) Additionally, a major systematic review of the literature did not demonstrate a difference in outcome based on timing.\(^4\) Clear definition of a time window for intervention will be essential to creating treatment guidelines. With that purpose in mind, 2 additional RCTs have been initiated. The North American HeADDFIRST (Hemicraniectomy And Durotomy on Deterioration From Infarction Related Swelling Trial), aimed to evaluate patient outcome after hemicraniectomy within 96 hours from symptom onset, and is awaiting publication. The HeMMI trial (Hemicraniectomy for Malignant Middle cerebral artery Infarcts) in the Philippines, is studying patient morbidity and mortality after decompressive surgery within 72 hours from symptom onset and is still in the process of recruiting patients.

**References**


**Surgical Age Limit**

As noted above, randomized trials to date have focused on patients 60 years of age and younger, thus leaving us with very few data regarding patients older than 60 years of age. The HAMLET displayed conflicting results with previous review series,\(^4\) with a trend toward better outcome in the upper age categories (51–61 years). These results raised questions about the existence of an age limit for surgical benefit. The DESTINY 2 trial is currently underway and will shed more light on the impact of surgery in patients older than 60 years.\(^9\)

**Conclusions**

Pooled analysis of the European trials discussed above provides Class I evidence for the performance of early decompressive craniectomy in the setting of large unilateral infarcts (volume > 145 cm\(^3\)) within 48 hours of the ischemic event.\(^1^1\) Given the potential tradeoff between survival and good neurological outcome, frank discussion with the patient and the family should be held early in the setting of an envisioned need for surgical decompression, while keeping in mind that 2 RCTs reported a trend of reduced disability among survivors. Although the surgical age limit has not yet been fully defined, very few data exist to support hemicraniectomy for patients older than 60 years, although individual circumstances may outweigh paucity of data issues. Further studies are needed to better define quality of life issues at long-term follow-up as well as age limit issues. Ultimately, MCA infarction with malignant edema is a devastating disease for which hemicraniectomy can play a positive role. New strategies are needed to enhance long-term outcomes, which will likely extend across the entire stroke continuum from the acute phase to the rehabilitation period.

**Disclosure**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Bendok, Batjer, Arnaout, Aoun. Acquisition of data: Arnaout, Aoun. Analysis and interpretation of data: Arnaout, Aoun. Drafting the article: Arnaout, Aoun. Critically revising the article: Bendok, Batjer.
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