implicated as protective, deleterious, or insignificant regarding oncological outcomes. Ultimately, akin to oncologists selecting the most efficacious systemic therapy by tumour-type, the field of onco-anaesthesia may evolve towards balancing analgesia based upon anticipated oncological impact. Pending prospective trials, this may mean reducing intraoperative opioid use for RCC.

Authors' contributions

Study design: AWS, MLH, JAC, RM, PR, KST, GWF, PJM, AAH, JSM
Analysis: AWS, MLH, JAC, KA, JRS, PR, KST, AAH, JSM
Drafting: AWS, RGD, JM, KST, JSM
Revising, final approval, agree to be accountable: all authors
Data acquisition: RM, RGD, JM, PR, KST, GWF, PJM, AAH, JSM

Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

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References

1. Dabestani S, Beisland C, Stewart GD, et al. Intensive imaging-based follow-up of surgically treated localised renal cell carcinoma does not improve post-recurrence survival: results from a European Multicentre Database (RECUR). *Eur Urol* 2019; **75**: 261–4
2. Kim R. Effects of surgery and anesthetic choice on immunosuppression and cancer recurrence. *J Transl Med* 2018; **16**: 8
3. Sekandarzad MW, van Zundert AAJ, Lirk PB, Doornebal CW, Hollmann MW. Perioperative anesthesia care and tumor progression. *Anesth Analg* 2017; **124**: 1697–708
4. Wigmore T, Farquhar-Smith P. Opioids and cancer: friend or foe? *Curr Opin Support Palliat Care* 2016; **10**: 109–18
5. Patanwala AE, Duby J, Waters D, Erstad BL. Opioid conversions in acute care. *Ann Pharmacother* 2007; **41**: 255–66
6. Kovac E, Firoozbakhsh F, Zargar H, Fergany A, Elsharkawy H. Perioperative epidural analgesia is not associated with increased survival from renal cell cancer, but overall survival may be improved: a retrospective chart review. *Can J Anaesth* 2017; **64**: 754–62
7. Okhunov Z, Juncal S, Ordon M, et al. Comparison of outcomes in patients undergoing percutaneous renal cryoablation with sedation vs general anesthesia. *Urology* 2015; **85**: 130–4
8. Cata JP, Keerty V, Keerty D, et al. A retrospective analysis of the effect of intraoperative opioid dose on cancer recurrence after non-small cell lung cancer resection. *Cancer Med* 2014; **3**: 900–8
9. Oh TK, Jeon JH, Lee JM, et al. Investigation of opioid use and long-term oncologic outcomes for non-small cell lung cancer patients treated with surgery. *PLoS One* 2017; **12**, e0181672
10. Du KN, Feng L, Newhouse A, et al. Effects of intraoperative opioid use on recurrence-free and overall survival in patients with esophageal adenocarcinoma and squamous cell carcinoma. *Anesth Analg* 2018; **127**: 210–6
11. Page GG, Blakely WP, Ben-Eliyahu S. Evidence that postoperative pain is a mediator of the tumor-promoting effects of surgery in rats. *Pain* 2001; **90**: 191–9

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Persistence of intracranial blood flow on cerebral angiography in brain death

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Editor—Brain death is a clinical state of complete, irreversible loss of cerebral function, given a known cause.[1] Brain death is recognised and accepted in most developed countries, although some variability exists in the exact criteria.[2] In Singapore, brain death certification requires a single test fulfilling seven clinical criteria: absent pupillary, corneal, oculocephalic, vestibulo-ocular, and gag reflexes; absent response to pain; and an apnoea test to a carbon dioxide tension of 6.7 kPa.[3] This is performed by two independent physicians not involved in the patient's care. In the context of potential organ procurement, neither can be part of the transplant team nor involved in the recipient's care.[3] Jurisdictions, such as the UK and Japan, require repeat testing.[2 4]

As brain death testing usually precedes withdrawal of extraordinary life support measures or organ procurement, it is an emotive topic of profound legal, ethical, and social import. Clinical testing of brainstem function alone suffices in many countries[1–4]; however, confounders, such as cervical spine instability, drug toxicity, or inability to perform apnoea testing, may preclude this.[5] Such situations require confirmation with ancillary tests demonstrating either electrical activity loss or cerebral blood flow arrest.[5]

Studies demonstrating cerebral circulatory arrest, such as cerebral angiography, are generally accepted for diagnosing brain death, as a brain with no blood supply becomes ischaemic and eventually progresses to cellular death. However, persistent cerebral perfusion provides little information on cellular metabolic activity or viability. Whilst Singapore and the UK[4] do not require ancillary tests unless clinical criteria cannot be fulfilled, France, Italy, and Japan mandate ancillary testing to diagnose brain death.[2 4] Here, we describe residual intracranial perfusion on cerebral angiography in two clinically brain-dead patients after decompressive craniectomy (informed consent for publication was obtained from a legally responsible representative for each patient).

In Case 1, a 74-yr-old gentleman was admitted after a fall with a past medical history of arterial hypertension, dyslipidaemia, diabetes mellitus, and a previous subcortical infarct. His Glasgow Coma Scale (GCS) was 5, and CT showed acute bilateral subdural haematoma, with midline shift and marked mass effect. Emergency left decompressive craniectomy was performed, and an intraparenchymal catheter revealed intracranial pressure (ICP) of 56 mm Hg. Immediate CT imaging showed new pontine and midbrain haemorrhages, worsening midline shift, and uncal herniation. Urgent right decompressive craniectomy was performed, and ICP was 70 mm Hg. Pupils were fixed and dilated. Sedation was stopped at 16 h; GCS remained at 3, with absent cough and gag reflexes. Intracranial pressure remained 63–84 mm Hg. At 72 h, all seven clinical criteria for brain death were fulfilled.

To provide the family with closure, four-vessel angiography was performed at 78 h. Bilateral common carotid and the left vertebral arteries were cannulated, demonstrating flow in bilateral internal carotid arteries, vertebrobasilar system, and posterior cerebral arteries, with attenuation of cortical branches (Fig. 1). During the study, cerebral perfusion pressure was 39–71 mm Hg (Supplementary Appendix A). However, local guidelines require the angiographic catheter to be positioned just proximal to the origin of the innominate

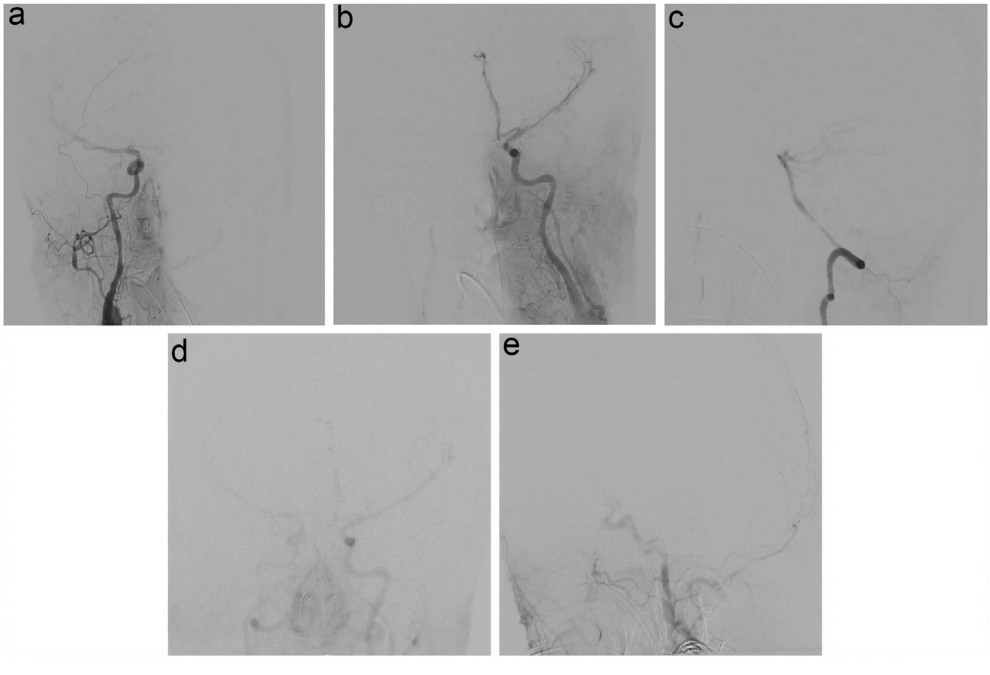

Fig 1. Anteroposterior views of the (a) right common carotid and (b) left common carotid, and (c) lateral view of the left vertebral artery angiography images obtained from the first selective four-vessel angiography study of Case 1, and (d) anteroposterior and (e) lateral images obtained from the second cerebral angiography study of Case 1. In all images, no cortical perfusion was present, and there was insufficient flow to produce a venous phase angiogram.

artery.[6] Thus, a repeat study was performed at 95 h as the catheter was placed more cranially than stipulated. From a catheter in the ascending aorta, proximal to the innominate artery, sluggish flow was seen in bilateral middle and anterior cerebral arteries, but absent in the cortex, posterior circulation, and venous system (Fig. 1) with cerebral perfusion pressures of 19–40 mmHg (Supplementary Appendix A). Withdrawal of care was discussed with the patient's family in view of the poor prognosis, with terminal extubation performed and ensuing cardiac death.

In Case 2, a 72-yr-old gentleman with a history of arterial hypertension, diabetes mellitus, and hyperlipidaemia was admitted after an unwitnessed fall. His GCS was 8, and CT imaging revealed bilateral subdural and right extradural haematoma with midline shift. Emergent decompressive craniectomy was performed, during which the brain was oedematous and herniated through the durotomy. Profound hypotension requiring high-dose inotropes and vasopressors ensued. An intraparenchymal catheter demonstrated an ICP of 60 mm Hg on closure. Pupils were fixed and dilated. Sedation was discontinued and GCS was 3, with absent cough and gag reflexes. At 48 h, all seven clinical criteria for brain death were met. However, as levetiracetam was administered on admission, the patient underwent cerebral angiography as required by local guidelines.[6] A catheter in the aortic arch demonstrated sluggish contrast flow into the intracranial arteries insufficient to produce a venous phase angiogram, with cerebral perfusion pressures of 41–43 mm Hg (Supplementary Appendix A). Withdrawal of care was discussed with the patient's family in view of the poor prognosis, and terminal extubation was performed with subsequent death.

Cerebral angiography has been regarded as a reference standard amongst ancillary tests for brain death.[5] However, persistent intracranial blood flow has been reported in clinically brain-dead patients on cerebral angiography,[6] CT angiography,[7] and radionuclide scanning,[8] despite absent electrical activity on electroencephalography in one report.[7] One study reported proximal opacification on four-vessel angiography in nine out of 32 patients certified brain dead.[6] Residual cerebral blood flow in brain death seems to occur in certain situations, such as where the cranium is no longer an enclosed space (e.g. craniectomies and ventricular drains)[9] and if insufficient time has elapsed for changes to fully develop. A 6 h interval between clinical testing and imaging has been suggested,[1] which was present in both cases. Cerebral angiography also carries the potential for injection artifacts.

We postulate that severely raised ICP reduced cerebral perfusion below critical thresholds, causing a period of cerebral circulatory arrest sufficient to cause significant, irreversible ischaemic neuronal damage, cellular death, and tissue fragmentation. Craniectomy opens the intact, rigid cranium that allows elevated ICP, and restores regional non-viable flow to irreversibly injured brain that may otherwise not occur with a closed skull. In both cases, persistent flow can be seen on cerebral angiography despite cerebral perfusion pressure below 60 mm Hg. The decision to repeat cerebral angiography in Case 1 further delayed withdrawal of care, which may have been unnecessary as residual flow in the context of decompressive craniectomy does not mean meaningful survivability. Cerebral angiography was performed in Case 2 because of levetiracetam therapy, but at therapeutic levels, levetiracetam does not cause respiratory depression and should not interfere with clinical brain death testing.

Patients clinically brain-dead with a decompressive craniectomy may show residual, but not completely absent, intracranial blood flow on cerebral angiography that is nonetheless incompatible with a non-vegetative outcome. Physicians should counsel families appropriately about this possibility of some residual flow that is nonetheless compatible with brain death.

Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

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References

1. Quality Standards Subcommittee of the American Academy of Neurology. Practice parameters for determining brain death in adults (summary statement). *Neurology* 1995; **45**: 1012–4
2. Citerio G, Crippa IA, Bronco A, et al. Variability in brain death determination in Europe: looking for a solution. *Neurocrit Care* 2014; **21**: 376–82
3. Ministry of Health of Singapore. *Manual on organ donation and transplantation*. Singapore: Ministry of Health; 2018
4. Chua HC, Kwek TK, Morihara H, Gao DQ. Brain death: the Asian perspective. *Semin Neuro* 2015; **35**: 152–61
5. van der Lugt A. Imaging tests in determination of brain death. *Neuroradiology* 2010; **52**: 945–7
6. Savard M, Turgeon AF, Gariépy JL, Trottier F, Langevin S. Selective 4 vessels angiography in brain death: a retrospective study. *Can J Neurol Sci* 2010; **37**: 492–7
7. Nguyen M, Bièvre T, Nadji A, Bouhemad B. Rapid brain death following cardiac arrest without intracranial pressure rise and cerebral circulation arrest. *Case Rep Crit Care* 2018; **2018**: 2709174
8. Ala TA, Kuhn MJ, Johnson AJ. A case meeting clinical brain death criteria with residual cerebral perfusion. *AJNR Am J Neuroradiol* 2006; **27**: 1805–6
9. Nunes DM, Maia Jr ACM, Boni RC, da Rocha AJ. Impact of skull defects on the role of CTA for brain death confirmation. *AJNR Am J Neuroradiol* 2019; **40**: 1177–83

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