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This book is dedicated to our families:
To my wife Willow, my two daughters Bay and Wyn, and my parents Neil and Susan.
Reuben

To my wife Caroline, and children Isaac, Benedict, and Dominic.
Alex

Foreword to First Edition

Joseph C. Maroon

While reviewing this volume on *Landmark Papers in Neurosurgery*, I thought of another book presented to me at the completion of my training at the Radcliffe Infirmary in Oxford—too many years ago. Mr Brian Cummins, then Senior Registrar, regularly thrashed me on the squash courts (although not *that* skilled!) next to the Radcliffe, when not on call. He shared his winning secret with the presentation of the classic—*The Theory and Practice of Gamesmanship or The Art of Winning Games without Actually Cheating* by Stephen Potter, another Oxonian. This volume by Reuben Johnson and Alexander Green is the ultimate neurosurgical 'gamesmanship' book for whoever reads it. For the resident, seminal large complex investigative studies—'game changing' themselves—are analysed, summarized, and then superbly critiqued. The essence of major papers such as the optimal timing for aneurysm surgery, the use of nimodipine, and the indications for decompressive surgery for the management of malignant cerebral infarction can be easily 'dropped' on rounds or in conferences with the appearance of having spent hours doing the same meticulous analysis as the authors—without really cheating! For the neurosurgical/neurological faculty, a few quick minutes are all it takes to refresh one's own database and present a learned discussion or lecture on the history of the use of steroids for cerebral oedema, the rationale for the extent of resection for malignant gliomas, the use of barbiturates in head injury, or how magnesium is neuroprotective in brain injuries.

For all in the neurosciences, the authors have distilled thousands of hours of literature review into concise, easily read, and critiqued summaries of papers on head injury, the treatment of spine and spinal cord diseases, and functional neurosurgery that are delightful to read and immediately practical in everyday patient care. Having participated in journal clubs and literature reviews for 25 years, this book, a landmark itself, has the obviousness of so many great innovations that makes the person reading it ask the question—why didn't I think of this myself? The scientific base and perspective gained from such a critical review of past neurosurgical classics prods the reader to look into the future of our specialty and ask, what's next? In his letter to Robert Hook on 5 February 1675 Isaac Newton wrote, 'If I have seen farther, it is by standing on the shoulders of giants'. With these landmark studies the authors have hoisted us high onto the shoulders of neurosurgical giants and the view of the past (as herein beautifully presented), the present, and the future of neurosurgery is breathtaking.

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Foreword to First Edition

Angelo Franzini

Neurosurgery is a lover who becomes ever younger while we grow older. Reading this book, I fell in love again with this young lady. I appreciated the enthusiasm of the authors who have solid experience in the field in reporting new perspectives and leading the reader through the chapters. Clear and understandable guidelines for each of the topics addressed in this book are presented for approaching the problems under discussion. The lectures demonstrate that it takes much longer to understand the indications for a specific surgical procedure than to learn how to perform the hands-on surgical procedure itself.

Moreover, the authors remind us that the management of CNS diseases in many instances may be controversial. The choice between more conservative and more aggressive 'radical' treatments may be difficult as in the surgical treatment of trigeminal neuralgia or even that of intracranial aneurysms. Reports from up-to-date cooperative studies in the chapter dedicated to neurovascular diseases make this book particularly rich and realistic at the same time.

A full range of theories and approaches are clearly examined to 'educate' both young and old neurosurgeons. Many of them too often focus their attention on a narrow sub-speciality topic such as cranial base surgery, functional neurosurgery, or spinal surgery.

A complete knowledge of all the fields of interest in neurosurgery is clearly not possible, but this book reminds us that many concepts are common and many surgical techniques must be shared among different neurosurgical applications. Endoscopy, neuronavigation, microsurgery, and stereotaxis are common instruments that all neurosurgeons must know in order to offer their patients the best therapeutic options.

Travelling through this book, neurosurgeons become aware of the fact that the knowledge of many other disciplines is mandatory in accomplishing that task. Anatomy and physiology are not enough. We need to know functional neuroimaging, physics, genetics, statistics, informatics, and computer technology… read this book.

Angelo Franzini
Neurosurgeon in Milan

Acknowledgements

We would like to extend our thanks to all the contributors to this book and also to the team at Oxford University Press for all their hard work in making this happen. In particular, we would like to thank Peter Stevenson and Eloise Moir-Ford from Oxford University Press and Papitha Ramesh from Newgen Knowledge Works Pvt. Ltd for helping us complete this project.

Contents

Abbreviations

5-ALA	5-aminolevulinic acid
A.comm	Anterior communicating artery
ACA	Anterior cerebral artery
ACAS	Asymptomatic Carotid Atherosclerosis Study
ALT	Alanine aminotransferase
APACHE	Acute Physiology and Chronic Health Evaluation
ARR	Absolute risk reduction
ASCI	Acute spinal cord injury
ASDH	Acute subdural haematoma
ASIA	American Spinal Injury Association
AVM	Arteriovenous malformation
BCNU	1,3-bis (2-chloroethyl)-1-nitrosourea or carmustine
BCT	Best conventional therapy
BFMDRS	Burke–Fahn–Marsden Dystonia Rating Scale
CA	Carcinoma
CAVATAS	Carotid And Vertebral Artery Transluminal Angioplasty Study
CDM	Conventional dose mannitol
CES	Cauda equina syndrome
Cg25	Cingulate gyrus area 25
Cg25WM	Subgenual cingulate white matter
CH	Cluster headache
CCH	Chronic cluster headache
CLEARIVH	Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage
CMM	Conventional medical management
CNS	Central nervous system
CPP	Cerebral perfusion pressure
CRASH	Corticosteroids Randomization After Significant Head Injury
CREST	Carotid Revascularization Endarterectomy versus Stenting Trial
CSDH	Chronic subdural haematoma
CSF	Cerebrospinal fluid
CT	Computed tomography
CTA	Computed tomography angiography
CVP	Central venous pressure
DBI	Diffuse brain injury
DBS	Deep brain stimulation
DECIMAL	Decompressive craniectomy in malignant middle cerebral artery infarction
DECRA	DECompressive CRAniectomy Trial

DESTINY	Decompressive surgery for the treatment of malignant infarction of the middle cerebral artery
DID	Delayed ischaemic deficit
DIND	Delayed ischaemic neurological deficit
DNT	Dysembryoplastic neuroepithelial tumour
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition
DXT	Deep X-ray therapy
EBRT	External beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
ECST	European Carotid Surgery Trial
ECT	Electroconvulsive therapy
EDH	Extradural haematoma
EEG	Electroencephalogram
EOR	Extent of resection
EORTC	European Organisation for Research and Treatment of Cancer Brain Tumour and Radiotherapy Group
EVA-3S	Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis trial
EVD	Extraventricular drain
FBSS	Failed back surgery syndrome
FIS	Functional Independent Survival
fMRI	Functional magnetic resonance imaging
GBM	Glioblastoma multiforme
GCS	Glasgow Coma Scale
GI	Gastrointestinal
GM	Grey matter
GOS	Glasgow Outcome Scale
GOSE	Glasgow Outcome Scale Extended
GPi	Globus pallidus internus
GSG	Gliadel Study Group
GTR	Gross total resection
HAMLET	Hemicraniectomy after middle cerebral artery infarction with life-threatening oedema trial
HDM	High-dose mannitol
HDRS	Hamilton Depression Rating Scale
HeaDDFIRST	Hemicraniectomy and durotomy on deterioration from infarction-related swelling trial
HHH	Hypertension, hypervolaemia, and haemodilution
HSS	Hypertonic saline solution
HSU	Health State Utility
ICA	Internal carotid artery
ICH	Intracerebral haemorrhage
ICP	Intracranial pressure
ICSS	International Carotid Stenting Study
IPH	Intraparenchymal haematoma
ISAT	International Subarachnoid Aneurysm trial

ISUIA	International Study of Unruptured Intracranial Aneurysms
IV	Intravenous
IVH	Intraventricular haemorrhage
JROSG	Japanese Radiation Oncology Study Group
KPS	Karnofsky Performance Score
LGG	Low-grade glioma
LP	Lumbar puncture
MCA	Middle cerebral artery
MCS	Motor cortex stimulation
MePred	Methyl prednisolone
MESCC	Metastatic spinal cord compression
MFS	Malignant-free survival
MGMT	O^6-methylguanine DNA methyltransferase
MISTIE	Minimally Invasive Surgery plus rt-PA for Intracerebral Hemorrhage Evaluation
mJOA	Modified Japanese Orthopaedic Association scale
MMI	Malignant MCA infarction
MRC	Medical Research Council
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
MVD	Microvascular decompression
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NASCIS	National Acute Spinal Cord Injury Study
NCCTG	North Center Cancer Treatment Group
NCICCTG	National Cancer Institute of Canada Clinical Trials Group
NHS	National Health Service
NSAID	Non-steroidal anti-inflammatory drug
NTR	Near total resection
NYIAVMS	New York Islands AVM Study
OCD	Obsessive–compulsive disorder
ODI	Oswestry Disability Index
P.comm	Posterior communicating artery
PAWP	Pulmonary artery wedge pressure
PBTTG	Polymer Brain Tumour Treatment Group
PCA	Posterior cerebral artery
PCO_2	Partial pressure of carbon dioxide
PCPC	Paediatric cerebral performance category scale
PD	Parkinson's disease
PDQ-39	Parkinson's Disease Questionnaire
PET	Positron emission tomography
PFS	Progression-free survival
PHVD	Post-haemorrhagic ventricular dilatation
PO	Per os
PRCT	Placebo-controlled randomized trial
PRL	Pre-operative prolactin

PROCESS	Prospective Randomized Controlled Multi-centre Trial of the Effectiveness of Spinal Cord Stimulation
PTS	Post-traumatic seizures
QOL	Quality of life
QOLIE	Quality of life inventory (Epilepsy)
RCT	Randomized controlled trial
RESCUEicp	Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intra-Cranial Pressure
REZ	Root entry zone
RPA	Recursive partitioning analysis
RR	Relative risk
RSI	Rapid sequence induction
RTOG	Radiation Therapy Oncology Group
SAH	Subarachnoid haemorrhage
SANTE	Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy
SAPPHIRE	Stenting and Angioplasty with Protection in Patients of High Risk for Endarterectomy
SBI	Sciatica Botherness Index
SCS	Spinal cord stimulation
SD	Standard deviation
SDH	Subdural haematoma
SF-36	Medical Outcomes Study 36-Item Short Form General Health Survey
SIVMS	Scottish Intracranial Vascular Malformation Study
SPACE	Stent-Protected Angioplasty versus Carotid Endarterectomy study
SPECT	Single-photon emission computed tomography
SPORT	Spine Patient Outcomes Research Trial
SRS	Stereotactic radiosurgery
SSRIs	Selective serotonin reuptake inhibitors
STASH	SimvaSTatin in Aneurysmal Subarachnoid Haemorrhage
STICH	International Surgical Trial in Intracerebral Haemorrhage
STIMEP	Assessment of Subthalamic Nucleus Stimulation in Drug Resistant Epilepsy
STN	Subthalamic nucleus
STR	Sub-total resection
SWT	Shuttle-walking test
TBI	Traumatic brain injury
TCD	Transcranial Doppler
TH	Tyrosine hydroxylase
THAM	Tromomethamine
TIA	Transient ischaemic attack
TN	Trigeminal neuralgia
TRISS	Trauma and Injury Severity Score
TSA	Transsphenoidal approach
TTP	Time to progression
UPDRS	Unified Parkinson's Disease Rating Scale
VAS	Visual analogue scale

VM	Ventral midbrain
VNS	Vagal nerve stimulation
WBRT	Whole brain radiotherapy
WFNS	World Federation of Neurological Surgeons
WHO	World Health Organization
WM	White matter

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Introduction

The absence of proof does not constitute the proof of absence.

Virchow (1880)

The correct treatment of a potentially lethal lesion depends upon an accurate knowledge of its natural history.

Wylie McKissock (1965)

What constitutes a landmark paper in neurosurgery is highly subjective. In a field as extensive as neurosurgery how can one really pick out a group of studies and say that they are more important than all the others? Any study that has significantly changed the neurosurgical specialty is certainly a landmark study and this will include those studies that have led to a paradigm shift in accepted methods of treating neurosurgical pathology. Studies that affect management decisions for common neurosurgical conditions are also landmark studies. This includes not only clinical trials of treatment modalities but also large epidemiological studies that elucidate the natural history of a disorder. In this volume, we have attempted to include those studies that we feel primarily fall into these two groups. Although the neurovascular, neuro-oncology, and head injury chapters formed the larger chapters in the first addition, this second edition includes a much extended chapter on functional neurosurgery reflecting the rapid expansion of this subspecialty. Furthermore, we have included a new chapter on pituitary surgery which we felt was missing from the first edition. We have included studies that have made a significant attempt to answer an important neurosurgical question even if they have not yet provided a satisfactory answer. In our view at least, these studies should be classified as landmarks, as they will highlight the difficulties of trying to design and carry out such studies in neurosurgical patients. However, in this volume we have not endeavoured to produce a 'roll of honour' of classic studies in neurosurgery, although many such studies have been referenced in the introduction to chapters and in the critiques of individual studies. In this way, there will, at the very least, be a doffing of our caps to such classic studies even if they have not been overtly included in this volume. Furthermore, although this volume is a collection of critiques of landmark studies rather than an evidence-based review of neurosurgery per se, we feel it is useful, where appropriate to stratify studies into the evidence class they represent. There are numerous methods to stratify clinical evidence and in this volume we have adopted the three-tier classification of evidence for therapeutic effectiveness based on that endorsed by the American Association of Neurological

Surgeons and the Congress of Neurological Surgeons. This consists of three tiers as follows:

Class I	Well-designed, randomized, controlled trial
Class II	Well-designed comparative clinical study, e.g. non-randomized cohort study or a case-control study
Class III	Case series, comparative study with historical controls, or case reports

This classification system gives an assessment of the degree of certainty regarding the results of a study. The certainty is proportionate to the class of study with Class I, II, and III reflecting high, moderate, and unclear certainties respectively. It should be noted that we are applying this scheme to individual studies in order to make our assessment as to what class of evidence the study represents. We would also emphasize that the classification of each study is based on our own assessment. We would, for example, classify a randomized trial that did not include a power calculation as a Class II study rather than a Class I study.

There are some studies that, although arguably landmark studies in the field of neurosurgery, have been omitted, which will need some brief explanation. We have avoided, for example, as much as possible case series that describe important advances in surgical technique. The reason for this is because it is specifically not our aim to chart the development of surgical techniques. In addition, we feel that surgical technique is also a matter of apprenticeship and schooling. The surgical methods a surgeon uses will be a product of his or her individual training and those aspects of their masters' craft they found most effective in their hands. This is part of the surgical art that is still a matter for the individual, and rightly so. The diversity in neurosurgical techniques is part of the rich tapestry of our specialty. However, we have included case series that have influenced neurosurgical practice. A case series may illustrate an important issue about the timing of surgery or provide valuable information about long-term outcomes following surgical intervention.

This volume is intended to be an informative tool to neurosurgical trainees and a useful review for practising senior neurosurgeons. Our overall aims are twofold. Firstly, to provide a succinct review and critique of the published studies. In many ways, this volume could be said to represent a minimum *corpus sapiendi* of the larger and more influential studies in neurosurgery. This we hope will act as an introduction to the literature to trainees and in particular those coming up to exams. We have, therefore, included here a brief discussion on the issues of trial design and also a brief explanation of some of the more common terms used in clinical trials. We also hope that this volume may be of interest to established neurosurgeons who have lived through the development of our specialty into what it is today.

We have primarily focused on the main results of studies that we feel are the most important and relevant. This usually equates to the primary outcome data in most studies. However, we have included secondary outcomes where these address key questions or dilemmas that need to be highlighted for completion. Similarly, we have been fairly unforgiving of post hoc analyses, but have endeavoured to include these where they provide important insights or may form the basis for further studies or trial designs. In this way, we may be criticized for giving an incomplete view of the findings of some studies. This is not our intention, but rather to highlight the take-home messages of the study so that they can be more easily remembered by the reader. In addition, we would emphasize that these critiques are our own interpretation of the studies and a review of published criticisms and we hope that these prove a valuable starting point for further reading.

Reuben D. Johnson and Alexander L. Green

Chapter 1

Neurovascular neurosurgery

AL Green, RD Johnson, JA Hyam, RSC Kerr

1.0 Introduction

The demonstration of a low mortality-rate by a new technique is of no value until an acceptable statistical method of assessment of the natural prognosis and of the proposed treatment is available.

Wylie McKissock (1965)

The first clinical trial performed in the field of neurovascular surgery was carried out by Wylie McKissock, Alan Richardson, and Lawrence Walsh at Atkinson Morley's Hospital, St George's, in London between 1958 and 1965, when they compared conservative and surgical treatment of anterior communicating aneurysms (McKissock *et al*., 1965). The results of the trial did not show any difference in mortality between the two groups. The surgical methods used varied throughout the trial to include aneurysmal clipping, ligation of the proximal anterior cerebral artery, wrapping the aneurysm with muslin, and ligation of the common carotid artery. Although the results did not show any benefit from surgical intervention, this single-centre study stands out as a landmark in neurosurgery for several reasons. Firstly, it is the first attempt at a randomized controlled trial (RCT) of surgical management of a common neurosurgical disorder. Secondly, the author's rationale for carrying out the trial was not just to evaluate surgery but to further elucidate the natural history of the lesion being treated. This point is of particular importance when considering current dilemmas that face the neurosurgeon, such as the management of unruptured intracranial aneurysms and spontaneous non-aneurysmal haematomas. Thirdly, the authors emphasize the limitations of carrying out single-centre studies in neurosurgery and indicate the need for large multi-centre studies.

We have been highly selective in the studies included in this chapter and have included those studies which we feel remain true to the founding principles of the McKissock trial. The first sections of this chapter deal with aneurysmal subarachnoid haemorrhage (SAH) and we have included studies which examine the natural history of aneurysms and their treatment. We have included, therefore, the International Cooperative Study by Kassell which addresses the timing of aneurysm surgery and prognostic factors associated with good and poor outcomes. We have also included the large study of unruptured aneurysms by the International Study of Unruptured Intracranial Aneurysms Investigators (ISUIA) which is an ongoing study addressing one of the most important and controversial problems facing neurovascular surgeons. The International Subarachnoid Aneurysm Trial (ISAT) has been included because of the widespread and profound influence this study has exerted on the management of ruptured intracranial aneurysms. As vasospasm is the greatest cause of neurological morbidity in patients who survive their primary aneurysmal bleed we have also included studies of strategies for the prediction, prevention, and treatment of vasospasm associated with aneurysmal SAH. We have included strategies for which there is an accepted evidence base, such as nimodipine, and which have become accepted practice, such as 'HHH' (hypertension, hypervolaemia, and haemodilution) therapy. In addition, we have included some studies which evaluate strategies that have been promising and for which the results of ongoing trials are keenly awaited, e.g. the use of statins. In a subsequent section of the chapter, the treatment of arteriovenous malformations (AVMs) is considered. The decision to treat AVMs depends on balancing the risk of treatment versus the natural history of AVMs. Unfortunately, the natural history of AVMs has been extremely difficult to elucidate, although there are two ongoing population-based studies in Scotland and New York. Nonetheless, the Spetzler–Martin grading system is a landmark in neurosurgery as it has produced an objective system by which outcome and risks of treatment can be applied to individuals with AVMs and for this reason it has been considered (Spetzler and Martin, 1986; Hamilton and Spetzler, 1994). Further sections of this chapter deal with the surgical management of spontaneous non-aneurysmal intraparenchymal haemorrhages (STICH I + II trials) and decompressive surgery for the management of malignant middle cerebral artery (MCA) infarction (DESTINY, DECIMAL, HAMLET, and HeaDFIRST trials). The final sections deal with the role of surgery in the management of carotid artery stenosis (NASCET and SPACE trials). There are, of course, some studies which many would consider to be conspicuous by their absence in this chapter. For example, there are some early classic studies demonstrating angiographic vasospasm, and determining the clinical manifestations and time course of vasospasm (Ecker and Riemenschneider, 1951; Stornelli and French, 1964; Fisher *et al*., 1977; Weir *et al*., 1978). There are numerous other examples that could have been included. However, we have endeavoured to keep each chapter concise and to include a selection of the largest published studies that cover most of the areas of neurovascular surgery which are relevant to the everyday practice of all neurosurgeons.

References

Clinical Effectiveness Unit. *National Study of Subarachnoid Haemorrhage*. London: The Royal College of Surgeons of England, 2006.

Ecker A, Riemenschneider PA. Arteriographic demonstration of spasm of the intracranial arteries, with reference to saccular arterial aneurysms. *J Neurosurg* 1951; **8**: 660–667.

Fisher CM, Roberson GH, Ojemann RG. Cerebral vasospasm with ruptured saccular aneurysm—the clinical manifestations. *Neurosurgery* 1977; **1**: 245–248.

Hamilton MG, Spetzler RF. The prospective application of a grading system for arteriovenous malformations. *Neurosurgery* 1994; **34**: 2–6.

McKissock W, Richardson A, Walsh L. Anterior communicating aneurysms: a trial of conservative and surgical treatment. *Lancet* 1965; **1**: 873–876.

Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. *J Neurosurg* 1986; **65**: 476–483.

Stornelli SA, French JD. Subarachnoid hemorrhage-factors in prognosis and management. *J Neurosurg* 1964; **21**: 769–780.

Weir B, Grace M, Hansen J, Rothberg C. Time course of vasospasm in man. *J Neurosurg* 1978; **48**: 173–178.

1.1 Timing of Aneurysm Surgery

Details of Study

The International Cooperative Study on the Timing of Aneurysm Surgery was the first large-scale study to look at this issue. Between December 1980 to July 1983 a total of 3521 patients were recruited out of 8879 patients with SAH. In addition to looking at the timing aspect of surgery, many other factors that influence outcome were addressed.

Study References

Main Study

There are two main references for the study: part 1 (overall management results) and part 2 (surgical results). Both are reviewed here.

Kassell NF, Torner JC, Haley EC Jr, **Jane JA, Adams HP, Kongable GL.** The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: overall management results. *J Neurosurg* 1990; **73**: 18–36.

Kassell NF, Torner JC, Jane JA, Haley EC Jr, **Adams HP.** The International Cooperative Study on the Timing of Aneurysm Surgery. Part 2: surgical results. *J Neurosurg* 1990; **73**: 37–47.

Related References

Graff-Radford NR, Torner J, Adams HP Jr, **Kassell NF.** Factors associated with hydrocephalus after subarachnoid hemorrhage. A report of the Cooperative Aneurysm Study. *Arch Neurol* 1989; **46**: 744–752.

Kassell NF, Torner JC. The International Cooperative Study on Timing of Aneurysm Surgery—an update. *Stroke* 1984; **15**: 566–570.

Study Design

Class of evidence	II
Randomization	None (see following text)
Number of patients	3521 (2922 had aneurysm surgery)
Length of follow-up	6 months
Number of centres	68 in 14 countries (24 in USA)
Stratification	Age Sex Presence of hypertension Site and size of aneurysm

- Aim of the study was twofold; firstly to define the relationship between timing of aneurysm surgery and outcome, secondly to document current medical and surgical management in a number of centres around the world.
- It was a prospective, observational, epidemiological survey.
- Assessments were performed by a neurologist and blinded to the timing of surgery.
- All patients admitted to each participant centre were enrolled, with four 'logs' completed for each—'SAH log', 'registration form', 'treatment form', and 'follow-up form'.

- Inclusion criteria: admission ≤3 days since first SAH from a saccular aneurysm (computed tomography scan/lumbar puncture (CT/LP) confirmation of bleed, angio/surgical confirmation of aneurysm).
- Exclusion criteria: delayed admission >3 days since bleed; multiple bleeds; no confirmation of aneurysm.
- A large number of patients were excluded for other reasons such as evacuation of haematoma, non-participating surgeon, lack of patient/carer consent, etc. but these are not listed as exclusion criteria per se.

Outcome Measures

Primary Endpoints

- 'Good result' or death as defined by the Glasgow Outcome Scale (GOS).
- Neurological examination.

Secondary Endpoints

- Pre-, intra-, and post-operative complications.

Results

Many demographic results including the age, sex, site and size of the aneurysm(s), and the presence of pre-existing hypertension are reported in the results. In 51% of patients, surgery was performed on day 0–3. About 75–80% of patients were considered in 'good condition' at the time of admission but at 6 months, only 58% had recovered to their premorbid state without neurological deficit. Nine per cent were moderately disabled, 5% severely disabled, 2% vegetative, and 26% died. Leading causes of death or disability, in descending order, were vasospasm (13.5%), direct effect of the bleed on brain parenchyma (10.6%), re-bleeding (7.5%), operative complications (4%), intracerebral haemorrhage (2%), hydrocephalus (1.7%), and other less common causes.

The most important results are probably the prognostic factors, as determined by a univariate analysis. These included:

- Level of consciousness ($p < 0.001$): 75% who were alert on admission had a good recovery, compared to 11% who were comatose.
- Age inversely related to outcome (26% between 70 and 87 years had a good outcome).
- No significant sex differences.
- Smaller aneurysms (<12 mm) had more favourable results.
- Outcome better if middle cerebral or internal carotid aneurysm (compared to vertebrobasilar or anterior circulation).
- Other good prognostic indicators included lower admission blood pressure, clot distribution on CT, absence of pre-existing medical conditions, absence of vasospasm, admission motor response, and orientation.

In addition to these results, a number of medical conditions such as pneumonia, cardiac disturbances, gastrointestinal (GI) bleeding, etc. were identified to commonly occur after admission. There was a considerable difference in outcome and mortality (death ranged from 0% to 66%) between centres—use of the Chi squared test determined that this was not related to activity of the individual centres.

Surgical Results

- At 6 months, 69% who had surgery had a good result, versus 14% dead. Compare this to the 58% good recovery overall. This effect was strongly related to age (90% good result in the 18–29 years age group versus 56% in the 60–69 years age group). Factors associated with good surgical outcome were similar to the overall prognostic factors.
- Patients who were alert pre-operatively had a more favourable prognosis (overall) if their operation occurred between days 0–3 or after day 10. Operatively mortality, however, only reduced after day 10.
- Patients who were drowsy pre-operatively had better outcomes when operated after day 10.

Conclusions

The main conclusions are that 75% of those admitted within 3 days are in good condition, with a 58% good recovery at 6 months, and 25% death rate. Vasospasm and re-bleeding were the major causes of death or disability, aside from the initial effects of the bleed. There were a number of prognostic factors including admission Glasgow Coma Scale (GCS) and age. The study concluded that there is considerable room for improvement.

Critique

This study was performed at a time when most neurosurgeons opted to wait several days after a SAH before operating. At this point, there was little doubt that operative results were better—the patient was medically stable, and the brain was less swollen and friable. The study was really a response to the question of whether the overall management results were better, i.e. by delaying surgery, some patients would suffer re-bleeds and others may suffer vasospasm that could not be adequately treated in the presence of an unsecured aneurysm. The study also sought to look at the epidemiological and prognostic factors in these patients, and was the largest study of its time. In this sense, the study was a well-designed epidemiological study and served as a preliminary to RCTs (although these came over 20 years later). Perhaps one of the criticisms of the study is the length of follow-up which was limited to 6 months. Patients with neurological deficits can still show improvement after this time, although the differences from a longer follow-up would probably be small.

This study had a very large impact on the management of patients with suspected aneurysmal SAH. It confirmed that patients with poor grade and older age, with pre-existing medical conditions have a very poor prognosis, and that these patients should not be operated on before day 10. It also had a profound effect on the timing of surgery of good grade patients, prompting an international change in practice to early surgery by day 3. The main difference today is that we now have the option of endovascular treatment. This is often performed on poorer grade patients within the vasospastic period, largely because it is less risky to do so. However, as a large number of aneurysms are still treated surgically, this study still has great relevance.

The timing of intervention for aneurysmal SAH remains controversial. Of particular note is a series of 391 patients from the Alfred Hospital in Melbourne who underwent surgery within 24 h following their initial bleed (Laidlaw and Siu, 2002). In this series, 83% of patients with good clinical grades had good outcomes with early surgery. In addition, in this case series, only 15% of patients with poor clinical grades had a poor outcome.

Reference

Laidlaw JD, Siu KH. Ultra-early surgery for aneurismal subarachnoid hemorrhage: outcomes for a consecutive series of 391 patients not selected by grade or age. *J Neurosurg* 2002; **97**: 250–258.

1.2 Radiological Predictors of Vasospasm

Details of Study

The Fisher Scale is commonly quoted in cases of aneurysmal SAH. The original paper is a landmark as it was an attempt to identify which patients would be higher risk for the development of vasospasm and delayed neurological deficits based purely on radiological factors. This was an observational study of 47 patients using presenting CT scan features to predict vasospasm measured by cerebral angiography.

Study References

Main Study

Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to subarachnoid haemorrhage visualized by computerized tomographic scanning. *Neurosurgery* 1980; **6**(1): 1–8; discussion 8–9.

Related References

Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Sander Connolly E, Loch Macdonald R, Mayer SA. Prediction of symptomatic vasospasm after subarachnoid haemorrhage: the modified Fisher scale. *Neurosurgery* 2006; **58**(7): 21–27.

Reilly C, Amidei C, Tolentino J, Jahromi BS, MacDonald RL. Clot volume and clearance rate as independent predictors of vasospasm after aneurysmal subarachnoid hemorrhage. *J Neurosurgery* 2004; **101**: 255–261.

Smith ML, Abrahams JM, Chandela S, Smith MJ, Hurst RW, Le Roux PD. Subarachnoid hemorrhage on computed tomography scanning and the development of cerebral vasospasm: the Fisher grade revisited. *Surg Neurol* 2005; *63*: 229–234; discussion 234–225.

Study Design

Class of evidence	III
Randomization	None. Observational
Number of patients	47
Outcomes	Primary outcome: Angiographic evidence of vasospasm
	Secondary outcome: Clinical signs of vasospasm
Number of centres	1

- 47 cases were analysed retrospectively at Massachusetts General Hospital, United States.
- Inclusion criteria:
  - SAH with at least one aneurysm demonstrated on angiography.
  - CT head performed within first 5 days after SAH.
  - Angiography had been performed between days 7 to 17 after SAH.

Outcome Measures

Primary Endpoint

- Incidence of vasospasm on cerebral angiography (none, slight–moderate, severe, particular to each vessel, e.g. <2 mm for intradural internal carotid artery).

Secondary Endpoint

- Incidence of clinical signs of vasospasm, correlated to the relevant arterial territory, e.g. hemiparesis, aphasia with middle cerebral artery (MCA); abulia, incontinence, drowsiness with anterior cerebral artery (ACA).

Results

Group	SAH distribution	n	Severe angiographic vasospasm	Clinical vasospasm
I	None	11	2	0
II	Diffuse only	7	0	0
III	Clot or thick layer	24	23	23
IV	Diffuse/none with cerebral or ventricular blood	5	0	0

- Although two patients with no SAH (Group I) on CT did develop angiographic severe vasospasm, none developed clinical vasospasm.
- Patients in Groups II and IV had no incidence of angiographic or clinical vasospasm; however, their numbers were small (n = 7 and n = 5, respectively).
- Twenty-three of 24 patients with localized clot and/or vertical thick layers of subarachnoid blood >1mm thickness (Group III) had angiographic and clinical signs of vasospasm.
- Correspondence between location of thick subarachnoid blood and site of severe vasospasm was almost exact.
- No statistical analysis was performed between groups.

Conclusions

Localized clot and/or vertical thick layers of subarachnoid blood >1 mm thickness (Group III) was highly predictive of development of angiographic and clinical vasospasm after aneurysmal SAH.

Critique

This is a small, retrospective, observational, single-centre study without statistical analyses, and therefore is limited by multiple potential sources of bias. However, it provided important progress at the time in the understanding of what determines outcomes in SAH patients and correlation of radiological and clinical features. Quantification of objective data to predict outcomes in neurosurgical disease was advancing around the time of this paper and followed closely behind the development of the Glasgow Coma Scale. Further, CT was a relatively new diagnostic tool in 1980 so this paper represents the period of advancement in the modern science and practice of mainstream neurosurgery. In Lyndsay Simon's critique of the paper, he describes as 'remarkable' their 'indication of a high degree of association between vasospasm and opacification of the basal cisterns' (Fisher *et al*., 1980, Discussion). This is now something that clinicians treating these patients take for granted.

The radiological evaluation was thorough. Radiological vasospasm was judged on cerebral angiography, still the gold-standard test of vascular arterial architecture. Further, they also considered clinical symptoms of vasospasm which is ultimately the most important outcome for patients. The paper itself is also instructive with careful listing and descriptions of the cisternal anatomy and rigorous disclosure of the luminal measurements they considered as mild, moderate, or severe radiological vasospasm.

The authors suggested that the subjective differences between each group made the results of this paper merely 'preliminary'. Accordingly, the Fisher grading has been revisited since in a much larger number of patients. Two studies found that the Fisher scale did not significantly correlate with development of symptomatic vasospasm (Reilly *et al*., 2004; Smith *et al*., 2005). Frontera *et al*. developed a Modified Fisher Scale using 1355 SAH patients from the placebo arm of the tirilazad trial, 451 (33%) of which developed clinical vasospasm (Frontera *et al*., 2006). They reassigned the groups according to whether the SAH was thin or thick and whether it was associated with intraventricular haemorrhage (IVH): (I) focal or diffuse thin SAH, no IVH; (II) focal or diffuse thin SAH, with IVH; (III) thick SAH, no IVH; (IV) thick SAH, with IVH. These groups had increasing odds ratios (ORs) for clinical vasospasm from 1.6 in Grade II, 1.6 for Grade III, to 2.2 for Grade IV. Other risk factors they identified were history of hypertension, early angiographic vasospasm, neurological grade, and elevated admission mean arterial blood pressure.

Understandably, with larger studies and more common CT usage it has been possible to refine the radiological predictors of vasospasm. To its credit, the grades describing thick SAH still conferred a higher OR, as predicted by the original Fisher study. Fisher's paper is a landmark from which our understanding of the relationship between radiological and clinical features in aneurysmal SAH has guided modern practice.

References

Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Sander Connolly E, Loch Macdonald R, Mayer SA. Prediction of symptomatic vasospasm after subarachnoid haemorrhage: the modified Fisher scale. *Neurosurgery* 2006; **58**(7): 21–27.

Reilly C, Amidei C, Tolentino J, Jahromi BS, MacDonald RL. Clot volume and clearance rate as independent predictors of vasospasm after aneurysmal subarachnoid hemorrhage. *J Neurosurgery* 2004; **101**: 255–261.

Smith ML, Abrahams JM, Chandela S, Smith MJ, Hurst RW, Le Roux PD. Subarachnoid hemorrhage on computed tomography scanning and the development of cerebral vasospasm: the Fisher grade revisited. *Surg Neurol* 2005; **63**: 229–234; discussion 234–225.

1.3 **Endovascular Coiling versus Aneurysm Clipping in Ruptured Aneurysms**

Details of Study

The International Subarachnoid Aneurysm Trial (ISAT) is the most comprehensive study comparing endovascular to surgical treatment in ruptured aneurysms. It has had a greater impact on treatment of ruptured aneurysms than any other study to date.

Study References

There is an initial study with 1-year follow-up looking at primary endpoints and several 'spin-offs' looking at secondary outcome measures.

Main Study

Molyneux A, Kerr R, Stratton I, Sandercock P, Clarke M, Shrimpton J, Holman R, for the International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet* 2002; **360**: 1267–1274.

Related References

Clinical Effectiveness Unit. *National Study of Subarachnoid Haemorrhage*. London: The Royal College of Surgeons of England, 2006.

Molyneux A, Kerr R; International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group, Stratton I, Sandercock P, Clarke M, Shrimpton J, Holman R. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomized trial. *J Stroke Cerebrovasc Dis* 2002; **11**: 304–314.

Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, Sandercock P, for the International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet* 2005; **366**: 809–817.

Molyneux AJ, Kerr RSC, Birks J, Ramzi N, Yarnold J, Sneade M, Rischmiller J, for the ISAT collaborators. Risk of recurrent subarachnoid hemorrhage, death, or dependence and standardized mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): long-term follow-up. *Lancet Neurol* 2009; **8**(5): 427–433.

Scott RB, Eccles F, Molyneux AJ, Kerr RSC, Rothwell PM, Carpenter K. Improved cognitive outcomes with endovascular coiling of ruptured intracranial aneurysms: Neuropsychological outcomes from the International Subarachnoid Aneurysm Trial (ISAT). *Stroke* 2010; **41**: 1743–1747.

Wolstenholme J, Rivero-Arias O, Gray A, Molyneux AJ, Kerr RS, Yarnold JA, Sneade M, for the International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. Treatment pathways, resource use, and costs of endovascular coiling versus surgical clipping after aSAH. *Stroke* 2008; **39**: 111–119.

Study Design

- Placebo-controlled randomized trial (PRCT).

Class of evidence	I
Randomization	Non-blinded coiling versus clipping
Number of patients	2143 (1073 coiled, 1070 clipped)
Length of follow-up	Primary outcomes: 1 year
	Secondary outcomes: Ongoing
Number of centres	43 (centres treating 60–200 cases per year)
Stratification	Age Sex World Federation of Neurosurgeons (WFNS) grade Aneurysm size and location Extent of blood on CT scan

- Patients were randomized after admission to a neurosurgical unit and after initial angiography. Out of 9559 patients assessed for eligibility, 2143 were deemed suitable for randomization.
- Inclusion criteria: SAH within 28 days (CT or LP proven); presence of aneurysm (proven by computed tomography angiogram (CTA) or formal angiogram); good enough clinical state to justify treatment; aneurysms judged to be suitable for either technique (opinion of both surgeon and neuroradiologist) with equipoise regarding which method would be best; consent.
- Exclusion criteria: >28 days since SAH; clinical condition considered unsuitable for either or both treatments; lack of consent; participation in another SAH trial.

Outcome Measures

Primary Endpoints

- Incidence of death or dependency; modified Rankin Scale (mRS).

Secondary Endpoints

- Subgroups—WFNS grade at randomization, age, Fischer grade, lumen size of aneurysm, aneurysm site.
- Incidence of re-bleeding from the treated aneurysm.
- Quality of life at 1 year.
- Frequency of epilepsy.
- Cost-effectiveness.
- Neuropsychological outcomes.
- Results of follow-up angiography.

Results

Of patients who underwent endovascular coiling, 23.7% were dependent or dead at 1 year compared to 30.6% who had their aneurysm surgically clipped (p <0.002). This led to a relative/absolute risk reduction of dependency or death at 1 year of 22.6%/6.9% respectively. Re-bleeding risk at 1 year was 2 per 1276 patient-years in the endovascular group versus 0 per 1081 patient-years in the surgical group (not significant).

Outcome		**Endovascular**	**Surgical**
Incidence of death or dependence (mRS 3–6)		23.5%	30.9%
Mortality at 1 year		85	105
Incidence of re-bleeding (fatality in brackets)	Before treatment	17(7)	28(19)
	Re-bleed <1year	45(22)	39(24)
	Re-bleed >1 year	7(2)	2(2)
Re-treatment rate	<1 year	121	32
	>1 year	15	1
Complete occlusion at first follow-up angiography		66%	82%
Incidence of seizures		60	112

Conclusions

The outcome, in terms of survival-free disability, is significantly better with endovascular treatment than with surgical clipping of a ruptured aneurysm.

Critique

There is no doubt that the ISAT trial has generated a large amount of controversy amongst neurosurgeons and interventional radiologists alike. Whatever the criticism, it is one of the few multi-centred, randomized trials in neurosurgery and most would admit that it is of considerable importance. However, some have argued that the results have been over-interpreted. One of the major criticisms is that it compares good interventional neuroradiologists to 'average' neurosurgeons rather than those who 'concentrate' on neurovascular surgery. In other words, there is an inherent bias in the recruiting centres as being those that have a strong interventional radiology interest. The ISAT group have countered this by stating that the trial is a 'pragmatic' trial. That is, it tries to determine the best outcome for a patient, in a real-life situation who would be transferred to their regional unit for diagnosis and treatment. It is not a trial of 'the best possible surgery versus the best possible endovascular treatment' but a trial of what is the best option for an 'average patient'.

A second criticism of the trial is the randomization process. The trial is biased towards small anterior circulation aneurysms (97.5%). To be fair, the ISAT investigators have never claimed that the trial indicates that all ruptured aneurysms should be coiled in preference to clipping. But some people have perhaps interpreted it thus. Also concerned with the randomization process is that the average time to randomization was slightly longer in the surgical group (1.7 versus 1.1 days) and this may have led to slightly worse outcomes in this group. Since the numbers of re-bleeds takes into account those that happen after randomization but before treatment, this may have led to a worsening of results in the surgical group.

Since the analysis is based on an intention-to-treat paradigm, some patients allocated endovascular treatment received clipping (for a variety of reasons including patient choice) and 38 allocated clipping crossed over to the endovascular group. However, the analysis is based on the original randomization choice and this has received some criticism in the literature.

Probably the most important criticism of the ISAT trial is that the primary endpoints were measured at 1 year and not subsequently. Therefore, the trial shows that in the initial phase, endovascular coiling may be better than surgical treatment. But does this necessarily translate into the long term? There is some evidence from early analysis of the secondary data that, in fact, the surgical group may just be slower to recover and that there is some improvement in mRS with time. Also, there is the issue of long-term re-bleed rates. The late re-bleed rate in the endovascular group is 0.21% per patient-year compared to 0.063% in the surgical group. This, coupled with the fact that the poor outcome at 1 year is much less than in the surgical group of patients <40 years of age, has led some ISAT investigators to suggest that surgery may be better in this age group.

This issue has been revisited by the original investigators using longer follow-up (range 6–14 years, mean 9 years) of the ISAT cohort (Molyneux *et al.*, 2009). Thirteen re-bleeds occurred overall after the first year from treated aneurysms: ten after coiling and three after clipping ($p = 0.06$ in the intention-to-treat analysis but significant when analysed according to actual treatment received, $p = 0.02$). This is an important result for several reasons. Firstly, it does confirm suspicions that aneurysms are more likely to re-bleed after coiling compared to clipping. However, the overall risk of death 5 years after treatment was still significantly lower in the coiling group (11% versus 14%, $p = 0.03$). Secondly, this re-bleed result also shows that clipped aneurysms do not confer a subsequent re-bleed rate the same as the general population, which has been assumed by many surgeons. Whether this statistic improves with the increased specialization among neurovascular surgeons can be speculated upon.

The neuropsychological outcomes from ISAT were published in 2010 (Scott *et al.*, 2010). 612 patients from the eight participating UK centres were followed up at 12 months with neuropsychological testing if there was no major physical disability (mRS 0–2). Cognitive impairment was lower in the endovascular coiling group compared to clipping (27% versus 39%, $p = 0.0055$), as was incidence of epilepsy. Again, many of the limitations of the trial are relevant to the interpretation of this result. In particular, as the vast majority of aneurysms were at anterior cerebral/anterior communicating arteries, clipping would entail some frontal lobe retraction and potentially gyrus rectus dissection, increasing the likelihood of cognitive deficits due to the aneurysm location-specific factors. Whether this is the case for aneurysms on other arteries is not answered by these results.

The authors have acknowledged the caution that should be taken in extrapolating the ISAT findings beyond the lesions studied. There is concern that the positive ISAT results have resulted in endovascular treatment being given the right to first refusal for all aneurysms and all patients (Darsaut *et al.*, 2013). Although advances in endovascular techniques and technology have occurred since the interruption of ISAT in 2002, whether this translates into better outcomes for all ruptured aneurysm patients has not been proven. Accordingly, the ISAT investigators have initiated ISAT Part II. This is another pragmatic RCT involving at least 50 international centres over 10–12 years aiming to address these questions.

Whatever the criticisms, ISAT has provided a wealth of useful data that will continue to be analysed for years to come. The trial has led to a huge shift from surgery to endovascular treatment in some centres, particularly in the United Kingdom and France. Time will tell whether this shift has been appropriate.

References

Darsaut TE, Jack AS, Kerr RS, Raymond J. International subarachnoid aneurysm trial—ISAT Part II: study protocol for a randomized controlled trial. *Trials* 2013; **14**: 156.

Molyneux AJ, Kerr RSC, Birks J, Ramzi N, Yarnold J, Sneade M, Rischmiller J, for the ISAT collaborators. Risk of recurrent subarachnoid hemorrhage, death, or dependence and standardized mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): long-term follow-up. *Lancet Neurol* 2009; **8**(5): 427–433.

Scott RB, Eccles F, Molyneux AJ, Kerr RSC, Rothwell PM, Carpenter K. Improved cognitive outcomes with endovascular coiling of ruptured intracranial aneurysms: Neuropsychological outcomes from the International Subarachnoid Aneurysm Trial (ISAT). *Stroke* 2010; **41**: 1743–1747.