THE APPLICATION OF ROBOTICS TO KEYHOLE TRANSCRANIAL ENDOSCOPIC MICROSURGERY

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“Do not go where the path may lead, go instead where there is no path and leave a trail.”

Ralph Waldo Emerson

ABSTRACT

Over the last decade, there has been a resurgence of clinical interest in keyhole transcranial endoscopic microsurgery as an alternative to conventional microsurgery in carefully selected cases. The supraorbital approach through an eyebrow incision may be considered one of the best examples of the keyhole concept. Although keyhole neurosurgery offers the possibility of reduced approach-related morbidity, it can also present substantial technical challenges. This thesis investigates the potential for robotic platforms to improve the safety and effectiveness of such keyhole approaches.

A qualitative survey of neurosurgeons was performed to identify the major technical challenges of keyhole neurosurgery, and a quantitative study of patents and publications performed to determine the technological innovations that might overcome these barriers. Three clear themes emerged: first, surgical approach and better integration with image guidance systems; second, intra-operative visualisation and improvements in endoscopes; and third, surgical manipulation and improvements in instruments. A community survey suggested that robotic platforms incorporating these technologies would be acceptable to patients and their relatives.

Existing robotic platforms were reviewed against the aforementioned requirements for keyhole neurosurgery. In a cadaver study, it was demonstrated that most frequently used surgical robot today, the da Vinci^{TM} platform, was neither safe nor feasible to use in keyhole neurosurgery, providing justification for further research.

Technological innovations were sought to address each of the identified barriers to keyhole neurosurgery, including: an on-demand augmented reality system; a 3-Dimensional and High-Definition endoscope; and articulated robotic instruments. In a series of laboratory studies, each proposed technological innovation was compared against the current gold standard using a validated model. These technologies were then integrated into a robotic platform for image guided endoscopic microsurgery. Subsequent preclinical and clinical studies have shown promise, but further work is necessary to evaluate safety and effectiveness.

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LIST OF ACRONYMS

5-ALA	5-aminolevulinic acid
2D	2-Dimensional
3D	3-Dimensional
CCD	Charge-Coupled Device
CONSORT	Consolidated Standards of Reporting Trials
CT	Computed Tomography
CUSA	Cavitron Ultrasonic Surgical Aspirator
DBS	Deep Brain Stimulation
DOF	Degrees of Freedom
ETV	Endoscopic Third Ventriculostomy
HD	High-Definition
IQR	Interquartile Range
ioMRI	Intra-operative MRI
ioCT	Intra-operative CT
ioUS	Intra-operative US
JRCO	Imperial College Joint Research Compliance Office
MARTYN	Modelled Anatomical Replica for Training Young Neurosurgeons
MEP	Motor Evoked Potentials
MIS	Minimally Invasive Surgery
MPR	Multi-planar reformatted Multi-planar reformatted (MPR)
MRI	Magnetic Resonance Imaging
NASA-TLX	NASA Task Load Index
RCSEng	Royal College of Surgeons of England
SBNS	Society of British Neurological Surgeons
SD	Standard-Definition
SPSS	Statistical Package for the Social Sciences
SSEP	Somatosensory Evoked Potentials
STN	Subthalamic nucleus
US	Ultrasound

CHAPTER 1 INTRODUCTION*

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1.1 Prologue

In 1924 the eminent American surgeon William Halsted expressed his belief *"...that the tendency will always be in the direction of exercising greater care when operating"*[1]. Today, the concept of Minimally Invasive Surgery (MIS) has been widely adopted into mainstream surgical practice. In general surgery, for example, large laparotomy incisions have been mostly replaced with several small laparoscopic incisions through which a laparoscope and laparoscopic instruments are passed. Keyhole approaches offer a number of improvements over traditional open techniques including less post-operative pain, fewer wound complications, and reduced length of stay in hospital[2-4]. These advantages are particularly pertinent in the elderly, the fastest growing segment of the population in the developed world, who may be less able to tolerate major surgical procedures[5].

Keyhole surgery is, however, an inherently demanding endeavour. The human body has a highly complex anatomical structure, often distorted by pathology and invariably shifting during the course of an operation, which makes planning an accurate and precise surgical approach difficult. Keyhole incisions necessitate the use of endoscopes to better visualise the surgical field, but most provide two-dimensional (2D) images impairing depth perception[6, 7]. Moreover, long instruments used through predefined ports possess a restricted range of movement and the so-called "fulcrum effect" can make surgical manipulation of tissue very challenging[8-10]. These issues are compounded in new methods such as Natural Orifice and Single Port Access surgery, which utilise a single anatomical corridor that further constrains instrument movement[11-13]. The clinical corollary is that robots that improve surgical approach, visualisation, and manipulation, have the potential to greatly enhance surgical performance and significantly advance patient care.

Surgical robotics remains a comparatively young field (Figure 1.1). The first report of robot-assisted surgery was in 1985, when a modified Puma 560 industrial robot (Advance Research & Robotics, Oxford, Connecticut) was used to define the trajectory of a brain biopsy[14]. Using this system, the neurosurgeon entered the brain lesions co-ordinates and an effector arm carrying a probe holder then moved to the correct position, allowing the surgeon to use the probe as a guide to trephination and

biopsy. Since this early description, numerous other robotic systems have been developed. At present, the most frequently used surgical robot worldwide is the da Vinci™ surgical system (Intuitive Surgical, Mountain View, California), a telesurgical system in which the surgeon remotely controls the robot's actions. To date, the da Vinci™ has been used in a wide range of surgical procedures – everything from hernia repair to coronary artery bypass[15, 16]. Despite the purported advantages of surgical robots, however, their use has generally remained limited to relatively few operations, such as radical prostatectomy[17].

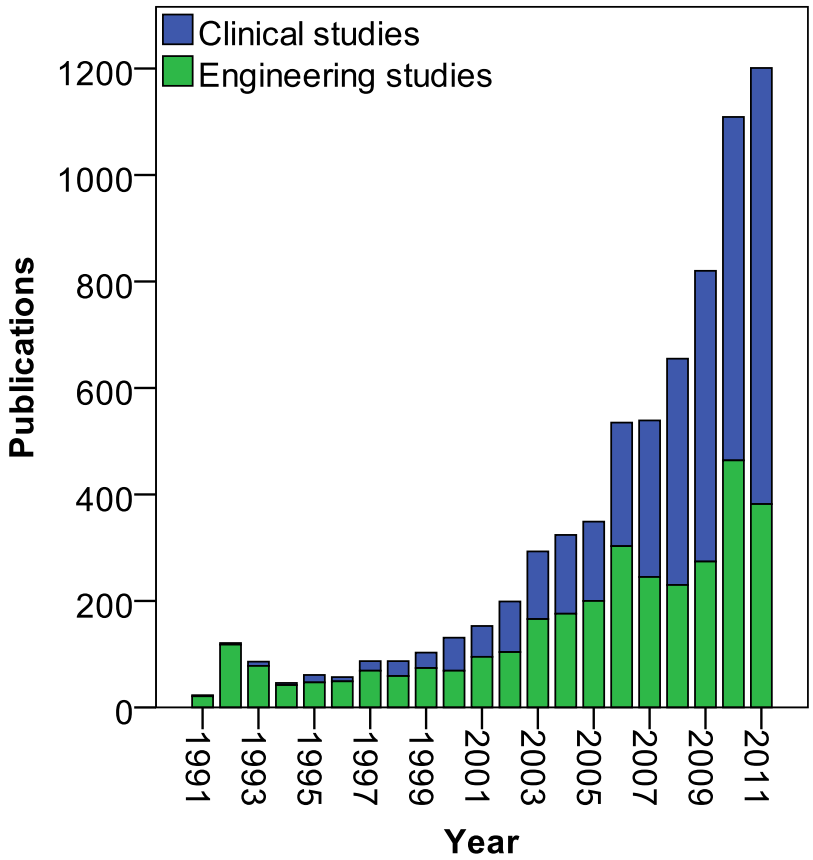


Figure 1.1 Number of publications on PubMed and IEEE Xplore over the last 20 years using the meta-terms "Surgery" AND "Robotics" (duplicates removed); filtered for studies on "Humans" (Clinical Studies) and others (Engineering Studies).

Robotic assistance should be appreciated as an adjunct to traditional MIS, rather than providing a *de novo* surgical approach. Clearly, there are a multitude of factors driving the popularity of robotic surgery[18], many of which might not be easily measurable using the quantitative data obtained through high quality trials and

national registries. Arguably the greatest role of contemporary first-generation robotic surgical systems is as a "great leveller", reducing the learning curve of keyhole approaches[19, 20], and enabling surgeons to perform MIS when they would otherwise resort to open surgery. The introduction of robot-assisted minimally invasive prostatectomy heralded an increase in the adoption of MIS versus open approaches from 1.4% in 2002 to 29.5% in 2008, with fewer associated complications reported and a reduced length of hospital stay[21]. Outside of urology, relatively few adult laparoscopic operations entail suturing, and the majority can be performed safely and effectively by most surgeons without the use of a surgical robot. Cholecystectomy, for example, was performed laparoscopically in over 90% of cases before the introduction of surgical robots[22]. Next-generation robotic platforms designed for operations that surgeons currently find technically challenging with standard instruments, such as keyhole brain surgery, may offer clear and unambiguous benefits over existing techniques, and provide strong clinical and economic justification for their use[23].

1.2 Aims

The main aims of this thesis are to:

1. Investigate the technical challenges of keyhole transcranial endoscopic microsurgery,
2. Evaluate technological solutions to these technical barriers, and
3. Integrate these technological features into a novel robotic platform.

1.3 Overview

The opening chapter provides a historical narrative of the evolution of cranial neurosurgery, from early extended craniotomies towards keyhole transcranial endoscopic microsurgery. The supraorbital approach through an eyebrow incision was used as an exemplar of the keyhole concept. The Modelled Anatomical Replica for Training Young Neurosurgeons (MARTYN) was modified to simulate the supraorbital approach, and a validation study performed.

Chapter 3 represents a clinical needs assessment and technological gap analysis. This was achieved through a qualitative survey of neurosurgeons to identify the major technical challenges of keyhole neurosurgery, and a quantitative study of patents and publications performed to determine the technological innovations that might overcome these barriers. A community survey was performed to evaluate whether robotic platforms incorporating these technologies would be acceptable to patients and their relatives. Existing robotic platforms were then critically appraised against these requirements, including a cadaver study assessing the most widely used surgical robot worldwide today, the da Vinci™ platform.

Chapter 4 addresses surgical approach and image guidance. A frequently cited drawback of existing triplanar image guidance systems is the need for surgeons to stop operating momentarily, apply a probe to the region of interest, and then take their eyes off the surgical field to view the image guidance monitors. The fusion of virtual 3D models and the actual operating field to provide an augmented reality may enhance the surgical workflow. A major concern over the use of augmented reality in surgery is that overlays may alter the attention of surgeons such that they fail to recognise critical events within the surgical field. To this end, chapter 4 comprises a laboratory-based randomised study comparing the efficacy and safety of various existing image guidance displays, including new augmented reality displays designed to mitigate or negate inattentional blindness.

Chapter 5 addresses intra-operative visualisation and endoscopy. Although the potential benefits of 3-Dimensional (3D) versus 2-Dimensional (2D), and High-Definition (HD) versus Standard-Definition (SD), endoscopic visualisation has long

been recognised in other surgical fields, such endoscopes have generally been considered too bulky for use in the brain. A systematic review was undertaken of all clinical studies comparing 3D and 2D endoscopy in the brain. Chapter 5 then evaluates the first commercially available 3D HD endoscope designed for brain surgery, and reports a laboratory-based randomised crossover study, comparing simultaneously the effectiveness of 3D versus 2D, and HD versus SD.

Chapter 6 addresses surgical manipulation and improvements in instruments. Among the greatest technical challenges in keyhole neurosurgery are the loss of triangulation with use of tube-shaft instruments through a single keyhole, and the small operative working spaces within the brain. To investigate this, a laboratory-based randomised crossover study comparing the performance in single-port versus multi-port surgery and small versus large operative working spaces was performed. Recognising that robotic articulated instruments may allow for improved triangulation, a series of studies were performed to provide detailed specifications for the design of such devices; the working spaces, forces, and instruments, used in microneurosurgery were all quantified. Prototype robotic articulated instruments were then evaluated in a pilot study of feasibility.

Lastly, Chapter 7 describes an integrated platform for image guided endoscopic microsurgery. A laboratory study was performed to assess the feasibility of the robot for use in the supraorbital approach. Early clinical translation of these technologies was also reported, including a first-in-human study using the 3D HD endoscope. In an attempt to better understand the process by which such advances are adopted into the wider clinical arena, the chapter concludes with an observational study on the rate and extent of clinical translation of technological innovation, and the factors that affect it.

1.4 Original contributions

The content of this thesis represents my original work, although such is the nature of academic research that I received support from co-authors and collaborators.

Chapter 2 The illustrative case was performed by Robert Reisch at the Klinik Hirslanden, Zurich. The MARTYN head was created by Martyn Cooke *et al* at the Royal College of Surgeons of England.

Chapter 4 The image guidance and augmented reality platforms were created by Philip Pratt at Imperial College London.

Chapter 6 The operative videos were collected by Robert Reisch at the Klinik Hirslanden, Zurich. The articulated instruments were created by Guang-Zhong Yang *et al* at Imperial College London.

Chapter 7 The integrated platform for image guided endoscopic microsurgery was created by Guang-Zhong Yang *et al* at Imperial College London. The study on clinical translation was performed jointly with Christopher Payne at Imperial College London. Christoph Meithke, John Doherty, and Ben Thomas, provided data on the Meithke DualSwitch^{TM} valve (B Braun, Melsungen, Germany).

1.5 Publications and presentations

1.5.1 Publications arising from this thesis

Marcus HJ, Nandi D, Darzi A, and Yang GZ. Surgical Robotics through a Keyhole: from Today's Translational Barriers to Tomorrow's 'Disappearing' Robots. IEEE Trans Biomed Eng. 2013; 60: 674-681

Marcus HJ, Hughes-Hallett A, Cundy TC, Nandi D, Yang GZ, and Darzi A. Robotic Surgery: Not everything that counts can be easily counted. BMJ 2013; 346: f2461

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1.5.2 Publications arising from work related to this thesis

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Marcus HJ, Zareinia K, Gan LS, Yang FS, Lama S, Yang GZ, and Sutherland GR. Surgical instrument forces exerted during robot-assisted neurosurgery: a cadaver study. Hamlyn Symposium, London. June 2013

Marcus HJ, Hughes-Hallett A, Pratt P, Clark J, Nandi D, Darzi A, and Yang GZ. Operating working spaces in keyhole neurosurgery; an MRI study. Hamlyn Symposium, London. June 2013

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Marcus HJ, Dyson E, Fu R, Chowdhury Y, Yang GZ, Darzi A, and Nandi D. Community consultation on attitudes towards robotics in neurosurgery. SBNS Autumn conference, Coventry. September 2014

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Wan Y, Shah N, and **Marcus HJ**. Comparing three-dimensional (3-D) with two-dimensional (2-D) endoscopes in transsphenoidal surgery: a systematic review. British Skull Base Society Meeting, London. January 2015

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1.5.4 Presentations arising from work related to this thesis

Chang TP, Sriskandarajah K, Cundy TP, Newton RC, **Marcus HJ**, Darzi A, and Yang GZ. Anatomical neck dissection for real time intraoperative in vivo in situ soft tissue morphology characterisation using confocal endomicroscopy. Hamlyn Symposium, London. June 2013

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CHAPTER 2 KEYHOLE TRANSCRANIAL ENDOSCOPIC MICROSURGERY*

*Content from this chapter was published or submitted as:

Marcus HJ, Seneci C, Payne C, Nandi D, Darzi A, and Yang GZ. The Application of Robotics to Transcranial Endoscope-assisted Microsurgery: A Critical Review of Existing Systems and Proposed Specifications for New Robotic Platforms. Neurosurgery. 2014; 10(1 Suppl Operative): 84-95

Marcus HJ, Hughes-Hallett A, Pratt P, Yang GZ, Darzi A, and Nandi D. Validation of MARTYN to simulate the keyhole supraorbital subfrontal approach. Ann R Coll Surg Engl (Suppl). 2014; 96: 120-1

Reisch R, **Marcus HJ**, Kockro RA, and Ulrich NH. The supraorbital keyhole approach: How I do it. Acta Neurochir (Wien). 2015 [Epub ahead of print]

2.1 The evolution of cranial neurosurgery: A historical review

Keyhole transcranial endoscopic microsurgery is the product of over century of technological progress in surgical approach, visualisation and manipulation (Figure 2.1 Evolution of cranial neurosurgery toward keyhole transcranial endoscopic microsurgical approaches.). Early pioneers such as Sir Victor Horsley, who was appointed the world's first neurological surgeon in 1886, habitually performed extended craniotomies to treat intracranial lesions[24]. Extended craniotomies were needed for a number of reasons[25, 26]. In these early cases pathologies were localised clinically and a large craniotomy was necessary to ensure the operating surgeon could locate the lesion. Intra-operative visualisation relied on ambient lighting in the operating theatre and a large craniotomy was required to illuminate the surgical field. Additionally, instruments used at the time were designed for general surgery rather than neurosurgery, necessitating large openings.

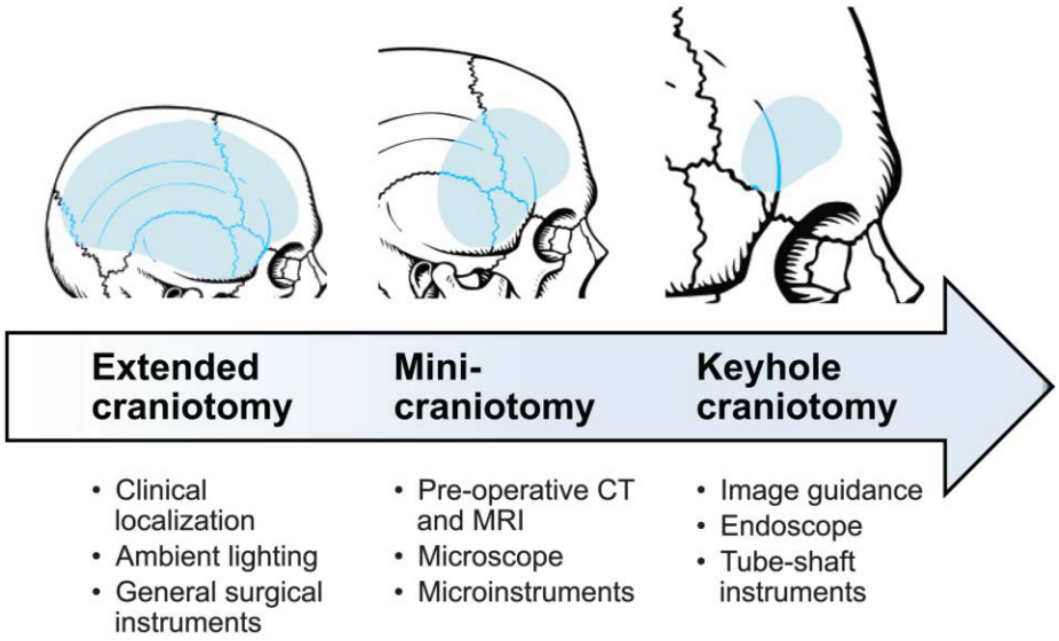


Figure 2.1 Evolution of cranial neurosurgery toward keyhole transcranial endoscopic microsurgical approaches.

Several advances contributed to the replacement of extended craniotomies with mini-craniotomies[25, 26]. The introduction of Computed Tomography (CT) in the early 1970s and Magnetic Resonance Imaging (MRI) in the 1980s allowed brain pathologies such

as tumours to be directly visualised, permitting far more targeted surgical approaches. Intra-operative visualisation was also greatly enhanced with the introduction of the operating microscope in the 1960s, improving illumination and magnification of the surgical field. In parallel to these developments, surgical instruments were adapted for use in microneurosurgery. Leonard Malis and M. Gazi Yasargil described the use of bipolar coagulation and purpose-designed microinstruments that allowed careful surgical dissection.

Over the last decade or so, further technological progress has led to the development of keyhole transcranial endoscopic microsurgical techniques. Image guidance systems that combine pre-operative imaging with live instrument tracking data to bring the real surgical field into alignment have been widely adopted by neurosurgeons, and are associated with shorter operating times, reduced blood loss and fewer major complications when compared with standard surgery[27]. Endoscopes provide a method of further increasing illumination and magnification, while extending the viewing angle, with keyhole approaches. Furthermore novel tube-shaft based surgical instruments have been designed for keyhole surgery permitting improved surgical manipulation through narrow surgical corridors compared with conventional microinstruments.

Axel Perneczky at the Johannes-Gutenberg University described a number of image guided endoscopic keyhole techniques utilising natural anatomical corridors within the brain to reach surgical targets. One large case series reported the use of a short eyebrow incision, a supraorbital keyhole craniotomy approximately 15mm x 25mm in diameter, and a subfrontal or frontolateral approach to the anterior cranial fossa and suprasellar regions. Over a 10-year period more than 450 patients underwent surgery to treat various pathologies including intracranial aneurysms, meningiomas, craniopharyngiomas and pituitary adenomas, with the vast majority making a good recovery (Glasgow Outcome Scale 5 in 86%, and 4 in 6.4%) in this heterogeneous group[28]. Keyhole modifications of the subtemporal, retrosigmoid, suboccipital, supracerebellar, and interhemispheric approaches have also been successfully utilised, providing a number of routes to reach the deep intracranial cisterns[25].

2.2 The supraorbital approach through an eyebrow incision: Surgical technique

2.2.1 Introduction

The aim of keyhole neurosurgery is to minimise approach-related morbidity by using tailored approaches that reduce exposure and manipulation of unaffected tissue. The supraorbital keyhole approach is one of the best examples of the keyhole concept.[29-32]

2.2.2 Relevant surgical anatomy

Important anatomical landmarks of the frontal area include the orbital rim, the supraorbital foramen, the temporal line, the level of the frontal cranial base, the impression of the Sylvian fissure, and the zygomatic arch. Special attention should also be given to the course of the superficial neurovascular structures, particularly the supraorbital nerve. These surface markings are used to define the borders of the craniotomy and planned skin incision (Figure 2.2a). Optimal placement of the craniotomy can be confirmed with the use of modern neuronavigation systems (Figure 2.2b).

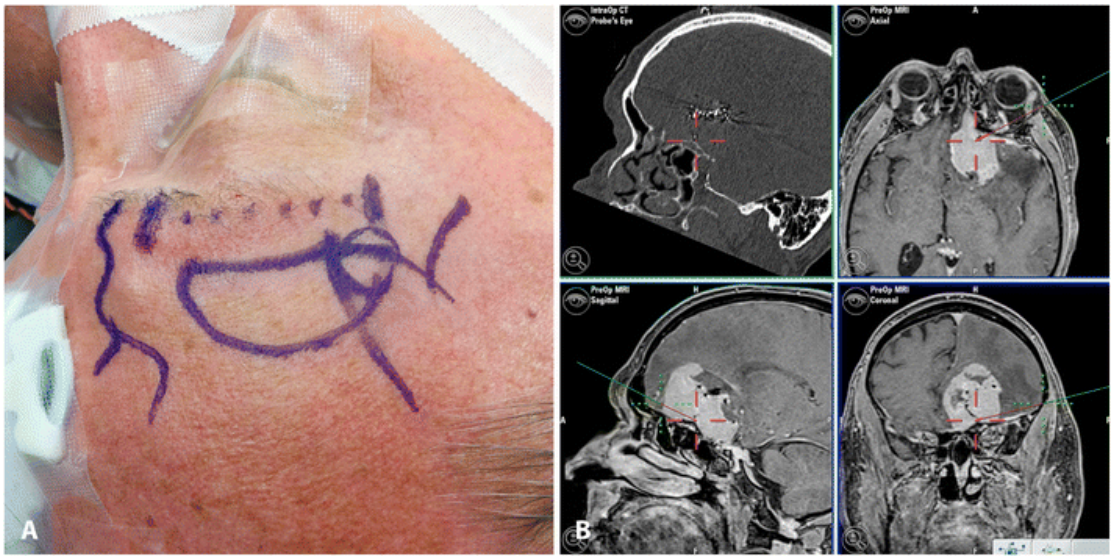


Figure 2.2. (a) Key anatomical landmarks are identified, and the planned craniotomy and incision marked. (b) In this case, a neuronavigation system (BrainLAB, Feldkirchen, Germany) was used to confirm the proposed surgical trajectory.

2.2.3 Indications and contraindications

The main indications for the supraorbital keyhole approach are lesions located within the suprasellar region and the surrounding central skull base. These include, but are not limited to, pituitary adenoma, suprasellar craniopharyngioma, tuberculum sella and olfactory groove meningioma, and most anterior circulation aneurysms. The supraorbital keyhole approach is technically challenging, restricting its use to selected cases.

2.2.4 Surgical technique

2.2.4.1 Positioning and preparation of the patient

The patient is placed supine on the operating table with their head fixed in a three-pin Mayfield head holder (Codman, Massachusetts, USA).

Initially, the head is elevated above the level of the thorax to reduce intracranial pressure. The head is then retroflexed 15-30° so that gravity causes the frontal lobe to fall away from the anterior cranial fossa and allow for retractor-free intracranial dissection. The degree of rotation depends on the target region, but for exploration of the central skull base, angles of 30-60° is usually appropriate.

2.2.4.2 Incision, craniotomy, and durotomy

Step 1. The skin incision is started laterally from the supraorbital incisura within the eyebrow and carried in a lateral-to-medial direction (Figure 2.3a). To achieve a cosmetically optimal result, the incision should follow the orbital rim. Note that the skin incision should not extend medially to the supraorbital nerve. After the skin incision, the subcutaneous dissection is continued in the frontal direction to achieve optimal exposure of the frontolateral supraorbital area.

Step 2. The frontal skin flap is temporarily retracted with holding sutures. The frontal muscle is then cut with a monopolar knife parallel to the orbital rim in a medial-to-lateral direction. As the temporal line is reached with the monopolar knife, the blade is turned 90° and carried along the temporal line in a basal direction to the zygomatic process of the frontal bone (Figure 2.3b).

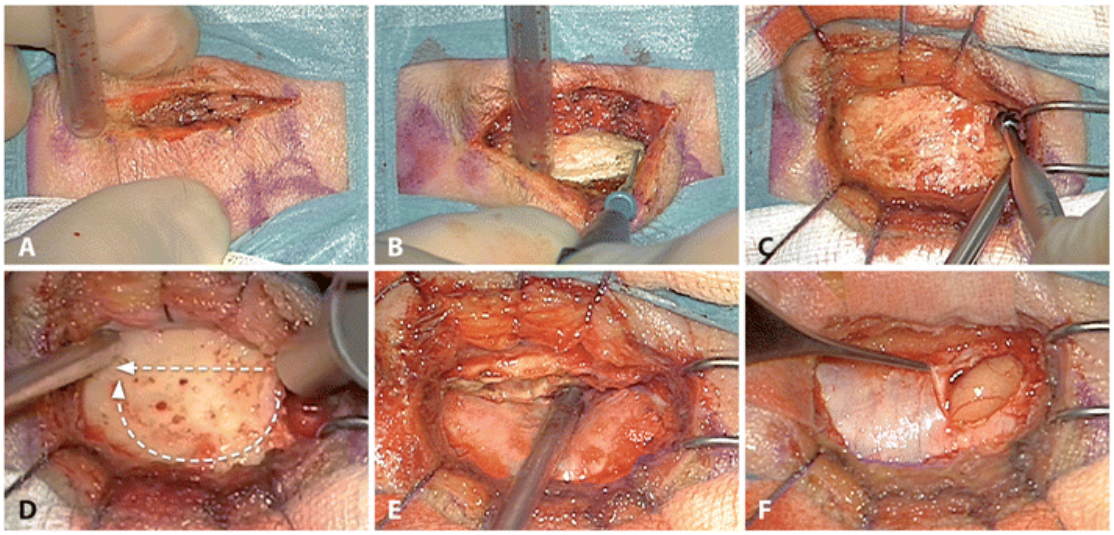


Figure 2.3. Surgical steps of the supraorbital keyhole approach corresponding to the illustrative case (see text for details).

Step 3. The temporal muscle is retracted laterally with a strong hook. Using this technique, exposure and mobilisation of the temporal muscle is restricted to a necessary minimum. The frontal and supraorbital muscles are retracted with sutures. A single frontobasal burr hole is then made using a high-speed drill (Figure 2.3c). Optimal placement of the burr hole is lateral to the temporal line at the level of the frontal cranial base, thus avoiding penetration of the orbit.

Step 4. After minimal enlargement of the burr hole with a 2-3 mm Kerrison punch and mobilisation of the dura, a straight line is cut with a high-speed craniotome parallel to the orbital rim in a lateral-to-medial direction, taking into account the lateral border of the frontal paranasal sinus (Figure 2.3d). Thereafter a “C” shaped line is cut from the burr hole to the medial border of the previously performed frontobasal line. In this way, a limited craniotomy is created with a size of approximately 25 x 15 mm.

Step 5. High-speed drilling is performed on the inner edge of the bone above the orbital rim, while protecting the dura (Figure 2.3e). Small osseous extensions of the superficial orbital roof, the so-called juga cerebralia, should also be drilled extradurally to obtain optimal intradural visualisation.

Step. 6. The dura is opened in a simple “C” shape and retracted in a basal direction. Note the limited exposure of the brain surface (Figure 2.3f).

2.2.4.3 Intradural dissection: An illustrative case

Magnetic Resonance Imaging (MRI) demonstrated a vividly enhancing large right frontal extra-axial lesion, consistent with a meningioma (Figure 2.4a-c). One week after successful partial embolisation, the tumour was surgically approached via a right-sided supraorbital keyhole.

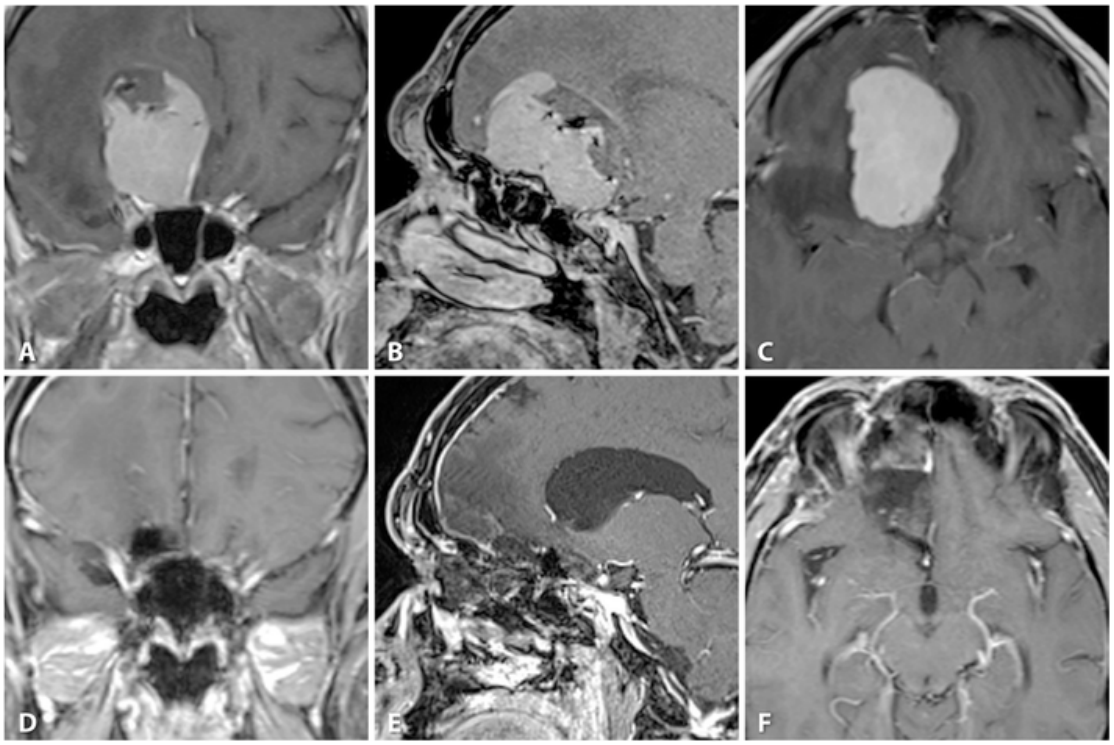


Figure 2.4. (a-c) T1-weighted triplanar MRI with contrast medium demonstrating a large right frontobasal and olfactory groove meningioma. (d-f) MRI 3 months post-operatively demonstrating complete tumour resection.

In this case the tumour exerted significant mass effect and elevated intracranial pressure was observed. However, with careful mobilisation of the frontal lobe, the deep subarachnoid cisterns could be reached without using an elevator (Figure 2.5a). After release of CSF, the tumour was approached in a retractor-free manner.

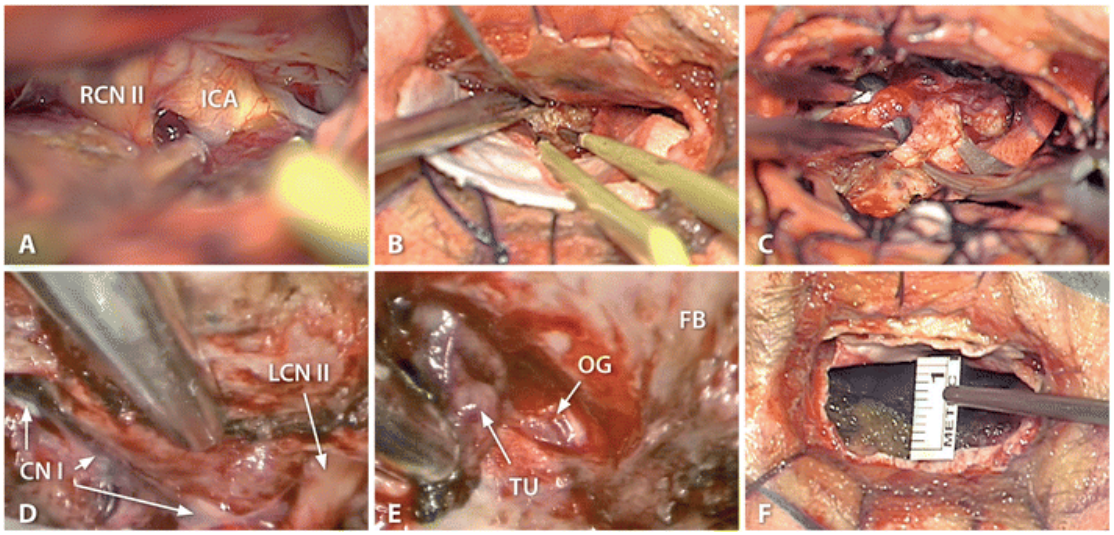


Figure 2.5. Surgical steps of removal of the frontobasal meningioma without use of a retractor. The last remnants were visualised and removed with an endoscope-assisted technique.

Initially, the tumour was coagulated and detached from the frontal skull base (Figure 2.5b). Thereafter, the tumour was removed piecemeal using grasping instruments, scissors and a Cavitron Ultrasonic Surgical Aspirator (Figure 2.5c). An endoscope was intermittently used to improve visualisation, allowing improved illumination and magnification, and a wider viewing angle. The intact left olfactory and both optic nerves could be clearly seen using the endoscope (Figure 2.5d); and the very last parts of the tumour in the olfactory groove were removed under pure endoscopic visualisation (Figure 2.5e). Tube-shaft instruments were used to permit surgical manipulation through a narrow surgical corridor.

2.2.4.4 2.2.5.4 Closure

On completion of the intracranial procedure, the dura is sutured closed in watertight fashion. The bone flap is replaced and secured with a Craniofix plate (Aesculap AG, Tuttlingen, Germany), and any craniotomy-defects filled with bone cement for a pleasant cosmetic outcome. The muscles are re-approximated, and the skin closed with subcutaneous and subcuticular sutures.

2.2.5 Post-operative management

Standard neurological observations are performed post-operatively. Wound drains are not placed and subcutaneous and subcuticular sutures obviate the need for later suture

removal. Patients are typically discharged 3-7 days post-operatively, and followed up in outpatient clinic at 6-12 weeks.

2.2.6 Complications

Inadequate pre-operative planning and poor patient positioning can impair subsequent exposure. Lesions close to the frontal skull base require retroflexion of 15°, while those situated more cranially require retroflexion of about 30°. Similarly, ipsilateral lesions require rotation of 10-15°, while those located in the olfactory groove require rotation of 45-60°.

A skin incision carried too medially can lead to post-operative numbness. The patient's surface anatomy should be carefully marked, including the supraorbital foramen, to reduce the risk of injury to supraorbital nerve.

Dissection and retraction towards the supraorbital rim can result in orbital hematoma, and should be minimised. Care should be taken when fashioning the burr hole to reduce the risk of inadvertently perforating the orbit. Penetration of the frontal paranasal sinuses can lead to post-operative CSF leak. Should a breach occur, repair with wax, pericranial fascia, or abdominal fat, is required.

In cases of elevated intracranial pressure, mobilisation of the frontal lobe may be challenging, and release of sufficient CSF is necessary.

During closure, meticulous haemostasis and a watertight dural closure are essential to prevent post-operative haemorrhage and CSF leak respectively. Inappropriate positioning and fixation of the bone flap can result in a poor cosmetic outcome. Ideally, the bone flap should be placed medially and frontally, with the Craniofix plate used for closure of the burr hole, and bone cement used for any remaining defect.

2.3 Simulation of the supraorbital approach using the Modelled Anatomical Replica for Training Young Neurosurgeons (MARTYN): A validation study

2.3.1 Introduction

The Modelled Anatomical Replica for Training Young Neurosurgeons (MARTYN), was created by the conservation team at the Royal College of Surgeons of England (RCSEng) to simulate traumatic pathologies, such as extradural haemorrhage, and has been used with great success at relevant workshops. A modified MARTYN head was developed in collaboration with the RCSEng that incorporates a vascular tree and pathology, allowing for the simulation of the keyhole supraorbital subfrontal approach[33]. Here, a short validation study is reported, assessing its realism (face validity), usefulness (content validity), and ability to differentiate levels of surgical experience (construct validity).

2.3.2 Materials and Methods

Fifteen participants were recruited from one university hospital. Participants completed a pre-study questionnaire on demographics and surgical experience, and were categorised as novices (completed zero neuro-endoscopic or -vascular cases), intermediates (completed at least one but <50 cases), or experts (completed ≥50 cases).

The MARTYN head consists of a polyurethane skull, latex dura and gelatine-based brain. Additionally, the head incorporates a Circle of Willis including a basilar tip aneurysm. A 25 x 15mm left supraorbital craniotomy was fashioned and a simple "C" shaped durotomy performed. A VisionSense III endoscope (VisionSense, Petach Tikva, Israel) was used for visualisation, and a probe for localisation.

Each participant reviewed a short video demonstrating the model, and was asked to identify the cerebral aneurysm, with instructions to minimise exposure and manipulation of brain tissue using cottonoid patties (Codman and Shurtleff, Massachusetts, USA) as they deemed appropriate. The task was considered complete when users applied the probe to the aneurysm (Figure 2.6).

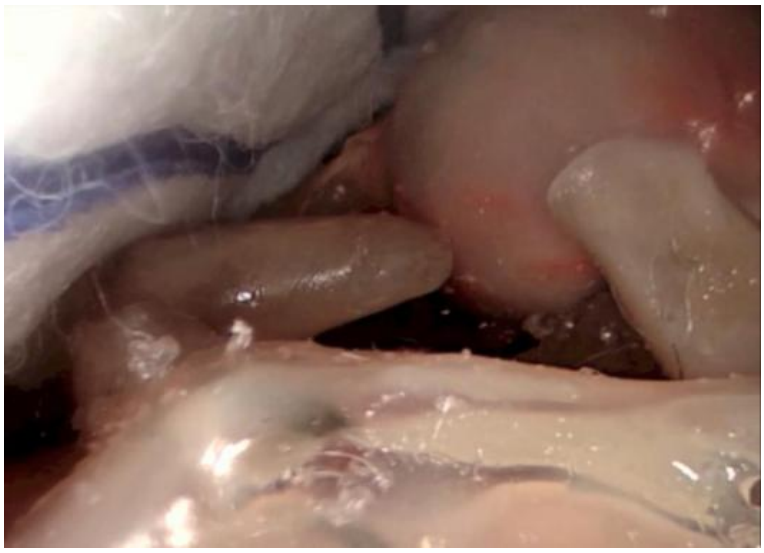


Figure 2.6. Endoscopic image demonstrating basilar tip aneurysm (top right). Note cottonoid patty within the operative field (top left).

After completion of the study, intermediate and expert participants completed a post-study questionnaire to assess the realism (face validity) and usefulness (content validity) of the model, on a five-point visual analogue scale (1 = worst; 5 = best). The time to task completion (seconds) was also recorded for all participants.

Data were analysed using SPSS v 20.0 (IBM, Illinois, USA). The median and interquartile ranges (IQR) were calculated for all outcomes measured. It was decided *a priori* that intermediate and experts would be combined when analysing construct validity. The differences in time to task completion between novices, and intermediates-experts, were compared using the Mann-Witney U test, with a value of $P < 0.05$ considered statistically significant.

2.3.3 Results

A total of 10 novices, 4 intermediates and 1 expert were recruited (Table 2.1). Overall, intermediate and expert surgeons rated the model as realistic (median score 4.0/5.0; IQR 4.0 – 4.0) and useful (median score 5.0/5.0; IQR 4.0 – 5.0), confirming face and content validity respectively. Intermediate and expert surgeons also completed the task in significantly less time than novices ($p = 0.0047$), confirming construct validity (Figure 2.7).

	Age, Median (IQR), years	Sex, Male:Female	Handedness, Right:Left
Novice (n = 10)	32.0 (29.8 – 33.8)	6:4	8:2
Intermediate (n = 4)	34.5 (32.5 – 36.3)	4:0	4:0
Expert (n = 1)	39.0	1:0	1:0
Intermediate and Expert (n = 5)	36.0 (33.0-37.0)	5:0	5:0

Table 2.1. Participant demographics.

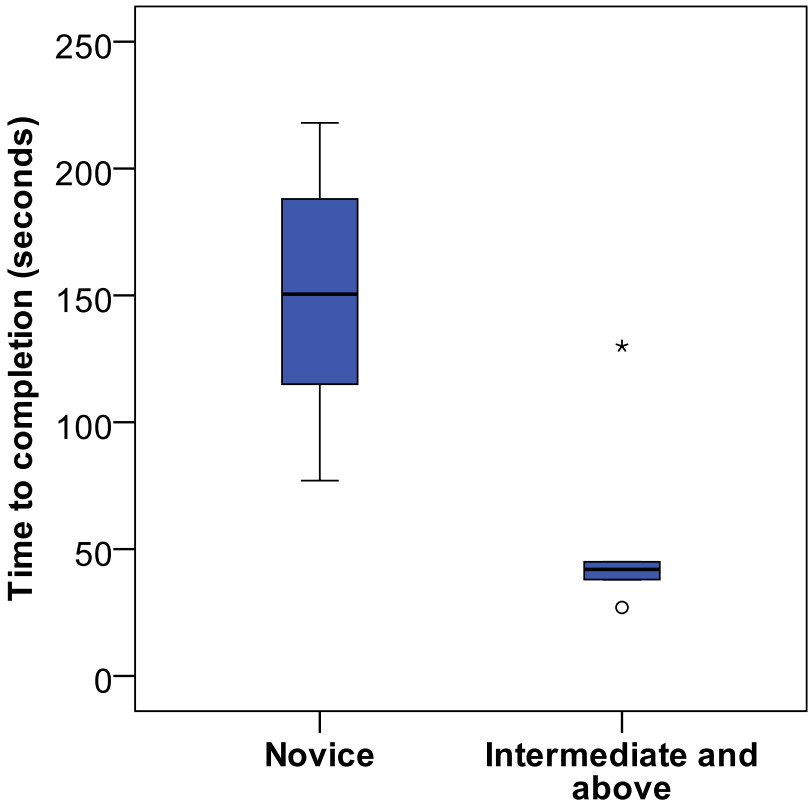


Figure 2.7. Box plot comparing time to completion in novices, and intermediates-experts. Points represent outliers (circle greater than 1.5 times the interquartile range; star greater than 3 times the interquartile range).

2.3.4 Discussion

In this study it has been demonstrated that simulation of the keyhole supraorbital subfrontal approach with the MARTYN head has face, content and construct validity. A major limitation of the present study was lack of experts familiar with this uncommon and difficult approach. Nonetheless, the significant difference in performance between novices and intermediates-experts supports use of the model.

With greater emphasis on reducing patient risk, simulators such as MARTYN provide a method to supplement clinical exposure, and evaluate operative proficiency, in a safe and controlled environment[34]. Moreover, and pertinent to this thesis, preclinical studies using MARTYN might allow for the evaluation of surgical innovations, to ensure new robotic platforms under development are safe and effective[33].

CHAPTER 3 CLINICAL NEEDS ASSESSMENT AND TECHNOLOGICAL GAP ANALYSIS*

*Content from this chapter was published or submitted as:

Marcus HJ, Cundy TP, Hughes-Hallett A, Yang GZ, Darzi A, and Nandi D. Endoscopic and keyhole endoscope-assisted neurosurgical approaches: A qualitative survey on technical challenges and technological solutions. Br J Neurosurg. 2014; 28(5): 606-610

Marcus HJ, Hughes-Hallett A, Kwasnicki RM, Darzi A, Yang GZ, and Nandi D. Technological Innovation in Neurosurgery: A Quantitative Study. J Neurosurg. 2015 [Epub ahead of print]

Marcus HJ, Seneci C, Payne C, Nandi D, Darzi A, and Yang GZ. The Application of Robotics to Transcranial Endoscope-assisted Microsurgery: A Critical Review of Existing Systems and Proposed Specifications for New Robotic Platforms. Neurosurgery. 2014; 10(1 Suppl Operative): 84-95

Marcus HJ, Hughes-Hallett A, Cundy TP, Yang GZ, Darzi A, and Nandi D. da Vinci Robot-Assisted Keyhole Neurosurgery: A Cadaver Study on Feasibility and Safety. Neurosurg Rev. 2015; 38(2): 367-371

Content from the chapter was presented as:

Marcus HJ, Dyson E, Fu R, Chowdhury Y, Yang GZ, Darzi A, and Nandi D. Community consultation on attitudes towards robotics in neurosurgery. SBNS Autumn conference, Coventry. September 2014

Marcus HJ, Hughes-Hallett A, Cundy TP, Yang GZ, Darzi A, and Nandi D. da Vinci Robot-Assisted Keyhole Neurosurgery: A Cadaver Study. Hamlyn Symposium, London. July 2014

3.1 Technical challenges: A qualitative survey of surgeons

3.1.1 Introduction

As reported in Chapter 2, the neurosurgical literature has reflected a resurgence of clinical interest in endoscopic neurosurgical approaches as alternatives to conventional microsurgical approaches in carefully selected cases[25, 26, 35]. Although such approaches promise reduced exposure and manipulation of brain tissue, they can also present substantial technical challenges that may limit their safety and efficacy. Identifying and understanding these barriers is a prerequisite to progress in the field. The aim of this study was to assess the technical challenges of endoscopic brain surgery, and the scope for technological innovations to overcome these barriers.

3.1.2 Materials and Methods

A qualitative study design was adopted to gain a broad understanding of the perceived technical challenges of endoscopic neurosurgery, and the potential for technological solutions. In contrast to quantitative studies, which seek to evaluate a large number of randomly selected participants representing the population of interest using closed surveys, qualitative studies generally sample a small number of participants in more detailed open surveys. Saturation of data collection in qualitative studies is said to occur when no new or relevant information emerges with further participants, which was estimated to require approximately 20 participants based on similar studies in other surgical fields[36].

3.1.2.1 Participants

All 249 full members of the Society of British Neurosurgeons (SBNS) were electronically invited to participate in an online survey on endoscopic neurosurgery. Only one attempt at contact was made with members, and the survey was closed one week following initial distribution as the number of responders had already exceeded our *a priori* estimate to achieve saturation.

3.1.2.2 Survey

Participating members were asked to disclose their name, surgical unit and subspecialty interests. The open-ended structured survey asked three questions.

Firstly, whether the surgeon presently utilises or has experience with endoscopic approaches. Secondly, what they consider to be the major technical barriers to adopting such approaches. Thirdly, what technological advances they foresee improving safety and efficacy in the field.

Responses were collected, anonymised, and consolidated in a single spreadsheet for qualitative analysis.

3.1.2.3 Data Analysis

Three authors analysed survey responses. Based on a preliminary screen, responses were first coded for indications of general philosophy on the utilisation of endoscopic approaches, and also for specific barriers to the adoption of such approaches. Subsequently, using iterative analysis, responses were parsed for themes by individual raters (Figure 3.1).

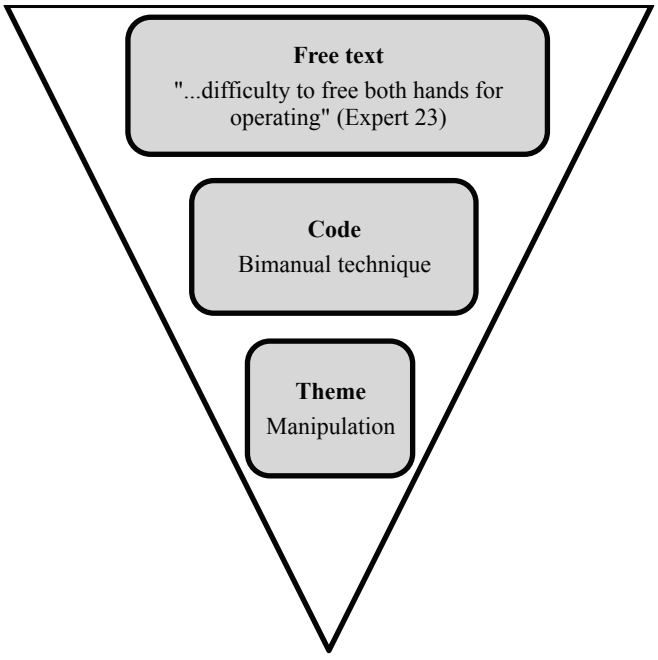


Figure 3.1. Qualitative analysis methodology.

After agreement was reached on themes, raters returned to the survey responses and binary coded for theme content. Raters initially performed this analysis independently; agreement was reached based on discussion during consensus meetings.

All counts were tallied and expressed as percentages. As each participant may have referenced multiple theme categories, percentage totals did not necessarily tally to 100. Completed surveys were assigned identifying labels based on chronological order of receipt, i.e. “Participant 1”, “Participant 2”, “Participant 3” etc.

3.1.3 Results

In all, 40 consultant neurosurgeons participated in the survey within a week of initial distribution (response rate 16.1%). Specialty interests of responding neurosurgeons were mostly distributed among neuro-oncology (53%), paediatric (43%) or skull base surgery (38%) (Table 3.1).

Subspecialty	Number of participants (%)
Neuro-oncology	21 (53%)
Paediatric	17 (43%)
Skull base	15 (38%)
Neurovascular	12 (30%)
Spine and peripheral nerve	12 (30%)
Trauma	7 (18%)
Functional	4 (10%)

Table 3.1. Subspecialty of neurosurgeons participating in survey.

Of the 40 neurosurgeons that took part in the study, 38 described their own endoscopic practice. The majority performed intraventricular procedures including endoscopic third ventriculostomy (63%) or endonasal transsphenoidal procedures (37%) (Table 3.2).

Practice	Number of participants (%)
Endoscopic third ventriculostomy and other intraventricular approaches	24 (63%)
Endonasal transsphenoidal and extended transsphenoidal approaches	14 (37%)
Transcranial endoscopic microsurgery	8 (21%)
Other e.g. endoscopic resection of intraparenchymal brain tumours	0 (0%)

Table 3.2. Practice of neurosurgeons participating in survey.

Thirty-five participants provided detailed opinions on the technical challenges of endoscopic neurosurgical approaches, and the scope for technological innovations to improve safety and efficacy in the field. Three clear themes emerged; 1) surgical approach and better integration with image guidance systems (20%), 2) intra-operative visualisation and improvements in endoscopy (49%), and 3) surgical manipulation and improvements in instruments (74%). Major themes and subthemes identified in the study are illustrated in Figure 3.2. Saturation of themes and subthemes were achieved after 5 and 25 participants respectively.

3.1.3.1 Surgical approach

Several neurosurgeons commented on the need for *"better image guidance system integration"* (Participant 25) into the surgical workflow. Five respondents additionally suggested that such systems could be used to guide *"navigatable flexible endoscopes"* (Participant 4) during the surgical approach, which would allow critical neurovascular structures to be avoided.

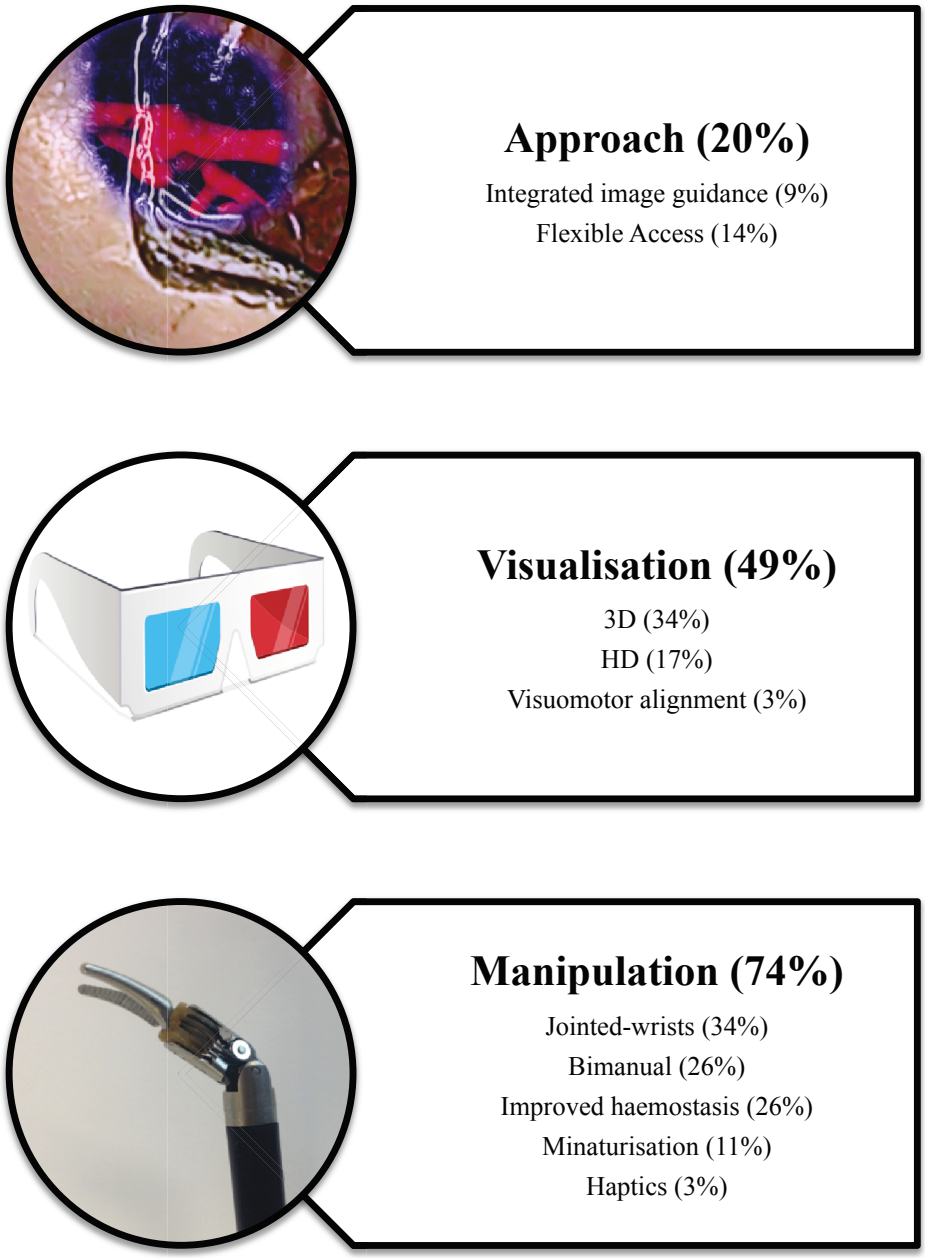


Figure 3.2. Themes and subthemes, in order of frequency that they were mentioned. Note that each respondent could mention several sub-themes, so totals do not tally to 100%. 3D = 3-Dimensional; HD = High-Definition

3.1.3.2 Intraoperative visualisation

Almost half of responding neurosurgeons described current endoscopic visualisation as a barrier to further adoption of the technique. The most highly cited subtheme was lack of *"3D and depth perception"* (Participant 21) provided by most presently available endoscopes, which impaired appreciation of complex spatial relationships

within the brain. One surgeon qualified their support by suggesting that *"3D will help the less experienced the most"* (Participant 33), and another cautioned that while improved imaging would be useful, they were *"not sure if 3D will be as good as it is hyped to be"* (Participant 35).

Several neurosurgeons commented on the *"quality of image"* (Participant 35) provided by endoscopes, and the need for *"better optics"* (Participant 4), and *"improved pictures…as they tend to degrade over time"* (Participant 22). One respondent felt that visuomotor misalignment was another limitation of current endoscopy platforms, stating that *"it is awkward…to have to look in one direction and operate in another"* (Participant 25).

3.1.3.3 Tissue manipulation

The majority of survey participants described technical difficulties with available endoscopic instruments as a major limitation of endoscopic neurosurgery. The most highly cited subtheme was lack of dexterity when using rigid instruments down a narrow surgical trajectory, *"...the majority of current instruments preclude true microsurgical techniques and rely mostly on traction and pulling"* (Participant 28). One surgeon described, for example, how *"...stitching or closing dura"* (Participant 10) was difficult or impossible to perform through endoscopic approaches. Several neurosurgeons felt that robotic articulated instruments might overcome this barrier, *"endoscopic micro-instruments with similar degrees of freedom as a Da Vinci™ robot"* (Participant 2).

Another common subtheme was the *"difficulty to free both hands for operating"* (Participant 23), thus limiting the bimanual manipulation that characterises microsurgical dissection. Several neurosurgeons expanded on this, explaining that it was *"difficult for the assistant to be of any help… so tends to be suction one hand and dissection other hand"* (Participant 33). A few respondents suggested that *"more user-friendly endoscope holders"* (Participant 23) or perhaps a robotic scope holder *"that would allow remotely controlled scope movement"* (Participant 18), might allow for bimanual manipulation.

Many neurosurgeons were concerned about adequate haemostasis, especially *"controlling major arterial bleeding"* (Participant 10). Participants felt that current bipolar forceps were inadequate during endoscopic approaches, and that improvements in their design would improve safety. Four neurosurgeons mentioned that *"lack of working equipment such as a CUSA that can fit down the scope"* (Participant 13) also limited the adoption of endoscopic approaches, particularly within the field of neuro-oncology. One surgeon described how endoscopic approaches lacked *"haptic quality"* (Participant 21) compared to conventional microneurosurgery, and that this might impact surgical performance.

3.1.3.4 General comments

One respondent emphasised that regardless of tool development, *"a fool with a tool is still a fool… the major limitation would be if the surgeon themselves fails to understand this."* (Participant 6). Two neurosurgeons recognised the long learning curve of endoscopic approaches to be a major limitation, and one surgeon commented that *"simulation and training"* (Participant 21), alongside tool development, would help overcome this.

3.1.4 Discussion

Endoscopy has been applied to the field of neurosurgery since the work of early pioneers such as Walter Dandy approximately a century ago[37]. In recent years, technological advances such as the development of image guidance systems, endoscopes with improved image quality, and tube-shaft instruments, have ignited a resurgence of enthusiasm in the field, with specific procedures such as Endoscopic Third Ventriculostomy (ETV) and endoscopic endonasal transsphenoidal hypophysectomy now relatively well accepted by the neurosurgical community in carefully selected cases[38, 39]. The analysis of responses to the present open-ended survey revealed that although opinion was varied on the technical challenges of endoscopic neurosurgery, and the scope for technological improvements to overcome these barriers, three major themes could be identified: surgical approach and better integration with image guidance systems (20%); intra-operative visualisation and improvements in endoscopy (49%); and surgical manipulation and improvements in instruments (74%).

3.1.4.1 Surgical approach

Image guidance systems are now widely used within neurosurgery and are associated with shorter operating times, reduced blood loss, and fewer complications than conventional surgery[27]. In light of the availability and use of image guidance systems it was, at first glance, somewhat counterintuitive that difficulty in surgical access was still identified as a significant limitation of present-day endoscopic neurosurgery. Several neurosurgeons reported the need for better integration of image guidance systems into the surgical workflow. It is speculated that the relative paucity of external landmarks and potential for disorientation in endoscopic approaches results in frequent interruptions during surgery to place the image guidance probe and turn away from the operative field to view the image display monitors. In the near future, augmented reality systems may allow for more seamless integration of image guidance systems by overlaying virtual targets onto the surgical scene[40-42].

3.1.4.2 Intra-operative visualisation

Endoscopic visualisation was also a major theme identified by respondents. Although endoscopy provides a much wider view angle through narrow surgical corridors compared to microscopy, most available endoscopy systems are impaired by far lower image quality and very few offer stereoscopy. To this end, it is anticipated that the development of high-definition (HD) and 3-dimensional (3D) endoscopes will overcome this hurdle. Early studies have already suggested that the use of such endoscopes allows for improved recognition of anatomical landmarks, and better appreciation of complex spatial relationships[43-47].

3.1.4.3 Tissue manipulation

Surgical manipulation was the theme most frequently identified by participants as the key to developing safer and more efficacious endoscopic neurosurgical approaches. Currently available instruments do not allow for dissection in the same way as conventional microsurgical approaches, reducing surgical dexterity to largely co-axial control through narrow corridors, and often limiting neurosurgeons to single-handed manipulation. Most neurosurgical operations, such as tumour resection, are therefore far more difficult to perform through keyhole approaches. Technological advances,

such as robotic instruments with articulated wrist-joints, may free neurosurgeons of ergonomic burdens imposed by "chopstick" surgery[48].

3.1.4.4 Limitations

There are several limitations of the present study. Notably, the sample size was small, and the response rate low, reflecting the adoption of a qualitative rather than quantitative study design. A qualitative methodology was selected as the aim of the study was to gain an understanding of the perceived technical limitations of endoscopic neurosurgery, and the possible role for technological advances, rather than measure the frequency of predefined opinions. Although all members of the SBNS were invited to participate in the survey, neurosurgeons almost certainly self-selected if they had a specialist interest in endoscopic neurosurgery, as reflected by the relatively high number of paediatric and skull base neurosurgeons responding (who were far more likely to be routinely involved with intraventricular and endonasal transsphenoidal approaches respectively). The *a priori* goal of saturation of themes and subthemes was achieved and it is likely that the key findings of the research are externally valid.

Another inherent limitation of the open-ended online survey study design was that it prevented probing of respondents' answers. However, it would not have been feasible to reach as many neurosurgeons if they were required to commit to time-intensive interviews. In any case, several neurosurgeons provided extended answers to the survey prompts, allowing fairly detailed analysis of the major themes and subthemes identified.

3.1.4.5 Conclusions

In conclusion, several common themes have been identified by neurosurgeons as important barriers to the adoption of endoscopic neurosurgery. These themes may be summarised as poor integration of current image guidance systems, lack of 3D visualisation with most presently available endoscopes, and limited scope for dextrous bimanual manipulation with rigid tube-shaft instruments.

3.2 Technological innovation: A quantitative study of patents and publications

3.2.2 Introduction

Having determined the major technical barriers to endoscopic neurosurgery, a study was then performed to identify potential technological solutions. Technological innovation within healthcare may be defined as the introduction of a new technology that initiates a change in clinical practice[49, 50]. Neurosurgery is a particularly technologically intensive surgical discipline, and new technologies have preceded many of the major advances in operative neurosurgical technique[23, 25]. While the study of innovation is a relatively mature academic field in social science and industry[51], its application in the healthcare setting has been largely qualitative in nature[52-56].

Patents may be defined as *"the right to exclude others from making, using, offering for sale, or selling an invention"* and represent a good metric of technology development[50]. Similarly, peer-reviewed publications in healthcare journals provide a measure of translational research. Technological innovation may therefore be characterised by a rise in both patent and publication data[57].

Recently, patent and publication data have been used to identify clusters of technological innovation in surgery, with emerging innovations lying on the exponential phases of their respective growth curves[58]. In this study, the same methodology has been employed to first determine the most influential technology clusters in operative neurosurgery over the last 50 years and subsequently to identify areas of contemporaneous growth to aid in the prediction of the important future technologies in neurosurgical practice.

3.2.1 Materials and Methods

3.2.1.1 Patent and publications

Patent data was obtained using proprietary software PatentInspiration (Ypres, Belgium), which searches the DOCDB database using data from over 90 countries[58]. Titles, abstracts and descriptions of granted patents were searched from 1960 to 2010 using the Boolean search term "neurosurgeon OR neurosurgical OR neurosurgery". Only single members of patent families were retrieved, to prevent duplication of data. Publication data was obtained using PubMed (National Library of Medicine, Maryland, USA), and the same search strategy.

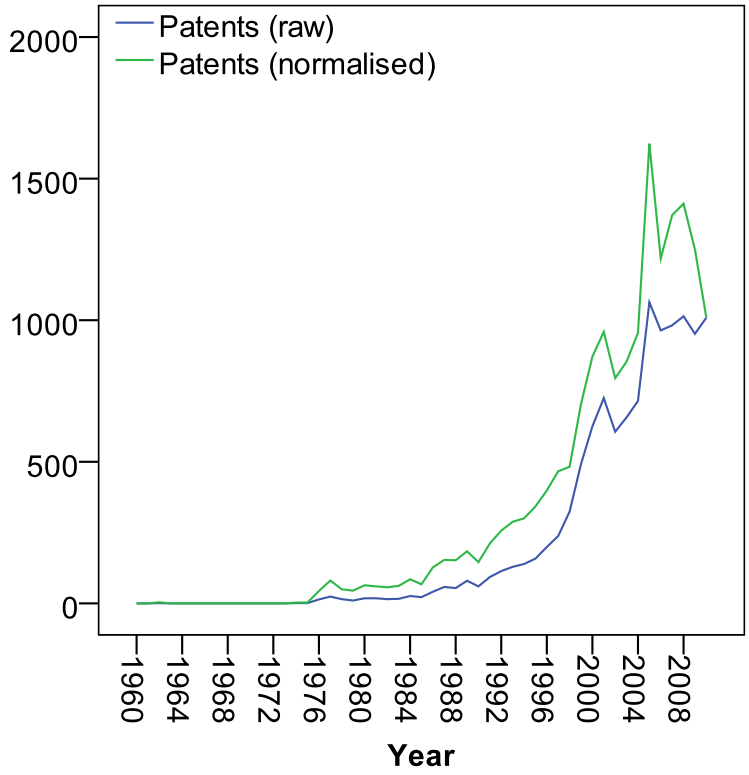
Over time both patent and publication counts have been rising exponentially in all fields (Figure 3.3). A previously described equation[58] was therefore applied to normalise both patent and publication counts using data from 2010 (the year reporting the greatest number of patents and publications).

3.2.1.2 Top performing technology clusters

Following compilation of the patent dataset, the top 50 performing patent codes over the last 50 years (those codes for which the greatest number of patents had been applied for) were identified[58]. Patent codes describing non-technological advances (such as drugs), or not relating to operative neurosurgery, were excluded. Remaining patent codes were grouped into clusters of related surgical technologies by two authors, with any disagreements arbitrated by a third author. The top performing technology clusters were then individually evaluated by performing further patent and publication searches (Table 3.3.).

The above methodology was then repeated for patents and publications over the last 5 years of the dataset, from 2005 to 2010. Comparison of the top performing patent codes over these different timescales allowed for more recent technological developments to be determined.

a.



b.

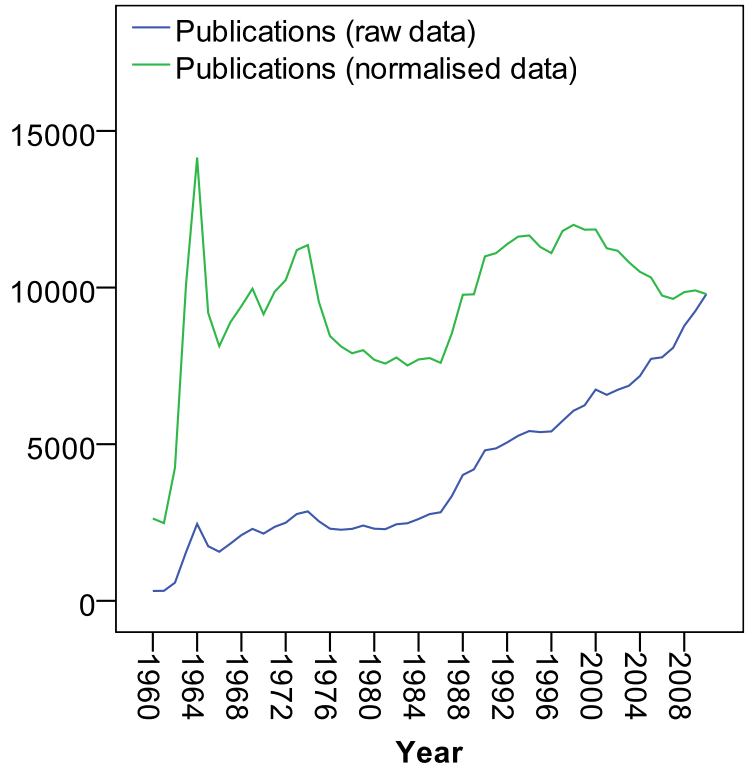


Figure 3.3. Plots of (a) patents and (b) publications related to neurosurgery over time.

Search strategies	
Image Guidance Devices	("image guidance" OR "image guided" OR "augmented reality" OR "image fusion" OR "image overlay" OR neuronavigation) AND (neurosurgery OR neurosurgeon OR neurosurgical)
Clinical Neurophysiology Devices including those measuring Motor Evoked Potentials and Somatosensory Evoked Potentials	("Motor Evoked Potentials" OR MEP OR "Somatosensory Evoked Potentials" OR SSEP) AND (neurosurgery OR neurosurgeon OR neurosurgical)
Neuromodulation Devices including those for Deep Brain Stimulation, Spinal Cord Stimulation, and Peripheral Nerve Stimulation	("deep brain stimulation" OR dbs OR "spinal cord stimulation" OR "spinal cord stimulator" OR "peripheral nerve stimulation" OR "peripheral nerve stimulator") AND (neurosurgery OR neurosurgeon OR neurosurgical)
Operating Microscopes	(microscope OR microsurgery OR microneurosurgery) AND (neurosurgery OR neurosurgeon OR neurosurgical)
Endoscopes	(endoscope OR endoscopy OR endoscopic OR neuroendoscope OR neuroendoscopy OR neuroendoscopic OR neuro-endoscope OR neuro-endoscopy OR neuro-endoscopic) AND (neurosurgery OR neurosurgeon OR neurosurgical)

Table 3.3. Search strategies.

3.2.1.3 Statistical analysis

Data were analysed with Statistical Package for the Social Sciences (SPSS) v 20.0 (Illinois, USA). Patent and publication data were plotted against each other to determine whether their relationship was monotonic. If so, Pearson's (r) or Spearman's rank (r_s) correlation coefficient was applied to determine the strength of

their relationship, depending on whether the association was linear or non-linear respectively.

3.2.2 Results

3.2.2.1 Patents and publications

In all, 11,672 patents and 208,203 publications relating to neurosurgery between 1960 and 2010 were identified. The original and normalised patent and publication data are presented in Figure 3.3. Normalised patent counts demonstrated a peak at 2005. Normalised publication counts demonstrated an early peak in 1964 and a late peak in 1998.

3.2.2.2 Top performing technology clusters

The top performing technology clusters over the 50 years are summarised in Table 3.4. Approximately half the patent codes concerned non-technological advances such as drugs. Of the remaining patent codes, the largest cluster was image guidance devices, accounting for 37.9% of those granted. The remaining technology clusters identified were: clinical neurophysiology devices (including those recording Motor Evoked Potentials and Somatosensory Evoked Potentials), neuromodulation devices (including those for Deep Brain Stimulation, Spinal Cord Stimulation, and Peripheral Nerve Stimulation), operating microscopes, and endoscopes.

The top performing technology clusters over the last 5 years were largely unchanged. The proportion of patent codes associated with endoscopes had increased slightly (6.3% versus 5.7%), while the proportion of patent codes associated with operating microscopes fell (4.3% versus 6.1%).

Rank	Technology cluster	Number of codes	Number of patents*
	1960 – 2010		
1	Image Guidance Devices	8	2625 (37.9%)
2	Clinical Neurophysiology Devices, including those measuring Motor Evoked Potentials and Somatosensory Evoked Potentials	4	1450 (21.0%)
3	Neuromodulation Devices, including those for Deep Brain Stimulation, Spinal Cord Stimulation, and Peripheral Nerve Stimulation	4	1294 (18.7%)
4	Operating Microscopes	2	420 (6.1%)
5	Endoscopes	2	391 (5.7%)
6	Miscellaneous	4	738 (10.7%)
	2005 – 2010		
1	Image Guidance Systems	9	1110 (46.0%)
2	Clinical Neurophysiology Devices, including those measuring Motor Evoked Potentials and Somatosensory Evoked Potentials	5	532 (22.0%)
3	Neuromodulation Devices, including those for Deep Brain Stimulation, Spinal Cord Stimulation, and Peripheral Nerve Stimulation	3	517 (21.4%)
4	Endoscopes	2	152 (6.3%)
5	Operating Microscopes	1	103 (4.3%)
6	Miscellaneous	5	391 (16.2%)

Table 3.4. Top 50 performing patent codes over (a) between 1960 and 2010, and (b) between 2005 and 2010. *Normalised data

3.2.2.3 Statistical analysis

The relationship between normalised patents and publication counts over time for the top performing technology clusters are illustrated in Figure 3.4 – 3.8. The plots of data on image guidance and neuromodulation devices demonstrated a highly correlated rapid rise (r_s = 0.87 and 0.83 respectively, $p < 0.001$). The plots of data on operating microscopes and endoscopes demonstrated a similar trend (r_s = 0.93 and 0.87, $p < 0.001$), before reaching a plateau in approximately 2000. The plot of clinical neurophysiology devices was unique among the technology clusters assessed, with a comparatively poorer correlation between patents and publications (r_s = 0.64, $p < 0.001$). Normalised patents demonstrated a rapid recent rise, while publications reached a plateau in 1993.

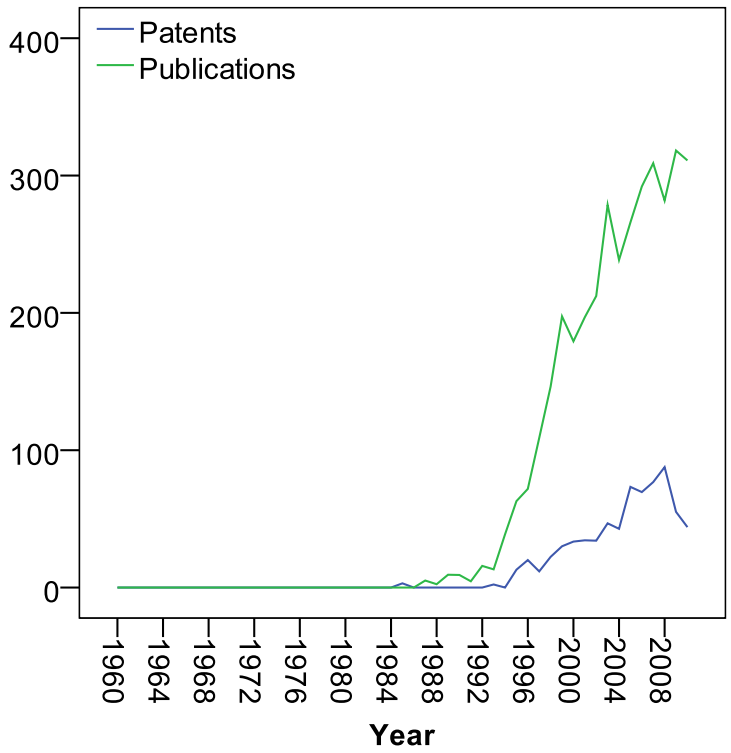


Figure 3.4. Plot of patents and publications over time concerning image guidance devices.

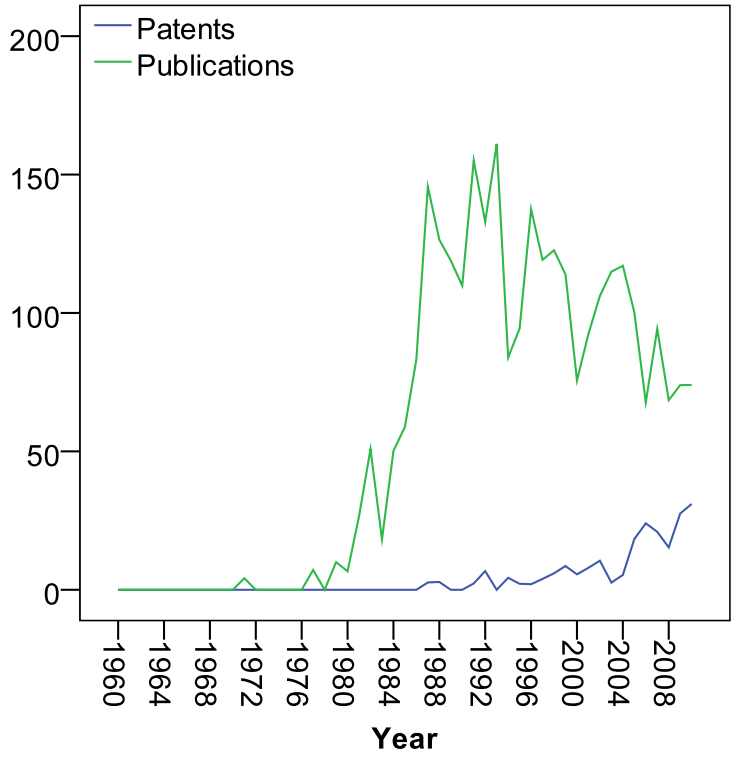


Figure 3.5. Plot of patents and publications over time concerning clinical neurophysiology devices.

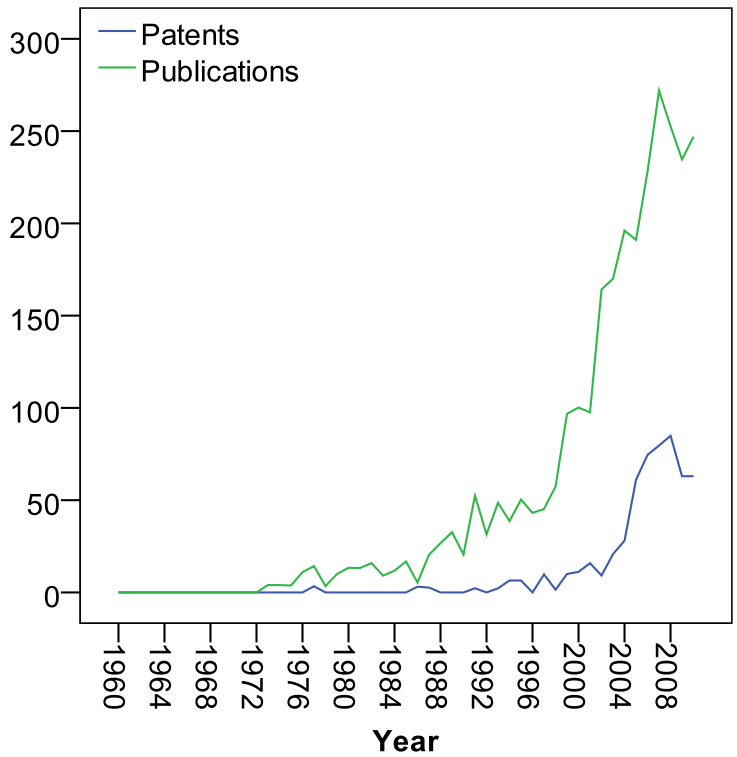


Figure 3.6. Plot of patents and publications over time concerning neuromodulation devices.

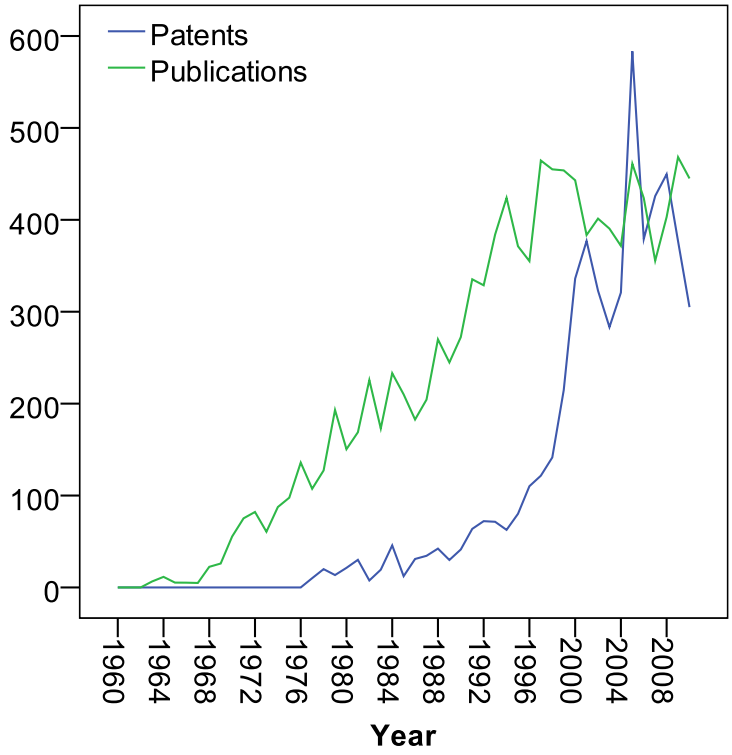


Figure 3.7. Plot of patents and publications over time concerning operating microscopes.

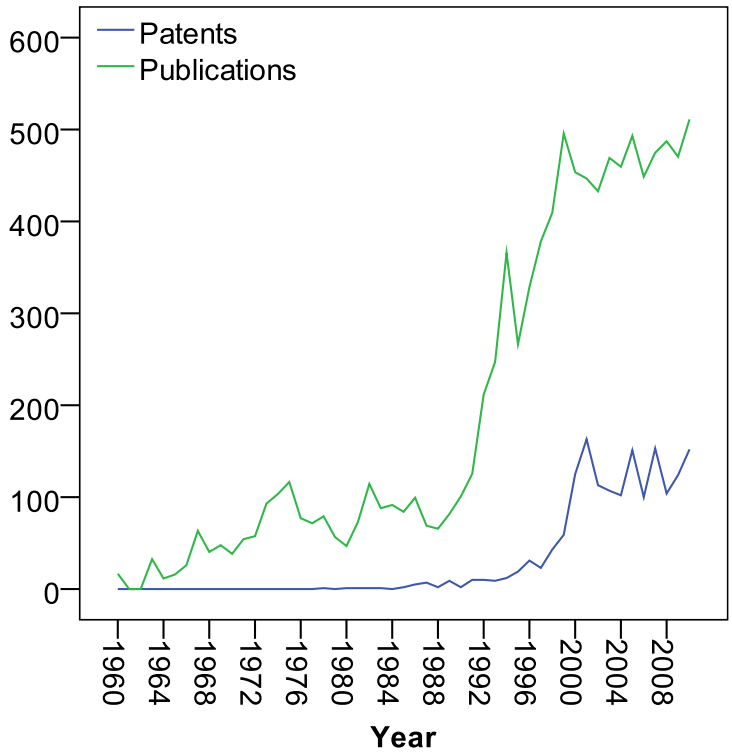


Figure 3.8. Plot of patents and publications over time concerning endoscopes.

3.2.3 Discussion

3.2.3.1 Principal findings

For the first time, this study has quantitatively evaluated technological innovation in neurosurgery. Among the major technology clusters identified, image guidance devices was dominant, accounting for almost half of the top performing neurosurgical technology patents within recent years. Endoscopes also featured highly within the top 50 performing patent codes. These technology clusters are well suited to overcoming the technical challenges of keyhole neurosurgery, corroborating the findings of the survey of surgeons reported in Chapter 3.1.

The Diffusion of Innovations theory describes the adoption curve of technological innovations as a sigmoid function, reflecting the normal variation in attitudes of individuals towards new ideas from early adopters to laggards (Figure 3.9)[51]. A similar curve is observed with technology clusters themselves, corresponding to the different phases of innovation[58]. The early take off in patenting and publication activity is associated with the *incubation* phase, when landmark work is produced. The rapid rise in patent and publication activity is associated with the *exponential growth* phase, when both industry and surgeons drive innovation. Finally, the plateau of patent and publication activity is associated with the *saturation* phase, characterised by technology refinement; in this phase manufactures continue to patent to maintain market dominance.

Applying the aforementioned framework to the present study, image guidance and neuromodulation devices demonstrated a highly correlated rapid rise in patents and publications ($r_s = 0.87$ and 0.83 respectively, $p < 0.001$), suggesting they are emerging technology clusters. The observed early take off in image guidance device patent and publication activity corresponds to the development of frameless techniques in the late 1980's and early 1990's[59, 60].

Operating microscopes and endoscopes were also found to have a highly correlated rise in patents and publications ($r_s = 0.93$ and 0.87, $p < 0.001$), but appear to have reached a plateau in 2000. Surprisingly, neurosurgeons were relatively late adopters of the surgical microscope. In 1957, over thirty five years after Nylén had pioneered

the use of surgical microscopes in otorhinolaryngology, Theodor Kurze used the technology to help remove a facial nerve schwannoma from a 5-year old patient[61]. Undoubtedly, the father of microneurosurgery was Gazi Yasargil, who in 1972 constructed a system of adjustable counterweights to counterbalance the otherwise cumbersome and unwieldy operating microscope, and popularised use of the operating microscope[61]. Endoscopes have been used by neurosurgeons for far longer than operating microscopes, but early endoscope technology was very limited and ill suited to the brain. In the late 1980's the development of the SELFOC® lens, Charge-Coupled Device (CCD) and fibre-optic light sources allowed for a wider viewing angle, superior image quality and greater illumination[62]. Specific endoscopic procedures such as Endoscopic Third Ventriculostomy (ETV) and endonasal transsphenoidal hypophysectomy are now well accepted by the neurosurgical community in selected cases[38, 39]. The different historical trajectories of operating microscopes and endoscopes are reflected in their respective growth curves, with the latter demonstrating a protracted incubation phase.

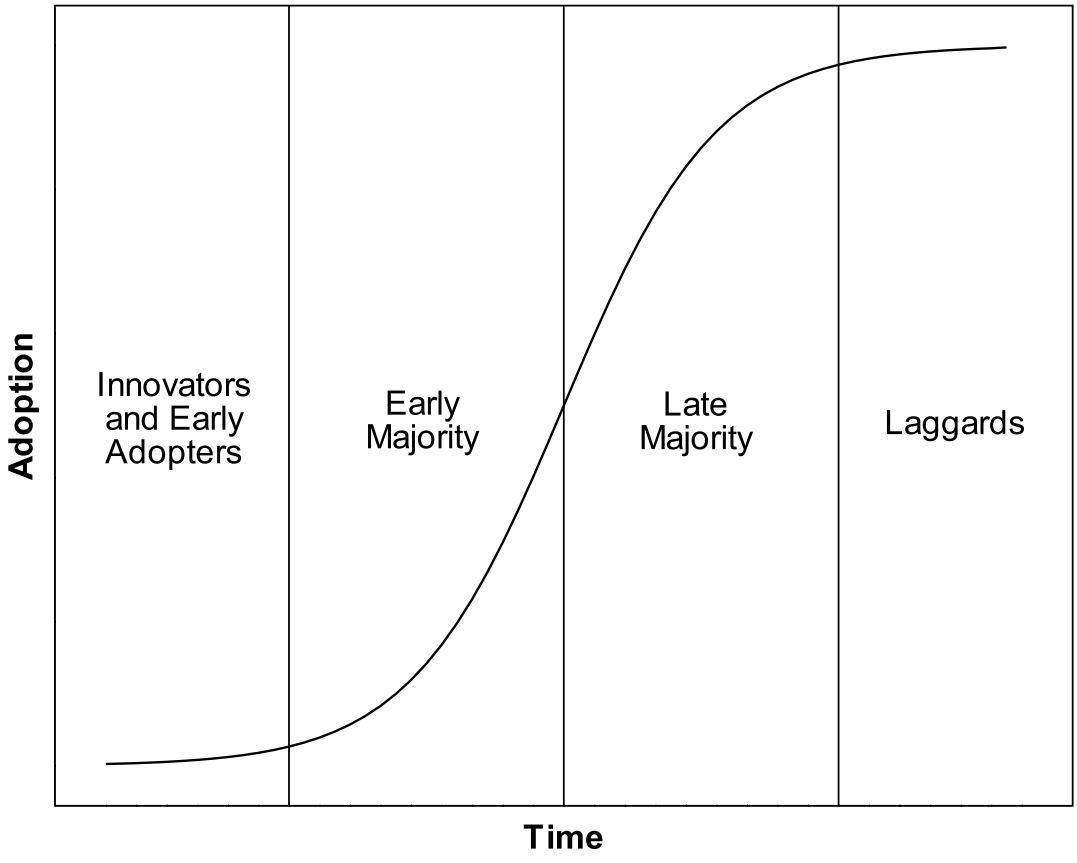


Figure 3.9. Innovation Adoption Curve.

Clinical neurophysiology had a distinct pattern with a poorer, though still significant, correlation between patents and publications ($r_s = 0.64$, $p < 0.001$). Patent data demonstrated a shallow rise, while publication data reached a plateau in 1993. The goal of intra-operative neurophysiological monitoring is to alert surgeons of neurological injury during an operation, in order to prompt actions that will prevent a permanent neurological deficit. The most common methods for intra-operative monitoring of neurophysiological function are Somatosensory Evoked Potentials (SSEPs) and Motor Evoked Potentials (MEPs). During the 1980s, a group at the Royal National Orthopaedic Hospital Stanmore, UK began to utilise SSEPs to monitor sensory tracts in the spinal cord, and other groups began to develop the means of recording MEPs after stimulation of the motor cortex or brain, corresponding to the exponential growth of publications during this period[63]. The comparatively flat growth trend in patents is similar to those described in mature technology clusters outside of healthcare, with industry leaders incrementally refining their patents to maintain their market share[64].

3.2.3.2 Comparison with other studies

Few previous studies have evaluated technological innovation in neurosurgery, and such studies have generally described specific technology clusters in a qualitative fashion[61, 62, 65]. In a two-part series, Ponce and Lozano searched for highly cited neurosurgical publications[66, 67]; in Part I they identified the top 100 papers appearing in journals dedicated to neurosurgery, and in Part II they considered highly cited neurosurgical publications in all journals. However, their focus was not on device innovation *per se*. Babu *et al* searched patents filed at the United States Patent and Trademark Office by members of the American Board of Neurological Surgeons[68]. Although primarily concerned with exploring the potential for conflict of interest, their study nonetheless utilised patents to measure device innovation in neurosurgery. Interestingly, while image guidance and electrical stimulation were highly represented, the fields in which patents were most commonly held were "tumour" and "spine". It is speculated that this may be because the present study searched all patents filed (rather than only those held by neurosurgeons), corrected for year-on-year growth in patent counts (rather than using absolute values, which would favour

recent patents), and classified devices by technology cluster (rather than by surgical field).

Within surgery in general, Hughes-Hallett *et al* first described the methodology used in the present study[58]. The top performing technology clusters of the last 30 years were minimally invasive surgery, robotic surgery, image guidance, surgical staplers and ophthalmic surgery. The trends of patents and publications in these technology clusters were also in keeping with Diffusion of Innovations theory. Image guidance and robotics demonstrated a highly correlated rapid rise (r_s = 0.94 and 0.98 respectively, $p < 0.001$) suggesting they were both in an exponential growth phase. Minimally invasive surgery was also highly correlated ($r_s = 0.95$, $p < 0.001$) but had reached a plateau, suggesting the technology cluster was in a saturation phase. Surgical staplers and ophthalmic surgery were poorly correlated ($r_s = 0.30$, $p = 0.10$ and $r_s = 0.46$ and $p = 0.009$ respectively), with a plateau in publications and a shallow rise patents. The fact that these patterns in patent and publication counts in general surgery corresponded so closely to those found within neurosurgery lends further support to the use of these metrics to quantitatively evaluate technological innovation.

3.2.3.3 Limitations

Although the present study applies a novel approach to quantitatively evaluate technological innovation within neurosurgery, several limitations must be acknowledged. First, the methodology relies on the implicit assumption that technological innovations result in patents. While true in most cases, surgeons may feel conflicted about patenting innovations if they believe it will limit the availability of a medical device, and therefore negatively impact on patient care. It is estimated that only 3% of registered neurosurgeons in the United States currently hold a patent[68]. Second, small nascent technology clusters are unlikely to be identified using the above methodology, and may be concealed within larger more mature technology clusters. Several patents for robotic instruments, for example, were identified under an image guidance patent code. Third, the search term "neurosurgeon OR neurosurgery OR neurosurgical", selected for patents unique to neurosurgery. Patents for generic technological innovations that did not explicitly state their application to neurosurgery, but could nonetheless be used in the field, were therefore not included

in the analysis. Finally, there may be a substantial time lag between patent application and patent granting.

3.2.3.4 Conclusions

In conclusion, this study has demonstrated, for the first time, the use of patent and publication data to quantitatively evaluate technological innovation in neurosurgery. Two technology clusters were identified that were directly relevant to the advancement of keyhole neurosurgery: image guidance devices, and endoscopes. Moreover, the growth pattern of these technology clusters over time could be described in terms of Diffusion of Innovations theory. Image guidance devices were found to be lying within a phase of exponential growth and as such can be forecast to have an increasing influence in the future of operative neurosurgery. In future studies, the same methodology may be applied to assess more specific technology clusters to assist in forecasting their potential influence.

3.3 Attitudes towards robotics: A quantitative survey of patients and their relatives

3.3.1 Introduction

Robotic platforms may integrate many of the aforementioned technological advances including image guidance, 3D endoscopy, and robotic articulated instruments. Surgical robots such as the da Vinci™ platform (Intuitive Surgical, CA, USA) have already been applied to keyhole surgical approaches elsewhere in the body, where they have the ability to improve visualisation and increase dexterity[15-17]. With a view towards developing similar platforms for keyhole neurosurgery, the purpose of the present study was to determine the acceptability of these robots to patients and their relatives.

3.3.2 Materials and Methods

A cross-sectional study of patients and their relatives was carried out from November 2013 to January 2014 at the Department of Neurosurgery, Imperial College Healthcare NHS Trust. Participants were recruited from outpatient clinics and inpatient wards in a convenience fashion. Ethical approval was not sought, as the focus of this study was the recruitment of patients and their relatives to plan and advise on future research.

A survey was developed that asked participants they had already heard about robotic surgery, and to rate on a 5-point Likert-scale their willingness to be operated on with (a) "smart" handheld robotic instruments, (b) a telesurgical robot that was fully under the control of the surgeon, but with the surgeon sitting in a separate console within the operating room, and (c) a supervisory controlled robot that was pre-programmed, but not under the direct control of the surgeon. Participants were also asked if they felt that further research in the field of surgical robotics was important. Demographic information was collected on age, sex, ethnicity, religion, and education.

Fisher's exact test was performed in order to identify participant characteristics associated with acceptability of different robotic platforms. Demographic data was dichotomised as: "age 65 or less", "age 66 or greater"; "male", "female"; "white",

"non-white"; "religious", "non-religious"; "GCSEs or less", "A-levels or more". Acceptability was also dichotomised as "agree" or "disagree", with neutral responses disregarded. A value of $P < 0.05$ considered statistically significant, with the Bonferroni correction applied ($n = 5$).

3.3.3 Results

In total, 69 patients and their relatives completed the survey, of which the most common age group was 36-45 years old (26/69; 37.7%), and just over half were male (53.6%; 37/69). Most participants were white (36/69; 52.2%), identified themselves as Christian (27/69; 39.1%), and had completed A-levels or above (49/69; 71.0%).

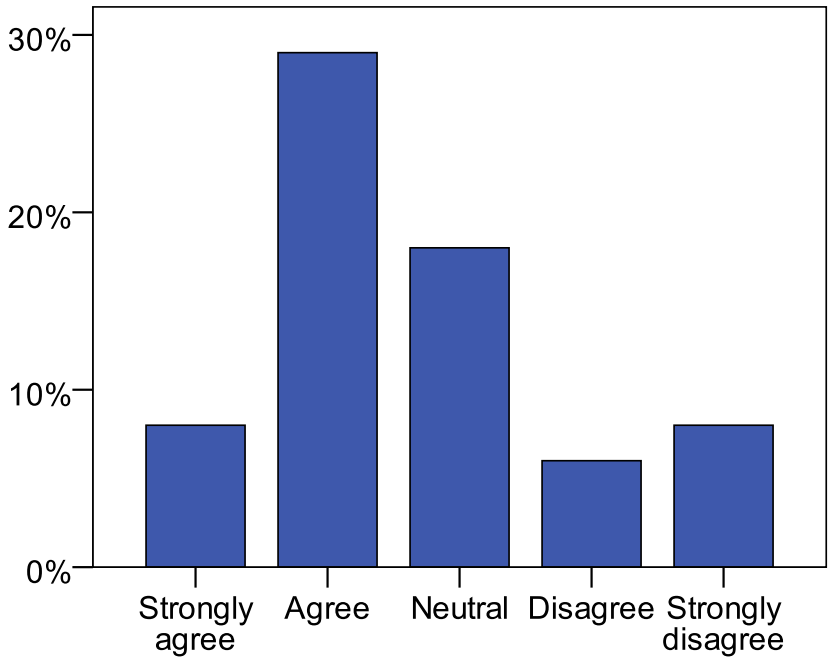


Figure 3.10. Willingness to be operated on by "smart" handheld robotic instruments.

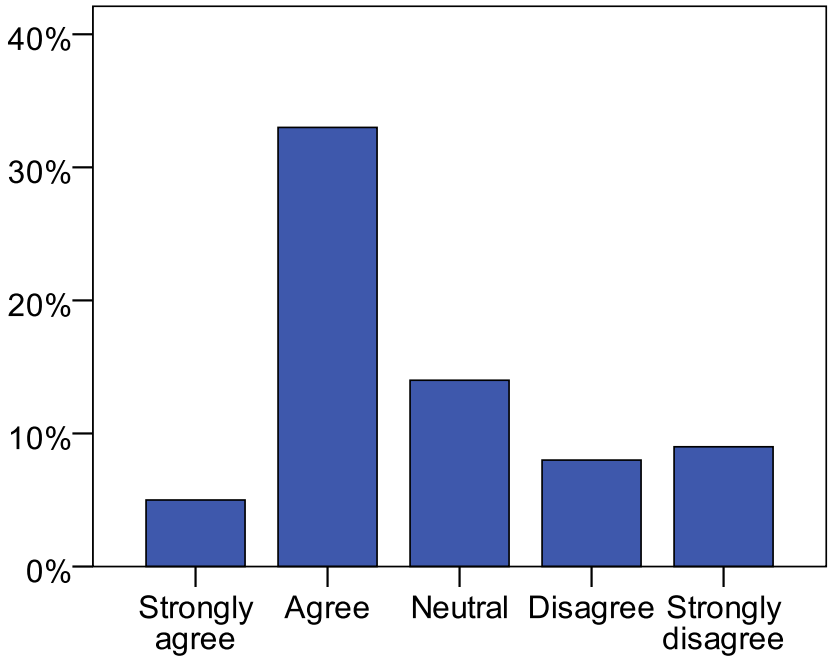


Figure 3.11. Willingness to be operated on by a telesurgical robot that was fully under the control of the surgeon, but with the surgeon in a separate console within the operating room.

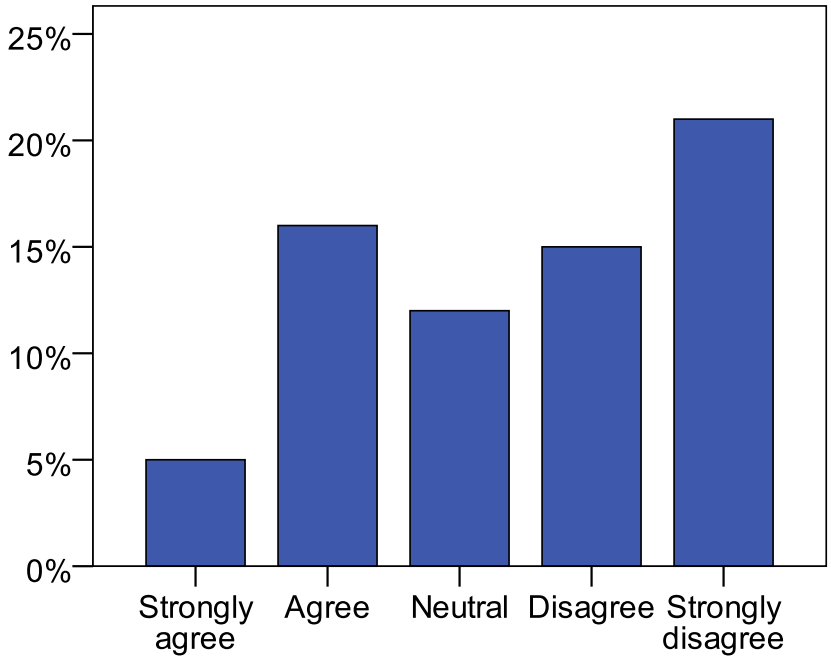


Figure 3.12. Willingness to be operated on by a supervisory controlled robot that was pre-programmed, but not under the direct control of the surgeon.

Approximately half the participants had heard of robotic surgery before (50.7%; 35/69). Figure 3.10-3.12 summarise the attitudes of participants towards different proposed robotic platforms. The majority would agree-strongly agree to be operated

on with "smart" handheld robotic instruments (53.6%; 37/69) or a telesurgical robot (55.1%; 38/69), but would disagree-strongly disagree on being operated on with a supervisory-controlled robot (52.2%; 36/69). Most participants would agree-strongly agree that further research in the field of robotic surgery is important (53/69; 76.8%). There were no demographic variables that were significantly associated with acceptability of different robotic platforms.

3.3.4 Discussion

3.3.4.1 Principal findings

In this study it has been demonstrated that the majority of patients and their relatives would consent to endoscopic neurosurgery with either "smart" handheld robotic instruments, or telesurgical robots. Conversely, most patients would be averse to undergoing neurosurgery with a supervisory controlled robot that was pre-programmed, but not under the direct control of the surgeon.

3.3.4.2 Comparison with other studies

The findings of this study are consistent with surveys in other surgical fields. In a recent internet survey of attitudes of the public towards robotic surgery, for example, Markar *et al* reported that existing telesurgical platforms were generally acceptable (52% comfortable-very comfortable), while pre-programmed robots were not (82% uncomfortable-very uncomfortable)[70].

3.3.4.3 Limitations

The present study has a number of limitations. Its single-unit and cross-sectional nature inherently limits the ability to generalise findings, as opinions are likely to vary according to region, and change over time. Participants were recruited in a convenience fashion from outpatient clinics and inpatient wards, which may have further affected the representation of the study sample. Moreover, participants self-completed the survey and may have not fully understood the different types of robotic platforms, though there is some evidence that self-completed surveys are more accurate as participants are not trying to please the interviewer[69].

3.3.4.4 Conclusions

Patient and Public Involvement (PPI) is playing an increasingly important role in both overseeing proposed research projects, and setting more global research agendas. To date, no studies have explored the attitudes of patients and their relatives towards robotics in neurosurgery. The findings of this study provide strong justification for research and development of more acceptable handheld or telesurgical robotic platforms. To this end, over three quarters of patients and their relatives were supportive of further research into robotic surgery towards developing these new platforms.

3.4 Evaluation of existing surgical robots: A literature review

3.4.1 Introduction

To date, over 30 robotic systems have been applied to neurosurgical procedures (Table 3.5; robots performing endovascular or radiosurgical procedures were excluded). The vast majority of these robots are best described as supervisory-controlled, and are designed for stereotactic or image guided surgery[14, 71-121].

3.4.2 Supervisory-controlled robots

As mentioned in Chapter 1.1, the first surgical robot, a modified Puma 560 industrial robot (Advance Research & Robotics, Oxford, CT), was used in 1985 to define the trajectory of a frame-based brain biopsy[14]. In this system the surgeon entered the co-ordinates of a brain lesion, the effector arm with the probe holder moved to the predefined location, and the surgeon then used the probe as a guide for trephination and biopsy. Many other supervisory-controlled robots have since been developed, with clinical studies illustrating their use in brain biopsy, and the implantation of Deep Brain Stimulation electrodes. Perhaps the most widely used supervisory-controlled robots within neurosurgery are the SpineAssist and Renaissance systems (Mazor Surgical Technologies, Caesarea, Israel). Although principally developed for pedicle screw placement, they have also received regulatory approval for use in the brain[98-109]. These robots offer a theoretical advantage over conventional surgery because of their high precision and accuracy[122], and may reduce radiation exposure of the patient and surgical team[123].

3.4.3 Telesurgical robots

A number of telesurgical robots have been utilised in neurosurgery[124-149]. One of the earliest examples of such a system was the Robot Assisted Microsurgery (RAMS) robot (NASA, Pasadena, California, USA)[127]. In a feasibility study, carotid arteriotomies were created and closed using either RAMS or conventional microsurgical techniques in 10 rats; the precision and technical quality, and error rate were comparable but the use of the RAMS robot was associated with a twofold increase in the procedure length.

Name and Company	Type	Features	Function	Selected Studies
Puma 200 (Advances Research and Robotics, Oxford, UK)	Supervisory controlled	Must be attached to BRW frame 6 DOF for decoupled positioning orientation and instrument insertion DC servomotors tracked by optical encoders Instruments held by pneumatic gripper	Stereotactic surgery	Kwoh, 1988; Drake, 1991
Neuromate (Integrated Surgical Systems, Sacramento, California, USA)	Supervisory controlled	May be attached to frame 6 DOF for decoupled positioning orientation and instrument insertion Tracked by X-rays or ultrasound	Stereotactic surgery	Benabid, 1987; Benabid, 1998; Li, 2002; Varma, 2003; Varma, 2006; Xia, 2008; Haegelen, 2010; Lefranc 2011
Minerva (Swiss Federal Institute of Technology, Lausanne and Zurich, Switzerland)	Supervisory controlled	Base mounted on horizontal carrier which moves on rails, and operates inside a CT scanner to account for brain shift Must be attached to the BRW frame 5 DOF	Stereotactic surgery	Koyama, 1990; Glauser, 1990; Fankhauser, 1994; Glauser, 1995; Hefti, 1998
Telerobot (Telerobot, Genova, Italy)	Supervisory controlled	Merging of microscope holder with frameless stereotaxy: Once trajectory defined brings optical axis of microscope into alignment In biopsy mode a 6 DOF robot arm moves probe along trajectory	Stereotactic surgery	Giorgi, 1995
MRI compatible robot (Mechanical Engineering Laboratory, AIST, MITI, Tsukuba, Japan and Harvard Medical School, Boston, MA, USA)	Supervisory controlled	Operates inside an MRI scanner to account for brain shift 5 DOF Ultrasonic motors and optical encoders Two long rigid arms reach into the surgical space and form a parallel linkage for manipulating an acrylic needle holder or guide	Stereotactic surgery	DiMaio, 2006
MKM (Carl Zeiss, Oberkochen, Germany)	Supervisory controlled	Merging of microscope holder with frameless stereotaxy: Once trajectory defined brings optical axis of microscope into alignment In biopsy mode a 6 DOF robot arm moves probe along trajectory	Stereotactic surgery	Levesque, 1999; Willems, 2001; Willems, 2003

Name and Company	Type	Features	Function	Selected Studies
AcuBot (John Hopkins University, Baltimore, USA)	Supervisory controlled	Base formed by bridge-like structure over table 6 DOF for decoupled positioning orientation and instrument insertion Instrument held by radiolucent needle driver	Stereotactic and image guided surgery	Cleary, 2002
MRI compatible endoscope manipulator (Mechanical Engineering Laboratory, AIST, MITI, Tsukuba, Japan)	Supervisory controlled	Operates inside an MRI scanner 4 DOF Ultrasonic motors End-effector is endoscope	Image guided surgery	Koseki, 2002
Evolution 1 (Universal Robot Systems, Schwerin, Germany)	Supervisory controlled	Hexapod robot with 6 DOF	Stereotactic and image guided surgery	Zimmermann, 2002; Zimmermann, 2004; Nimsky, 2004; Bumm, 2005
RobaCKa (Heidelberg, Germany)	Supervisory controlled	Previously an industrial robot	Craniotomy	Korb, 2003; Eggers 2005
Neuromaster (Robotic Institute Beihang University, Beijing, China)	Supervisory controlled	6 DOF	Stereotactic surgery	Junchuan, 2004
MARS, Renaissance and SpineAssist (Mazor Surgical Technologies, Caesarea, Israel)	Supervisory controlled	Attaches directly to a bony element of the surgical field 6 DOF End-effector is tool holder	Stereotactic and Image guided surgery	Shamir, 2005; Lieberman, 2006; Barzilay, 2006; Sukovich, 2006; Joskowicz, 2006; Shoham, 2007; Togawa, 2007; Pechlivanis, 2009; Devito, 2010; Kantelhardt, 2011; Hu 2012; Heinig, 2012; Ringel 2012; Roser 2013

Name and Company	Type	Features	Function	Selected Studies
Pathfinder (Prosurgics, UK)	Supervisory controlled	Base attaches to Mayfield head clamp 6 DOF Tracked using fiducials End-effector is tool holder	Stereotactic surgery	Eljamel, 2006; Eljamel, 2009; Deacon, 2010; Brodie, 2011
LWR-II (Wessling, Germany and Ausberg, Germany)	Supervisory controlled	7 DOF End-effector is linear guide for drill/screw	Image guided surgery	Ortmaier, 2006
Surgiscope (ISIS Intelligent Surgical Instruments and Systems, Saint Martin d'He`res, France)	Supervisory controlled	Merging of microscope holder with frameless stereotaxy: Once trajectory defined brings optical axis of microscope into alignment In biopsy mode a 7 DOF robot arm moves probe along trajectory	Stereotactic surgery	Lollis, 2009; Bekelis, 2012
NISS (National Neuroscience Institute, Singapore)	Supervisory controlled	Planning on console (NeuroPlan); Consists of base robot (Neurobase) with 5 DOF (2 motorized and 3 manual) which positions a hexapod manipulator (NeuroPod) Optical tracking (NeuroVision)	Stereotactic surgery	Chan, 2009
Soft-Tissue Intervention and Neurosurgical Guide - STING (Imperial College, London, UK)	Supervisory controlled	Steerable probe	Stereotactic surgery	Frasson, 2010
Vision Guided Hybrid Robot Prototype System for Stereotactic Surgery (School of Mechanical Engineering and Automation, Beihang University, Beijing, China)	Supervisory controlled	Hybrid robot consisting of a passive serial arm, and an active 4 DOF parallel frame for trajectory	Stereotactic surgery	Wei, 2011

Name and Company	Type	Features	Function	Selected Studies
ROSA (Medtech, Montpellier, France)	Supervisory controlled and Shared control	6 DOF	Stereotactic and Image guided surgery	Lefranc, 2012
CRANIO (RWTH-Aachen / Lehrstuhl für Biomedizinische Technik, Aachen, Germany)	Supervisory controlled (initial) Telesurgical (current)	Hexapod robot with 6 DOF	Craniotomy	Bast, 2006; Engelhardt, 2006; Cunha-Cruz, 2010
MRI guided biopsy probe (University of Toronto, Toronto, Canada)	Telesurgical	Operates inside an MRI scanner to account for brain shift 6 DOF Hydraulic linear actuator End-effector is biopsy needle	Stereotactic surgery	Raoufi, 2008
Robot-Assisted Microsurgery System – RAMS (NASA, Pasadena, California, USA)	Telesurgical	6 DOF	Microsurgery	Le Roux, 2001
NeuroArm (University of Calgary, Calgary, Canada)	Telesurgical	Console provides visual, auditory and force feedback Manipulator operates inside an MRI scanner to account for brain shift Two arms each with 8 DOF Piezo-electric motors, optical encoders and force sensors End-effectors mimic surgeons hands and can interface with newly designed micro instruments	Microsurgery	Louw, 2004; Pandya, 2009

Name and Company	Type	Features	Function	Selected Studies
MM-1 (Faculty of Medicine and School of Engineering, Tokyo, Japan)	Telesurgical	The base has passive 6 DOF Two robotic arms 6 DOF approximately 5mm in diameter Each arm attached to DC servomotors mobilizing tip flexion and forceps grip and release	Microsurgery	Morita, 2005
Master-slave Robotic Platform for micro-neurosurgery (School of Engineering, University of Hongo, Tokyo, Japan)	Telesurgical	Cartesian configuration of slave manipulators Two arms each with 7 DOF End-effectors are bent- or straight-forceps	Microsurgery	Mitsuishi, 2012
Da Vinci™ (Intuitive Surgical, Sunnyvale, California, USA)	Telesurgical	Console has stereoscopic vision Manipulator includes two articulated working arms with 7 DOF (three at the endo-wrist) A separate camera arm carries a rigid 3D endoscope	Minimally Invasive Surgery	Aaronson, 2002; Ponnusamy, 2009; Lee, 2010; Kim, 2010; Yang, 2011; Deboudt, 2012; Perez-Cruet, 2012
NeuRobot (Shinshu University School of Medicine, Matsumoto, Japan)	Telesurgical	Console has stereoscopic vision Manipulator based on endoscope with instrument channels (10mm in diameter) 9 DOF (three at the micromanipulators) using ultrasonic motors End effectors are a rigid 3D endoscope with two tissue forceps and a laser	Minimally Invasive Surgery	Koyama, 2002; Miyata, 2002; Hongo, 2002; Goto, 2003; Hongo, 2006; Takasuna, 2012

Name and Company	Type	Features	Function	Selected Studies
Neurosurgical Robot for Brain Tumour Removal (Nagoya Institute of Technology, Nagoya, Japan)	Telesurgical	The base can be attached to the head clamp Manipulator based on endoscope with instrument channels (10mm in diameter) 3 passive DOF (at base) and 6 active DOF (two at the micromanipulators) End effectors are 3D endoscope, optical light guides, irrigation and suction	Minimally Invasive Surgery	Arata, 2011; Arata 2012
Craniostar (University of Heidelberg, Heidelberg, Germany)	Shared control	Handheld	Craniotomy	Kane, 2009
Safe Trephination System - STS (RWTH-Aachen, Aachen, Germany)	Shared control	Handheld Utilises soft tissue preserving sawing tool and autonomous control of cutting depth	Craniotomy	Follmann, 2012
Steady Hand system (John Hopkins University, Baltimore, USA)	Shared control	7 DOF for tremor filtering	Microsurgery	Matinfar, 2007; Kazanzides, 2008

Table 3.5. Summary of existing neurosurgical robots and their features. BRW = Brown-Roberts-Wells; DOF = Degrees Of Freedom; DC = Direct Current; CT = Computed Tomography; MRI = Magnetic Resonance Imaging.

NeuroArm (University of Calgary, Calgary, Canada) is a robot purpose built for microneurosurgery that is endowed with a number of distinct features[128, 129]. The console provides visual, auditory and tactile feedback to the operating surgeon. The robot is MRI compatible, allowing real-time imaging during procedures to account for brain shift. The manipulator consists of two arms, each with 8 degrees of freedom (DOF), with end-effectors that mimic a surgeon's hand, and interface with microinstruments. Early reports from the NeuroArm case series' have been promising but its use at present is limited to microneurosurgery rather than endoscopic neurosurgery.

A team in Tokyo, Japan has also constructed a telesurgical robot to assist with microneurosurgery. The MM-1 robot consists of a passive base with 6 DOF, and two robotic arms each with 6 DOF[130]. In validation studies, closure of partial arteriotomies and end-to-end anastomosis of the ICA was performed successfully in 20 rats. The frontotemporal transsylvian approach, suboccipital retrosigmoid, and endonasal transsphenoidal approaches were also performed in cadavers. Although a significant learning curve was demonstrated, surgical performance quickly reached a plateau, and the procedure durations were still unacceptably long. Furthermore, the manipulators were felt to be too bulky to be used in the delicate operative field. Recently, the same research group has developed a modified master-slave robot platform, with two robotic arms each with 7 DOF, and either bent- or straight-forceps as end-effectors[149]. In feasibility studies the robot was able to perform a number of manoeuvres including end-to-end anastamoses of 0.3mm artificial vessels, which is very difficult to do manually, though with a longer task completion time.

The da Vinci™ surgical system (Intuitive Surgical, Sunnyvale, California, USA) is the most frequently used telesurgical robot worldwide but is not as yet widely used for neurosurgery. Unlike the abovementioned robots, the da Vinci™ system is designed for endoscopic keyhole surgery. A camera arm equipped with two lenses is used to generate a high-resolution stereoscopic image display. Instruments are carried by two or three working arms, which include articulated endo-wrists that increase surgical dexterity. In addition, the system allows for tremor filtering and motion scaling, allowing more delicate tissue manipulation. A major advantage of the da Vinci™ system is the ergonomic benefit provided by the anthropomorphic master

console that restores the visuomotor alignment of the camera and surgical instruments. The da Vinci™ robot has been successfully used in a broad range of surgical procedures, particularly within the field of urology. Several groups have demonstrated the feasibility of using the da Vinci™ system in spinal surgery[132-140]. In a recent cadaveric study the da Vinci™ system was used during a supraorbital approach and the issue of arm collisions within a narrow surgical corridor was cited as a key drawback, which could interrupt operative workflow, and also raises safety concerns[150].

NeuRobot (Shinshu University School of Medicine, Matsumoto, Japan) was the first telesurgical robot designed specifically for keyhole neurosurgery[141-146]. The system has a single-shaft design approximately 10mm in diameter containing a 3D endoscope, and three sets of micromanipulators, each with 3 DOF (rotation, neck swinging, and forward/backward motion). Although the system was able to perform relatively simple surgical procedures in cadavers and human studies, the authors report the system was limited by lack of manoeuvrability of the micromanipulators and robot itself.

Another Japanese group have recently developed a similar Neurosurgical Robot for Brain Tumor Removal (Nagoya Institute of Technology, Nagoya, Japan)[147, 148]. As with NeuRobot the robot has a single-shaft design approximately 10mm in diameter, containing a 3D endoscope, an irrigation system, and a volume control suction tool, with 2 DOF at the instrument tips. Although preliminary evaluation of the robot on a phantom demonstrated feasibility it is likely that, as with NeuRobot, the restricted working space will limit its clinical use.

3.4.4 Handheld shared control robots

Only a handful of handheld shared controlled systems have been described in the literature for use in neurosurgery[151-154]. Shared controlled systems exploit both the precision of a robot in the control of the surgical instruments and the natural manipulation skill of the surgeon. In the Steady Hand System (John Hopkins University, Baltimore, USA), for example, the surgical instrument is held by both the robot and operator which allows finer, tremor-free motion control of the instrument,

and also lets surgeons to define critical no-go areas to be avoided[151, 152]. Similarly, the Craniostar (University of Heidelberg, Heidelberg, Germany) and Safe Trephination System (RWTH-Aachen, Aachen, Germany) allow surgeons to fashion craniotomies along predefined paths, while reducing the risk of dural injury[153, 154]. Another advantage of these handheld systems is ease in which they can be integrated into the surgical workflow compared to telesurgical systems that suffer from long setup times.

3.5 Evaluation of the da Vinci™ Surgical System: A cadaver study

3.5.1 Introduction

As outlined in the above review, a group has recently reported the application of the da Vinci™ surgical system to assist with the supraorbital subfrontal approach through an eyebrow skin incision in a cadaver study[150]. While the authors concluded that such robot-assisted approaches were probably feasible, they noted several drawbacks including the lack of suitable instruments such as bone cutters, and the risk of arm collisions, and highlighted the need for further studies. The goal of the present cadaver study was therefore to confirm and extend these preliminary findings by applying the da Vinci™ surgical system to a range of keyhole neurosurgical approaches.

3.5.2 Materials and Methods

Ethical approval was obtained from the Proportionate Review Sub-committee of the National Research Ethics Service (NRES) Committee East Midlands. A formalin-fixed cadaver head was obtained from the Department of Anatomy, Imperial College London. Two surgical residents performed the procedures under the supervision of two senior clinical authors, who are experienced in minimally invasive neurosurgery and robot-assisted surgery respectively.

The cadaver head was secured in a Mayfield clamp and a Budde-halo retractor system attached (Integra, New Jersey, USA). An Albert Wetzlar operating microscope (Albert Wetzlar GmbH, Wetzlar, Germany) and high-speed drill (B. Braun, Melsungen, Germany) was used to fashion several previously described keyhole craniotomies, approximately 20-30mm in diameter[25, 155]: supraorbital subfrontal; retrosigmoid; and supracerebellar infratentorial. Craniotomies were not extended to accommodate the da Vinci™ system; instead, the aim was to determine the suitability of the robot to typical keyhole craniotomies. In each approach a simple durotomy was performed, and the flap retracted.

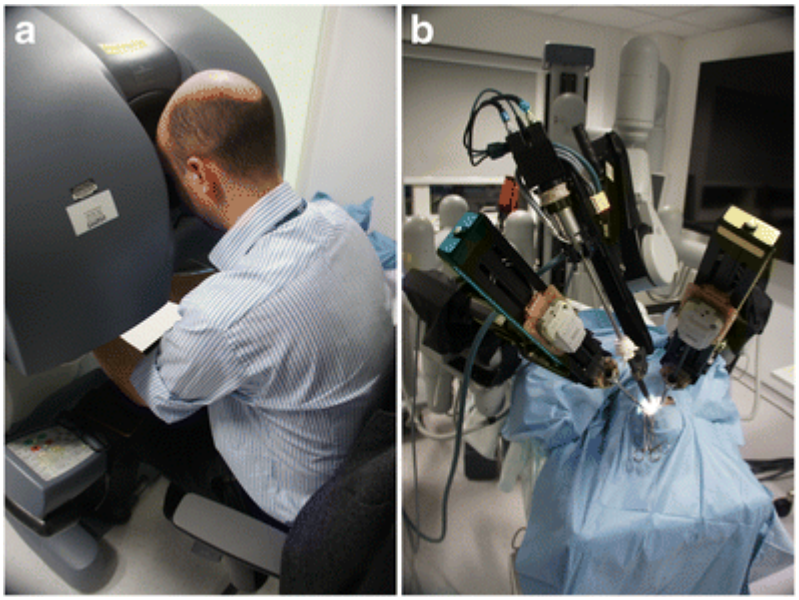


Figure 3.13. Arrangement of the da Vinci™ master-slave system. (a) The surgeon is seated comfortably at the console, and remotely controls the robots actions. (b) The surgical cart includes an endoscope and instrument arms, and carries out the procedure. Note the difficulty in parallel insertion of the instrument arms through a single keyhole craniotomy.

The standard da Vinci™ robotic system was used intradurally, and arachnoid dissection performed towards the deep-seated cisterns. The surgeon remained non-sterile at the robot console, while an assistant was available throughout the procedure to exchange robotic instruments (Figure 3.13). Both 0° and 30° upwards facing 12mm endoscopes were introduced into the keyhole craniotomy for visualisation. Standard 8mm and smaller 5mm instruments were used for tissue manipulation. Throughout each procedure detailed feedback was obtained, including images of the operating room arrangement, and of the endoscope feed.

3.5.3 Results

It was not possible to simultaneously pass the 12mm endoscope and instruments through the keyhole craniotomy in any of the approaches performed, irrespective of whether two standard 8mm instruments or smaller 5mm instruments were used (Figure 3.14). Instead, the endoscope had to be placed outside the craniotomy, limiting the illumination, magnification, and wide-angle view provided.

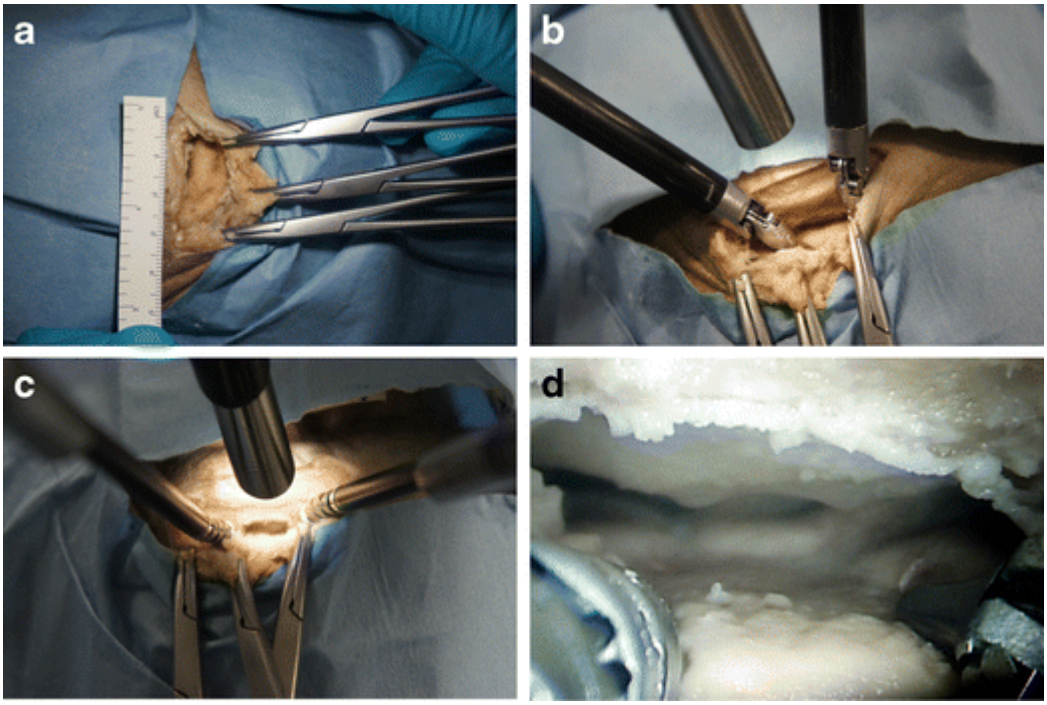


Figure 3.14. Left supraorbital subfrontal approach through an eyebrow incision demonstrating: (a) keyhole craniotomy approximately 25 x 15mm in size, (b) a 12mm endoscope and two standard 8mm instruments were unable to enter the keyhole simultaneously, (c) a 12mm endoscope and two smaller 5mm instruments were also unable to enter the keyhole simultaneously, and (d) endoscopic visualisation was therefore limited.

Dissection with the da Vinci™ instruments was restricted to superficial structures, approximately 20mm from the craniotomy. The large instrument arms could not be placed in parallel through the keyhole craniotomy, and therefore could not be advanced to the deep cisterns without significant clashing (Figure 3.13). The smaller 5mm instruments were comparatively easier to pass through the keyhole craniotomy, but utilised tentacle-like continuum tools shafts rather than the articulated wrist-joints that characterise standard 8mm instruments. The result, paradoxically, was that the smaller 5mm instruments had less dexterity than standard 8mm instruments in the spatially constrained intracranial cisterns (Figure 3.15). The range of 5mm instruments was also limited, with no bipolar forceps or suction-irrigation available. Nonetheless, all the robotic instruments used during the study allowed for greater dexterity than existing rigid tube-shaft instruments.

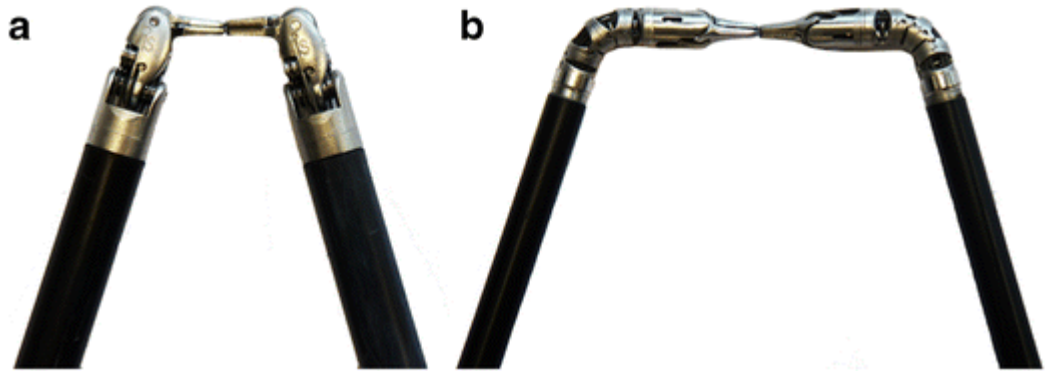


Figure 3.15. Comparison of (a) 8mm da Vinci™ instruments with articulated wrist-joints, and (b) 5mm da Vinci™ instruments with tentacle-like continuum tools shafts.

The da Vinci™ console offered considerable ergonomic advantages over the existing operating room arrangement, allowing the operating surgeon to remain non-sterile and seated comfortably throughout the procedure (Figure 3.13). The visualisation provided by the 3D endoscope provided an immersive view of the operative field. Control of the instruments was intuitive, and allowed for motion scaling and tremor filtering. However, the lack of haptic feedback was a notable limitation.

3.5.4 Discussion

3.5.4.1 Principal findings

In this cadaver study, it has been demonstrated that use of the standard da Vinci™ robotic system in keyhole transcranial endoscopic microsurgery is neither safe nor feasible. Arguably the greatest role of surgical robots is as a "great leveller", allowing surgeons to perform keyhole approaches when they would otherwise resort to open surgery[156]. To this end, technically challenging keyhole neurosurgical approaches are ideal targets for such surgical robots. Regrettably, in its present form the da Vinci™ robotic platform is ill suited to brain surgery given its multiple large and bulky arms, limited selection of instruments, and lack of haptic feedback.

3.5.4.2 Comparison with other studies

In a related study, Thakre *et al* sought to evaluate the performance of the da Vinci™ platform in increasingly small workspaces[157]. It was noted that a cube had to be at

least 40mm in size to simultaneously pass both the endoscope and instruments, at least 50mm in size to perform standard surgical drills, and at least 60mm in size to do so without significant collision between the instrument arms (albeit with difficulty). These findings broadly corroborate those of the present study, in which it was not possible to simultaneously pass both the endoscope and instruments through keyhole craniotomies approximately 20-30mm, and instruments clashes prevented dissection towards the deep intracranial cisterns (Table 3.6).

While several studies have reported the use of the da Vinci™ robot in spinal and peripheral nerve surgery[132-134, 136-140], only one previous cadaver study has described the use of the da Vinci™ robot in keyhole brain surgery[150]. Hong *et al* described the application of the da Vinci™ robot to the keyhole supraorbital approach and, in contrast to the present study, found it was generally feasible, though they did comment on instrument clashes and lack of proper tools. It is speculated that this discrepancy may be due to their longer incision and larger craniotomy, and their use of brain retractors.

Recently, a group from the University of Washington has proposed new multiport approaches to the anterior cranial fossa that are better suited to the da Vinci™ robotic platform[158]. In order to overcome the narrow funnel effect generated from arms in close proximity, and the steep angle of approach to the skull base, they suggest transnasal and bilateral medial orbital ports for the camera and instruments respectively. While such novel approaches may be more viable from a technical standpoint, they carry a greater risk of approach-related morbidity than standard keyhole approaches.

	Diameter	Visualisation with endoscope	Manipulation with 8mm instruments	Immersive console
Keyhole craniotomy	20mm	Limited	Limited	Full
	30mm	Limited	Limited	Full
	40mm	Full	Limited	Full
	50mm	Full	Full but with instrument collisions	Full
	60mm	Full	Full without collisions, but with difficulty	Full
Minicraniotomy	70mm or greater	Full	Full	Full

Table 3.6. Summary of the limitations of the da Vinci™ platform in small working spaces using data from the present cadaver study (diameter <40mm), and the previous preclinical study by Thakre *et al*[18] (diameter ≥40mm).

Alongside the technical challenges to the use of the da Vinci™ robotic platform in keyhole neurosurgery highlighted in the present study, several other barriers also exist[48]. Arguably the greatest drawback to existing surgical robots is economic. The current da Vinci™ robot, for example, is priced at over £2 million, carries substantial maintenance costs, and requires additional training of the surgeons and nurses involved with its use. Next generation robotic platforms may mitigate these limitations. Over time, the large and expensive multipurpose robots of today are likely to be replaced by smaller and more affordable robots tailored to particular procedures[48].

3.5.4.3 Limitations

The present cadaver study has several inherent limitations. The cadaver brain was formalin-fixed, and was therefore not as a compliant as the living brain, though pathology resulting in cerebral oedema can be similarly tense. The cadaver brain also didn't allow for assessment of haemostasis, which is frequently cited as a limitation of keyhole approaches. Animal studies might better address the issue of haemostasis, but there are very few animal models with brains of a similar size to humans, such studies would be logistically difficult to organise, and also raise ethical concerns.

3.5.4.4 Conclusions

In conclusion, keyhole transcranial endoscopic microsurgical techniques are technically challenging approaches that may greatly benefit from surgical robotics. However, the most widely used surgical robot worldwide today, the da Vinci™ platform, is neither safe nor feasible to use in keyhole neurosurgery. There is therefore a strong argument for research into next-generation robots, better suited to such approaches.

3.6 Proposed specifications for new robotic platforms

Although a multitude of robots have been applied to neurosurgery, it can be seen from the above that few are applicable to minimally invasive techniques, and no robots are in widespread clinical use in the field. New robotic platforms in minimally invasive neurosurgery must possess clear and unambiguous advantages over conventional approaches if they are to achieve significant clinical penetration. Here, broad specifications are outlined for new robotic platforms designed to assist with keyhole transcranial endoscopic microsurgical approaches.

It is likely that most systems in the near future will adopt a master-slave arrangement with the surgeon sitting comfortably at a console controlling the robots actions. This will restore visuomotor alignment and provide considerable ergonomic benefits, particularly in cases in which the patient is placed in a seated position, such as those utilising the supracerebellar infratentorial approach, that presently require the operator to stand hunched over with their arms outstretched for several hours.

In order to safely approach pathology, new surgical robots must be fully integrated with image guidance systems, and augmented reality displays utilised at the surgical console to improve the operating room workflow.

Visualisation in new robotic systems will be achieved through cameras providing uninterrupted illumination, magnification and wide-angle images of the operative field. High-definition and 3D endoscopes have recently been developed, and the incorporation of such devices into surgical robots would allow for unparalleled views within the brain.

Bimanual manipulation of delicate tissue will require at least two working channels for instruments in putative robotic systems. Robotic end-effectors should be miniaturised to a size comparable with conventional microinstruments, with the smallest tips measuring approximately 1-2mm. Perhaps most importantly these instruments must have sufficient degrees of freedom to operate within the small working spaces used in keyhole approaches; robotic articulated designs will almost certainly be invaluable in this context.

The next three technical chapters address each of these technical challenges and technological solutions in turn: surgical approach and augmented reality; intra-operative visualisation and 3D HD endoscopy; and tissue manipulation and robotic articulated instruments. The final technical chapter describes a robotic platform that integrates these technologies, and associated early preclinical and clinical studies.

CHAPTER 4 SURGICAL APPROACH: AUGMENTED REALITY*

*Content from this chapter was published or submitted as:

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Content from the chapter was presented as:

Marcus HJ, Pratt P, Hughes-Hallett A, Cundy TP, Marcus AP, Yang GZ, Darzi A, and Nandi D. Comparative effectiveness and safety of image guidance systems in surgery: a preclinical randomised study. The Academy of Medical Sciences Spring Meeting, London, February 2015

4.1 Image guided surgery and augmented reality: A literature review

4.1.1 Introduction

Image guided surgery correlates imaging data to the operating field to help localise anatomical and pathological structures in real-time. The initial steps towards image guided surgery were taken over a century ago, barely a week after Roentgen's first paper on the use of X-rays was published, when a British surgeon used the new technique of X-ray imaging to guide the removal of an industrial sewing needle from a woman's hand[159]. Alongside these early advancements in imaging, two further concepts emerged during the 19th century that were important for image guided neurosurgery: the idea that certain regions of the brain are especially important for certain brain functions (cerebral localisation), and that these regions can be located by the use of surface landmarks (craniocerebral topography). In a landmark publication in 1908, Horsley and Clarke described the use of a stereotaxic instrument to investigate the structure and functions of the cerebellum in animals[160]. By fixing a frame to the animal's head and aligning it with the external auditory meati and the lower margins of the orbits as reference points, they were able to describe lesions using a Cartesian (3D) co-ordinate system. Spiegel and Wycis later extended the technique to humans by utilising air ventriculograms to identify markers within the brain itself, and improve the accuracy of surgical localisation further[161]. Stereotactic frame neurosurgery continues to be employed by neurosurgeons today, particularly when very precise point localisation of deep-seated targets is required e.g. thalamic biopsy. However, the technique has a number of disadvantages that generally prohibits its use in open craniotomies. First, rigid fixation of the head ring is uncomfortable for patients, particularly children. Second, applying the head ring, then transporting the patient between the operating theatre and imaging department, and then subsequently transferring computer generated co-ordinates to the head-frame is both cumbersome and time-consuming. Finally, the frame acts as a mechanical obstruction hindering surgical access during the operation.

Several developments late in the twentieth century were responsible for expanding the scope of image guided surgery. The introduction of Computed Tomography (CT) scanning in the early 1970s and Magnetic Resonance Imaging (MRI) in the 1980s

both greatly enhanced pre-operative localisation of brain tumours and related structures, and also encoded images digitally. In addition, rapid improvements in computing power allowed for greater use and manipulation of this raw imaging data. These technologies enabled several teams to move beyond the constraints of stereotactic frame neurosurgery, and establish frameless techniques. A group working at the Dartmouth-Hitchcock Medical Centre reported the successful use of fiducial markers on the scalp as reference points to localise the position of the operating microscope and present a single dynamically updated tomographic image[59]. Later, a team working at the Vanderbilt University Medical Centre, also using fiducial markers, constructed a freely movable mechanical localising arm and displayed its position on three orthogonal CT planes simultaneously[60]. The image guidance systems currently in use by neurosurgeons ("neuronavigation systems") are even less intrusive, often relying on surface mapping rather than fiducial markers, and on optical tracking of wireless pointers rather than mechanical localising arms[162].

The result of these advances in frameless stereotactic techniques has been the widespread adoption of image guidance in neurosurgery. Image guidance platforms have two distinct roles in surgery: first, to help define the overall surgical approach to lesions; and second, to facilitate unambiguous tissue dissection, particularly in the context of oncological resection[163]. To date, most image guidance systems in neurosurgery have been designed for the former, helping surgeons define the skin incision, craniotomy, and corticotomy. To this end, a case-control study of patients undergoing meningioma resection at the National Hospital for Neurology and Neurosurgery (NHNN) suggested that the use of neuronavigation was associated with shorter operating times, reduced blood loss, and fewer major complications when compared with standard surgery[27].

The use of image guidance during oncological resection requires very high accuracy and precision[163]. Studies evaluating the role of existing image guidance systems in brain tumour resection are limited and have reported mixed findings[164]. A single-centre randomised controlled trial on the effectiveness of neuronavigation in resecting solitary intracerebral contrast-enhancing tumours failed to demonstrate a significant impact on the extent of resection, and median survival was actually shorter, though the investigators noted it was underpowered[165].

Stage	Description	Potential Advances
Acquisition and segmentation	Acquire images pre-operatively, construct 3D model, and identify anatomy and pathology	Fusion of multimodal images such as MRI-DTI, DSA/CTA/MRA, PET/fMRI Auto-segmentation to recognise anatomy and pathology
Tracking	Track instruments in space	Combine tracking technologies (e.g. Optical and Electromagnetic) Real-time tracking with intra-operative imaging such as ioCT or ioMRI
Registration	Bring virtual and surgical fields into alignment	Better non-rigid body transformation in the context of brain shift
Brain shift correction	Account for intra-operative brain shift	Biomechanical model of brain deformation Use of stereopsis, ultrasound, ioCT or ioMRI to account for brain shift
Image display	Present image guidance information to surgeon	Stereoscopy and autostereoscopy Augmented reality

Table 4.1. Common stages of image guided surgery.

Contemporary neuronavigation systems share a number of common features (Table 4.1). Pre-operative images are acquired, a virtual 3D model is constructed and pathological and anatomical structures are identified (acquisition and segmentation). The positions of surgical instruments are accurately and precisely tracked in space, invariably with respect to a reference point (tracking). The virtual and real spatial maps are brought into alignment (registration). Predicted or measured intra-operative brain shifts may be accounted for (brain shift correction). Lastly, the appropriate images are presented to the operating surgeon (image display). This narrative review will explore advances in image display including those that allow the fusion of virtual and real images (augmented reality).

4.1.2 Search strategy

The Cochrane Central Register of Controlled Trials (CENTRAL), PubMed and EMBASE databases were searched between January 1990 and December 2014. Relevant combinations of free-text search terms [(image guid*) OR (augmented reality) OR (image fus*) OR (image overlay) OR (neuronavigation)] AND [(endoscop*) OR (keyhole)] AND [(neurosurg*)]. An English language restriction was applied. Reference lists of selected papers were also reviewed and expert opinions sought to identify any missing manuscripts.

4.1.3 Multiplanar reformatted display

The final component of neuronavigation is the display of images in such a way that the operating surgeon is able to localise a point in the operative field unambiguously. To this end, several image display technologies have been developed including multi-planar reformatted display (MPR), 3D imaging, and augmented reality. MPR has been used since the advent of CT, and remains the most widely adopted technique. While early computing systems were only capable of slicing data along orthogonal axes (rows and columns), present day systems are able to present images in any plane including views that are perpendicular to, or in the plane of, the probe[166]. A drawback of contemporary MPR is that the surgeon must use the information from image slices to construct, in their own mind, a potentially complex 3D representation of anatomical and pathological structures.

4.1.4 Three-dimensional display

The display of 3D data may be accomplished either by projecting the entire volume[167], or groups of surfaces within the volume[168], onto the 2D viewing screen. Direct volume rendering requires that each voxel be assigned a colour and opacity using a transfer function. Ray-tracing or similar techniques are then used to compute the path of light rays through these volumes and produce a projection image. Surface rendering requires that the image be segmented and that the surfaces of structures of interest are identified and extracted[169, 170]. Surface rendering is often used in conjunction with texture mapping to display the characteristics of the original data onto selected surfaces.

Stereoscopic visualisation allows surgeons to view 3D data on 3D displays. The advantages of stereoscopic display over conventional 2D displays have long been debated, but studies on robot-assisted endoscopic surgery have suggested that, at least in some circumstances, 3D displays are associated with improved performance[171]. The Montreal Neurological Institute group have used stereoscopic visualisation for pre-operative planning for a number of years, and have reported considerable success with the technique[172, 173].

Most available 3D displays require users to wear polarising or active liquid crystal display (LCD) shutter glasses, which can be uncomfortable over long operating periods. Autostereoscopy systems allow users to perceive 3D images with the naked eye. In a recent study, the Dextroscope workstation (Bracco AMT, Singapore) was used alongside an autostereoscopic monitor system (MD20-3-D; Setred SA, Sweden) to plan intracranial approaches for 33 patients[174]. The authors reported generally favourable findings with no adverse effects such as nausea or fatigue described (although motion sickness questionnaires were not administered).

4.1.5 Augmented reality display

All of the aforementioned approaches presently require neurosurgeons to stop operating momentarily, apply a probe to the region of interest (potentially near critical neurovascular structures), and then take their eyes off the surgical field to view the image guidance monitors. In minimally invasive neurosurgical procedures, the relative paucity of anatomical landmarks often necessitates more frequent use of image guidance, which can increase the operating time considerably. The fusion of virtual 3D brain models and the actual operating field to provide an augmented reality may therefore enhance the operating room workflow and improve safety. Augmented reality may make use of "optical see-through" or "video see-through" technology.

In optical see-through, optical combiners both allow light from the operative field to pass, and also reflect light from monitors displaying graphical images. Although ill-suited for endoscopic neurosurgical approaches, several groups have constructed optical see-through augmented reality systems that utilise the optical axis of microscopes to overlay relevant navigation data[175-177]. Unfortunately, many users of

these systems have reported difficulty fusing natural images with virtual overlays. Moreover, the methods of image injection in these systems are almost invariably monoscopic resulting in 2D overlays that act as a further barrier to image fusion.

In video see-through a digital video feed of the operative site is combined electronically with a graphical representation of critical anatomy or pathology[178]. Video see-through has been used in head mounted displays such as the DEX-ray[179, 180]. The DEX-ray system consists of a tracked handheld probe containing a small video-camera that looks over the probe's tip into the surgical field, allowing accurate and real-time augmented reality display. Clinical cases using the system have demonstrated feasibility and shown promise. However, while the DEX-ray may be useful for pre-operative planning, it is not well suited to use intra-operatively because it does not feed into the surgeon's standard operating display. In addition, because images are obtained from a single video camera, only monoscopic image display is possible.

Video see-through augmented reality systems have also been described, albeit to a limited extent, in combination with endoscopy to assist during minimally invasive neurosurgical procedures[40-42]. The most cited of these studies is that of Kawamata *et al*, who developed an augmented reality system consisting of a 2.7mm rigid endoscope (Olympus, Tokyo, Japan), an optical tracking system, and a controller to overlay endoscopic live images with wire-frame models of tumours and neighbouring anatomical landmarks[40]. In a series of 12 patients with pituitary tumours undergoing endoscopic transnasal transsphenoidal hypophysectomy, the authors felt that the system improved operative workflow. An inherent limitation of the system is that the endoscopic live images are monoscopic, and virtual overlays are therefore presented in 2D, significantly impairing depth perception. To compensate for this, the group colour-coded the wire-frame virtual overlays: the tumour was coloured blue when located more than 10mm from the tip of the endoscope, yellow when located less than 10mm away, and red when the tip was within the tumour.

The recent introduction of stereo-endoscopes suitable for minimally invasive neurosurgery (VisionSense, New York, New York) raises the possibility of augmented reality systems with 3D overlays. Interestingly, although stereoscopic

displays offer an advance on conventional monoscopic systems, many users may still have difficulty appreciating the depth of shaded renderings despite stereoscopic and kinetic cues[181-183]. It has been suggested that for virtual structures to be perceived to be embedded within tissues they must appear at least somewhat occluded[184]. Several different visualisation techniques have been developed to improve depth perception in augmented reality systems[185]. One proposed solution is to instead use wire frames and texture-mapped dot patterns[181]. Another method relies on Non-Photorealistic Rendering (NPR), which provides a see through vision of the embedded virtual object whilst maintaining the salient anatomical structures of the exposed surface that serve to occlude the object. Studies comparing NPR against standard augmented reality overlay have demonstrated that the former is associated with significantly improved depth perception[184]. To date, NPR has not been used in neuronavigation systems, and the feasibility and efficacy of implementing the technology in minimally invasive neurosurgical approaches remains uncertain.

Case series utilising augmented reality to aid surgical localisation have generally been encouraging, suggesting that such technology may improve the operating room workflow[40, 181, 186, 187]. However, no prospective studies have yet compared augmented reality against other image display formats, and the potential benefits in terms of patient outcome offered by the technique have therefore not been validated. Indeed, the use of augmented reality has recently been reported as being associated with inattentional blindness in surgeons[188]. This study compared 32 surgeons of varying experience performing an endonasal navigation exercise on a cadaver. Surgeons were randomised into groups with or without augmented reality. Although the group with augmented reality were more accurate, they were less likely to identify unexpected findings. The authors of the study speculate that augmented reality may have lead to perceptual blindness in a number of ways including attentional tunnelling, increased visual clutter and jitter, and an additional camouflage effect. Further investigation is warranted, as it may be that alternate image displays, or on-demand augmented reality, might limit or negate the effects described.

4.2 Comparative effectiveness and safety of image guidance systems in surgery: A preclinical randomised study

4.2.1 Introduction

As outlined in the review above, image guidance systems are increasingly important tools in surgery, and have been widely adopted in neurosurgery over the last decade. Nonetheless, the evidence for the comparative effectiveness and safety of these image guidance systems remains limited. Case-control studies report that the use of image guidance is associated with improved patient outcomes when compared to standard surgery,[27] but commentators have suggested that clinical randomised studies are now neither practical nor ethical[189].

The aim of this laboratory study was to compare simultaneously the effectiveness and safety of various image guidance systems utilising triplanar and augmented reality displays, against standard surgery, using a keyhole neurosurgical approach as an exemplar.

4.2.2 Materials and Methods

The Imperial College Joint Research Compliance Office (JRCO) approved the study protocol. The Consolidated Standards of Reporting Trials (CONSORT) statement was used in the preparation of this manuscript[190].

4.2.2.1 Participants and study settings

Fifty novices were recruited from one university hospital. Participants were deemed suitable for inclusion if they had no prior experience of endoscopic surgery (performed zero). Written informed consent was obtained from all participants.

4.2.2.2 Trial design

A preclinical randomised study design was adopted, comparing: (1) no image guidance, (2) triplanar display of axial, sagittal and coronal images, (3) always-on solid overlay augmented reality, (4) always-on wire mesh overlay augmented reality, and (5) on-demand inverse realism augmented reality.

The Modelled Anatomical Replica for Training Young Neurosurgeons (MARTYN) head (Royal College of Surgeons of England, London, UK), with an accompanying circle of Willis including a basilar tip aneurysm, was utilised[33]. The model consists of a gelatine-based brain, encased within a latex dura, and a polyurethane skull. The study reported in Chapter 2.3 confirmed that the MARTYN head is realistic (face validity), useful (content validity), and able to discriminate between surgeons of different experience (construct validity), with respect to the supraorbital subfrontal approach[191]. A 25 x 15mm left supraorbital craniotomy was fashioned using a high-speed drill (B. Braun, Melsungen, Germany). The high-speed drill was then used to remove the inner edge of the bone above the orbital rim, and the jugae cerebralia. A simple "C" durotomy was performed, and the flap retracted basally.

A VisionSense III endoscopy system (VisionSense, Petach Tikva, Israel) was used for visualisation. The High-Definition zero degree rigid endoscope is 4mm in diameter and 18cm in length, providing a resolution of 1920 x 1080 pixels. Images were displayed using a 42" stereoscopic screen.

A CT scan of the MARTYN head was performed and the vascular tree and aneurysm manually segmented using itk-SNAP v2.4.0 (www.itksnap.org),[192] and smoothed and decimated using MeshLab v1.3.2 (www.meshlab.sourceforge.net). The model head was fixed in place with a Mayfield clamp and a Budde-halo retractor system attached (Integra, New Jersey, USA). An NDI Polaris Optical Tracking System (Northern Digital Inc., Ontario, Canada) was used to track the endoscope and image guidance probe with respect to a reference frame. Rigid registration of surface fiducials was used to relate the head and CT scan coordinate frames. Manual alignment of a reference object was then used to determine the hand-eye transformation from the camera tracking frame to the camera frame defining the projection to display coordinates. Concatenated together, the results of these calibrations were used to map renderings of the CT segmentations onto captured images of the model head. Custom software was used to generate the different image display modalities and to record the probe path length (Figure 4.1 and Figure 4.2).

Participants were randomly allocated using a computer-generated sequence into five groups to determine which image display modality was utilised. Blocked

randomisation was used to ensure that ten participants were evenly allocated into each group. Each participant was shown a short video demonstrating the endoscopic supraorbital approach in the MARTYN head, and given several minutes to familiarise themselves with the image guidance system. They were then asked to identify the basilar tip aneurysm using a probe, with instructions to minimise their exposure and manipulation of brain tissue with use of cottonoid patties (Codman and Shurtleff, Massachusetts, USA), as they deemed appropriate. The task was considered complete when users applied the probe to the aneurysm.

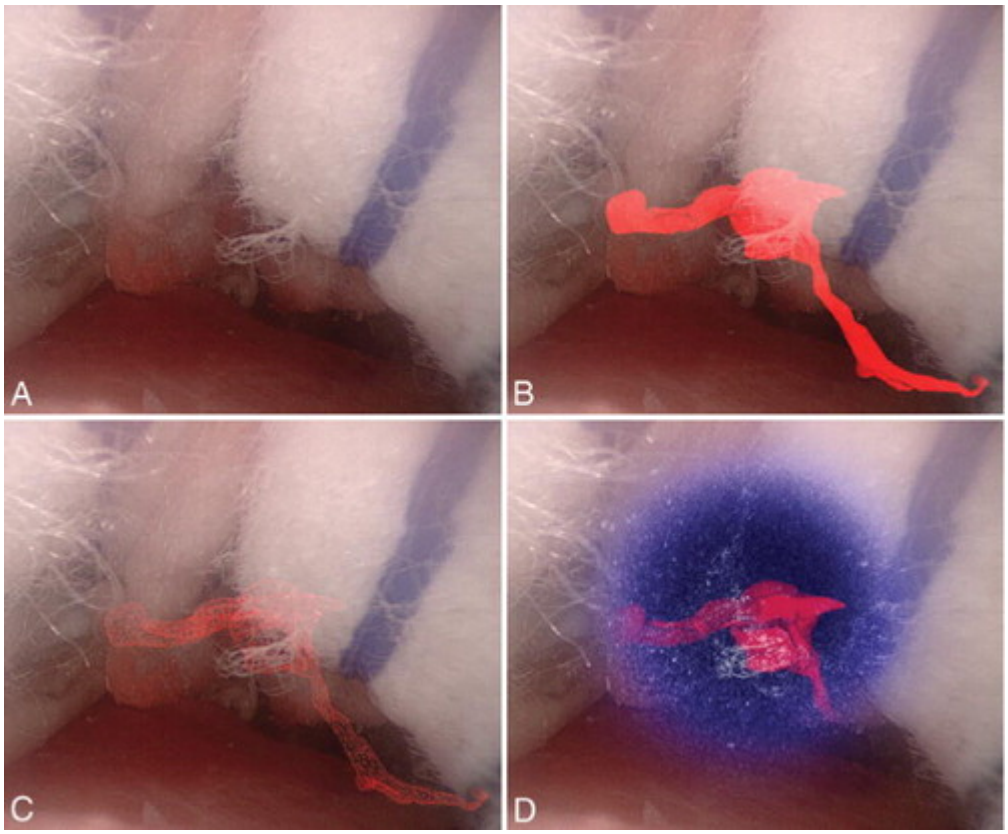


Figure 4.1. Augmented reality overlays of the segmented vascular tree (red): (a) no image guidance, (b) always-on solid overlay, (c) always-on wire mesh overlay, and (d) on-demand inverse realism overlay.

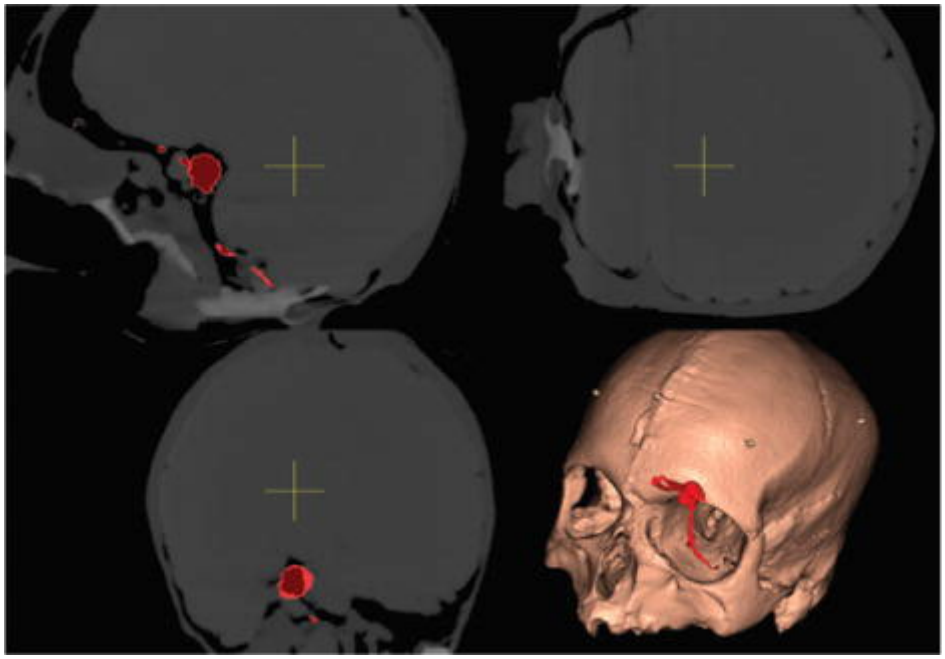


Figure 4.2. Triplanar image guidance display of the segmented vascular tree (red) with axial, coronal and sagittal sections centred over the probe tip.

A surgical clip was placed over the left posterior cerebral artery, approximately 5mm from the aneurysm, and within the surgical trajectory, providing an unexpected finding to assess inattentional blindness (Figure 4.3).

4.2.2.3 Outcomes

The primary outcomes were time to task completion (seconds), and tool path length (millimetres). The secondary outcomes were recognition of the unexpected finding (prompted), and subjective depth perception (5-point Likert scale). Whereas participants were aware of the image display modality they were using, the data analysts were blinded to their allocation.

4.2.2.4 Statistical analysis

The sample size was calculated on the basis of recently published work, preliminary data, and anticipated ease of participant recruitment[191]. It was estimated that to detect a reduction in time to task completion from 152 to 92 seconds (SD 48 seconds), with a two-sided 5% significance level and a power of 80%, a sample size of at least 10 participants was necessary in each group.

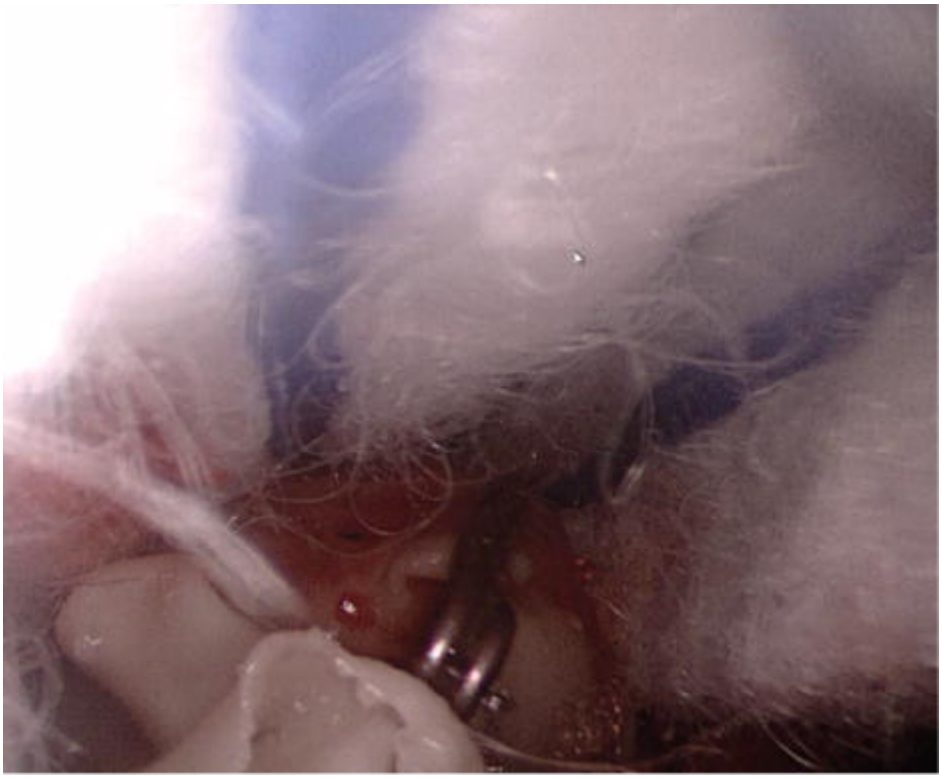


Figure 4.3. Endoscopic image demonstrating cottonoid patties (top), and an unexpected aneurysm clip (lower centre), within the operative field.

Data were analysed with SPSS v 20.0 (IBM, Illinois, USA). The median and interquartile ranges were calculated for all outcome measures, and nonparametric tests performed, with a value of $p < 0.05$ considered statistically significant. The time to task completion, tool path length, and subjective depth perception were compared using the Kruskal-Wallis one-way analysis of variance. The proportion of users recognising the unexpected finding was compared using the Chi Square or Fisher's Exact test (if less than 80% of the cells had an expected frequency of 5 or greater). If a significant difference was identified in any of the outcomes the following groups were then directly compared, with the Bonferroni correction ($n = 4$; $p < 0.0125$): no image guidance versus any image guidance, triplanar image display versus any augmented reality display, always-on solid overlay versus on-demand inverse realism, and always-on solid overlay versus always-on mesh overlay.

4.2.3 Results

4.2.3.1 Baseline demographic data

The demographics of the participants are summarised in Table 4.2. Of the 50 participants recruited, 35 were medical students and 15 were junior doctors; none had yet embarked on formal surgical training. There was no significant difference in demographics or experience between the groups. All participants that were enrolled completed the study, and no losses occurred after randomisation.

4.2.3.2 Primary Outcomes

The median and interquartile ranges of the primary outcomes are summarised in Table 4.3. The time to task completion and tool path length in the various study groups was significantly different ($p = 0.007$ and $p = 0.002$, respectively); they are illustrated in Figure 4.4 and Figure 4.5. In subsequent analysis, the time to task completion and tool path length was significantly lower when utilising any form of image guidance (triplanar display, always-on solid overlay, always-on wire mesh overlay, and on-demand inverse realism overlay) compared to no image guidance ($p < 0.001$ and $p = 0.003$, respectively). The tool path distance was also lower in groups utilising augmented reality (always-on solid overlay, always-on wire mesh overlay, and on-demand inverse realism) compared to triplanar image display ($p = 0.010$). There was no significant difference in the primary outcomes between the different augmented reality overlays.

4.2.3.3 Secondary Outcomes

The secondary outcomes are summarised in Table 4.3. All videos were reviewed and the surgical clip was visible in all cases. The proportion of participants that recognised the unexpected finding in the various study groups was significantly different ($p = 0.025$). All but one participant recognised the aneurysm clip in the control arm (90% recognition of unexpected finding) while less than half recognised it when utilising any form of image guidance, including conventional triplanar display ($p = 0.003$). Always-on solid overlay resulted in the greatest inattentional blindness (20% recognition of unexpected finding). Always-on wire mesh and on-demand overlays mitigated but did not negate inattentional blindness, and were comparable to

triplanar displays (40% recognition of unexpected finding in all groups). The subjective depth perception also varied significantly in the augmented reality groups ($p = 0.015$). Solid overlay resulted in significantly worse subjective depth perception than wire mesh and inverse realism ($p = 0.031$ and $p = 0.008$, respectively).

	Age, Median (IQR), years	Sex, Male:Female	Handedness, Right:Left
No image guidance (n = 10)	24 (22 – 25)	4:6	8:2
Triplanar display (n = 10)	23.5 (21 – 26.5)	4:6	10:0
Always-on solid overlay (n = 10)	24.5 (22.3 – 25)	6:4	10:0
Always-on wire mesh overlay (n = 10)	21.5 (20.3 – 24)	4:6	9:1
On-demand inverse realism overlay (n = 10)	23.5 (22 – 24.5)	5:5	10:0
All groups (n = 50)	23.5 (21.3 – 25)	23:27	47:3
p	0.664	0.863	0.225

Table 4.2. Participant demographics.

	Time to task completion* (s)	Path length* (mm)	Recognition of unexpected finding**	Depth perception*
No image guidance	88.5 (61.8 – 150.5)	2938.5 (1411.8 – 5955.8)	9/10 (90.0%)	N.A.
Triplanar display	30.5 (16.5 – 64.8)	1384.0 (1183.8 – 2873.0)	4/10 (40.0%)	N.A.
Always-on solid overlay	19.5 (16.3 – 64.3)	795.0 (371.0 – 1624.8)	2/10 (20.0%)	2.0 (1.0 – 3.0)
Always-on wire mesh overlay	25.5 (17.8 – 52.8)	641.0 (406.5 – 1798.5)	4/10 (40.0%)	3.5 (2.0 – 4.0)
On-demand inverse realism overlay	26 .0 (13.0 – 41.5)	639.5 (314.5 – 1068.8)	4/10 (40.0%)	4.0 (2.8 – 4.0)
p	0.007	0.002	0.025	0.015

Table 4.3. Summary of results according to image guidance used. *Values reported are median (interquartile range), and probability using the Kruskal-Wallis one-way analysis of variance. **Values reported are number of participants (percentage), and probability using Fisher's exact test.

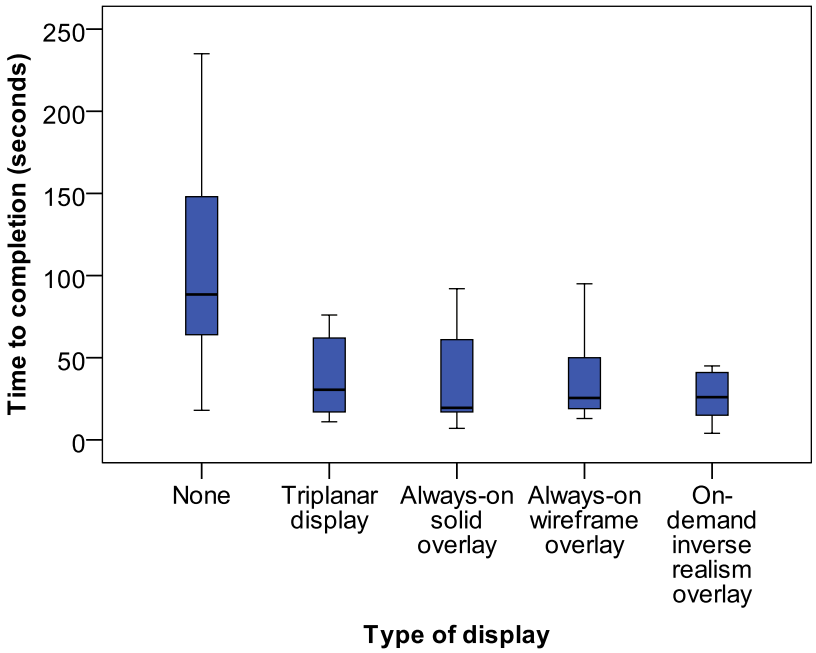


Figure 4.4. Graph illustrating time to completion with different image guidance displays.

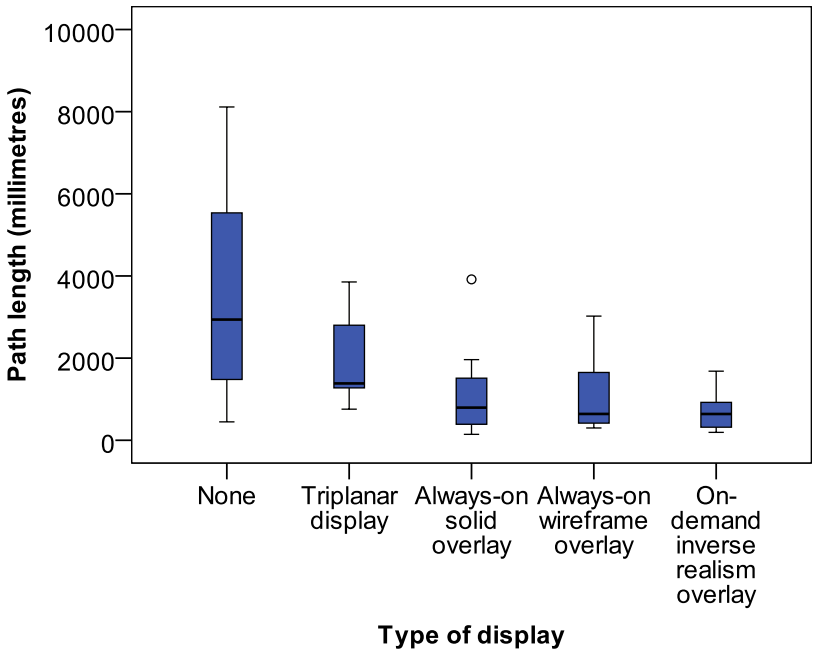


Figure 4.5. Graph illustrating path distance with different image guidance displays. Circle represents an outlier (greater than 1.5 times the interquartile range).

4.2.4 Discussion

4.2.4.1 Principal findings

Image guidance technology is among the most rapidly emerging innovations in surgery[58]. Although the evidence for the use of image guidance in surgery remains limited, systems utilising triplanar display have already achieved substantial clinical penetration in neurosurgery. The recent development and refinement of augmented reality displays offers the possibility of improved operating room workflow[40-42, 187]. In the coming years, technological advances are likely to promote further the dissemination of augmented reality technology in surgery. This randomised study is the first to simultaneously compare the effectiveness and safety of image guidance systems utilising triplanar and augmented reality displays, against standard surgery, in a validated preclinical model. To this end, this study's findings confirm the utility of image guidance systems in neurosurgery, and suggest that new augmented reality platforms with always-on wire mesh or on-demand inverse realism overlays may result in improved surgical performance. However, it must be acknowledged that all image display modalities, including existing triplanar display, carry a risk of inattentional blindness.

4.2.4.2 Comparison with other studies

Image guidance systems have two potential roles in surgery: first, to help guide the overall surgical approach to pathology; and second, to facilitate unambiguous tissue dissection[163]. Currently, most image guidance systems are designed for the former, allowing surgeons to define precisely a narrow surgical corridor to deep-seated pathology, thus minimising the risk of iatrogenic injury. In the present preclinical randomised study, all image guidance systems resulted in significantly reduced time to completion and tool path length compared to standard surgery ($p < 0.001$ and $p = 0.003$, respectively). Surprisingly, as reported in the narrative review above, no clinical randomised studies have evaluated the role of contemporary image guidance systems to help define the surgical trajectory, though case-control studies have concluded that the use of image guidance is associated with shorter operating times, reduced blood loss, and fewer major complications, than standard surgery[27].

In the present study, image guidance with augmented reality displays led to a significantly reduced tool path length compared to image guidance with existing triplanar display ($p = 0.010$). Augmented reality displays may improve the surgical workflow by obviating the need for the surgeon to repeatedly stop operating, apply the probe to the region of interest, and turn away from the operating field to view the image guidance monitor. In a previous preclinical randomised study, augmented reality improved the accuracy of surgical trainees in identifying skull base landmarks on a cadaver, compared to no image guidance[187]. The investigators noted that they did not include a triplanar display as comparison, and could therefore not comment on the relative merit of augmented reality over existing image guidance platforms.

The use of augmented reality has been reported as being associated with inattentional blindness in surgeons, raising important safety concerns[188]. In the present study, all image guidance displays resulted in considerable inattentional blindness ($p = 0.003$), despite the surgical clip being clearly visible in all the videos reviewed. Always-on solid overlay was associated with the greatest inattentional blindness (20% recognition of unexpected findings). Wire mesh and on-demand overlays mitigated but did not negate inattentional blindness (40% recognition of unexpected findings in all cases). Interestingly, image guidance with existing triplanar displays also resulted in comparable inattentional blindness (40% recognition of unexpected findings), suggesting that it is the cognitive load rather than the overlay *per se* that is important.

An additional concern with augmented reality systems has been the issue of subjective depth perception. At present, the majority of endoscopes in clinical use are 2D, with augmented reality overlays presented in kind. The recent introduction of 3D and HD endoscopes may allow for stereoscopic augmented reality systems. In keeping with existing literature in the field, the present study found that even with such binocular cues, many users continue to struggle to appreciate the depth of solid overlays (median 2.0/5 on Likert scale)[181-184]. To this end, wire mesh and inverse realism overlays resulted in better subjective depth perception (median 3.5/5 and 4.0/5 on Likert scale, respectively).

4.2.4.3 Limitations

It should be noted that this study has a number of limitations. All the study participants were novices yet to embark on formal surgical training. Selection of novices, rather than intermediates or experts, allowed for a relatively homogenous sample; this was essential as the assessment of inattentional blindness with an unexpected finding meant a crossover study design could not be adopted.

Novice participants may have had difficulty in identifying the aneurysm, or recognising the surgical clip as an abnormal finding. However, all participants observed a short video introducing the MARTYN head and demonstrating the Circle of Willis and basilar tip aneurysm. Moreover, the fact that 90% of participants in the control group did recognise the aneurysm clip, suggests the observed inattentional blindness was the result of the use of image guidance rather than surgical inexperience.

None of the study participants had prior experience with image guidance, and all were given a few minutes to familiarise themselves with the equipment. It is likely that greater familiarity would have resulted in improved performance and less inattentional blindness.

The supraorbital subfrontal approach was selected as an exemplar keyhole approach but it is infrequently performed even among experienced neurosurgeons. The approach was chosen as it is recognised as technically challenging, and may benefit from image guidance[155]. In addition, a preclinical model with face, content, and construct validity was readily available[191].

The MARTYN head is comparatively low fidelity, particularly with respect to its internal structure. The result is that the triplanar view lacks anatomical detail, and this may have had an impact on task performance. However, the use of segmented rather than plain images likely mitigated for this (Figure 4.1).

4.2.4.4 Conclusions

In conclusion, this study has demonstrate that the use of image guidance systems with augmented reality overlays significantly reduced the time to task completion and tool path distance, but in some cases also increased the risk of inattentional blindness. The use of on-demand inverse realism or wireframe overlays may represent an optimal solution, allowing for improved effectiveness, while maintaining a safety profile comparable to existing triplanar displays.

The generalisability of this study is likely to depend on several factors including the experience of the surgeon, and the complexity of the surgical approach. With greater experience, surgeons learn to use anatomical landmarks to guide their surgical trajectory, and the benefits of image guidance almost certainly lessen. Similarly, in relatively straightforward surgical approaches, there may be little advantage to the use of image guidance. Nonetheless, these findings support the need for less experienced surgeons using image guidance systems, particularly when undertaking complex approaches, to be carefully supervised by experts that are less cognitively loaded and better able to identify potential complications.

CHAPTER 5 INTRA-OPERATIVE VISUALISATION: 3-DIMENSIONAL HIGH-DEFINITION ENDOSCOPY*

*Content from this chapter was published or submitted as:

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Marcus HJ, Hughes-Hallett A, Cundy TP, Di Marco A, Pratt P, Nandi D, Darzi A, and Yang GZ. Comparative Effectiveness of 3-D versus 2-D and HD versus SD Neuroendoscopy: A Preclinical Randomized Crossover Study. Neurosurgery. 2014; 74(4): 375-81 – featured on the BBC News article "Head space: Finding a way to do 3D surgery on the brain" http://www.bbc.co.uk/news/health-25743600

Content from the chapter was presented as:

Wan Y, Shah N, and **Marcus HJ**. Comparing three-dimensional (3-D) with two-dimensional (2-D) endoscopes in transsphenoidal surgery: a systematic review. The British Skull Base Society Meeting, London. January 2015

5.1 Comparative effectiveness and safety of 3-Dimensional versus 2-Dimensional endoscopy: A systematic review

5.1.1 Introduction

Although the first endoscope was developed over 200 years ago by the German physician Philip Bozzini, it was not until the early 20th century that endoscopes incorporated magnifying lenses and light sources that allowed their use within the brain[37]. While many surgeons contributed during the early years of endoscopic neurosurgery, the father of the field was undoubtedly Walter Dandy. After early failed attempts at using a cystoscope to perform choroid plexus fulguration and removal, Dandy invested a great deal of effort helping to engineer endoscopes for neurosurgery, and refining his surgical technique. Unfortunately endoscopes remained frustrating instruments to use and progressively fell out of favour following the advent of cerebrospinal fluid shunts to treat hydrocephalus in the 1950's and the emergence of operating microscopes in the 1960's. In subsequent years the development of the SELFOC® lens (Go!Foton, New Jersey, USA), Charge-Coupled Device (CCD) and fibre-optic light source improved the viewing angle, image quality and illumination provided by endoscopes, and heralded a resurgence of the field. The last decade has seen a number of further technologies created with the promise of improving visualisation during keyhole neurosurgical approaches.

At present, most endoscopes used in skull base surgery are 2-Dimensional (2D), limiting depth perception. Moreover, there is some evidence that some endoscopic skull base procedures, such as pituitary surgery, may be associated with a greater risk of vascular complications[193]. The recent introduction of 3-Dimensional (3D) endoscopes may therefore improve the effectiveness and safety of these approaches.

Several groups have described the development and use of 3D endoscopes in neurosurgery, though these generally remain SD at present. Perhaps the earliest reported in-human attempt utilised a 4.7mm rigid endoscope (Vista Medical Technologies, California, USA) with dual Charge Coupled Devices (CCD) allowing 3D visualization (640 x 480 pixels) during fenestration of a right middle fossa arachnoid cyst and excision of a large craniopharyngioma with suprasellar

extension[194]. Although the study confirmed the feasibility of 3D endoscopy, the authors noted that the end-display technologies available at the time (in this case a head mounted device) significantly limited clinical utility. Modern 3D endoscopes now utilise stereoscopic dual-flatscreen systems, which are more easily integrated into the surgical workflow.

In this systematic review, the evidence is synthesised on whether, in patients undergoing endoscopic skull base surgery, 3D endoscopy confers an advantage over conventional 2D endoscopy, in terms of effectiveness and safety.

5.1.2 Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement was used in the preparation of this manuscript.

5.1.2.1 Search Methods

The Cochrane Central Register of Controlled Trials (CENTRAL) and PubMed databases were searched between January 1990 and December 2014. The Boolean search term (pituitary OR transsphenoidal OR "skull base") AND (endoscope or endoscopic or endonasal) AND (3D OR 3-D OR "3 dimensional" OR "3-dimensional" OR "three dimensional" OR "three-dimensional") was used. An English language restriction was applied. Reference lists of selected papers were also reviewed, and expert opinion sought, to identify additional eligible manuscripts. Two authors independently identified articles using the above search criteria.

5.1.2.2 Inclusion and exclusion criteria

Titles and abstracts were screened to identify publications that (1) featured adult patients undergoing skull base surgery, (2) compared 2D and 3D endoscopy, and (3) reported on effectiveness or safety. Full articles were subsequently obtained and further assessed for eligibility. Discrepancies were resolved by discussion with the senior author.

5.1.2.3 Data extraction

The following data was extracted from eligible full articles: (1) study design, (2) study group characteristics including the number of subjects, and pathology (3) effectiveness including extent of resection, and operating time, and (4) safety including vascular complications, visual complications, cranial nerve injury, diabetes insipidus, cerebrospinal fluid leak, meningitis, and death. Epistaxis was not considered a vascular complication.

Corresponding authors were contacted to provide supplemental data when required. In circumstances when this was not possible, data was extrapolated using the original results reported.

5.1.2.4 Appraisal of evidence

The Jadad and Methodological Index for Non-Randomised Studies (MINORS) scoring systems were used to guide evaluation of the quality of randomised and non-randomised studies respectively[195, 196]. Studies of greater quality were given appropriately greater weighting in the qualitative analysis.

5.1.3 Results

A total of 163 articles were pooled from the electronic databases (Figure 5.1). Of these, 152 articles were excluded on the basis of their title and abstract because they did not present original data, did not feature adults undergoing endoscopic skull base surgery or models of these approaches, did not include both a 2D and 3D group, or did not report on effectiveness or safety. Full text screening of the remaining 11 articles led to the exclusion of a further 8 articles. In all, 3 articles were identified that satisfied the inclusion criteria, comprising two retrospective cohort studies, and one case-control study[197-199].

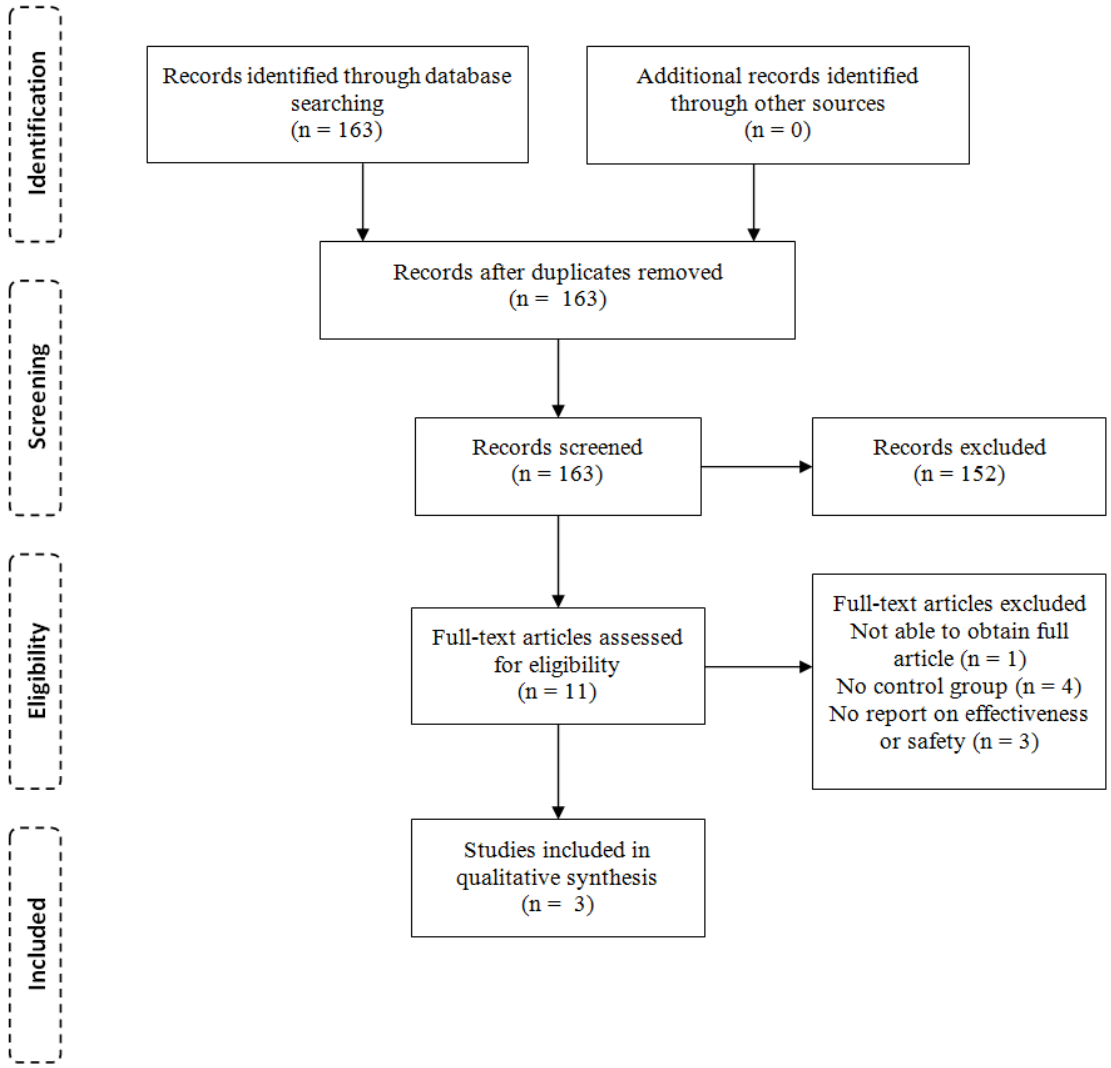


Figure 5.1. PRISMA flow diagram

5.1.3.1 Clinical studies

The overall quality of all the three included clinical articles was 12/24 using the MINORS system. None of the included studies used an unbiased assessment of the endpoint, or provided a prospective calculation of the study size.

A total of 244 patients undergoing endoscopic pituitary surgery were reported – 140 (57.4%) with 2D endoscopes, and 104 (42.6%) with 3D endoscopes (Table 5.1). In all clinical cases, a Karl Storz endoscope (Karl Storz, Tuttlingen, Germany) was used for 2D HD visualisation, and a VisionSense II endoscopy system (VisionSense, Petach Tikva, Israel), for 3D SD visualisation.

Tabaee *et al* provided data on the extent of resection[199]. In their case control-study of 13 patients undergoing pituitary surgery with a 3D endoscope, they reported gross total resection in 10 patients. In the remaining patients pituitary macroadenoma had extended into the cavernous sinus, and an intentional subtotal resection was performed with tumour adherent to the sinus left behind.

All three studies provided data on the operating time. The range of operating time was 142.6 to 162.6 minutes. There was no significant difference in the operating time between the 2D and 3D groups. However, Barkhoudarian *et al* did report that in the subset of patients undergoing pituitary adenoma surgery, the operating time was significantly less in the 3D compared to the 2D group (148 vs. 174 minutes; $p = 0.03$)[197].

Barkhoudarian *et al* and Kari *et al* provided data on complications[197, 198]. CSF leak was the most common complication (n = 23; 10.6%), followed by diabetes insipidus (n = 11; 5.0%), and ophthalmoplegia and visual loss (n = 3; 1.4%). There was no significant difference in the rate of complications between the 2D and 3D groups (17.3% vs. 16.5% respectively).

Table 5.1. Clinical studies comparing 2D and 3D endoscopic skull base surgery. DI = Diabetes Insipidus; CSF = Cerebrospinal fluid *Excluding cases invading the cavernous sinus, in which subtotal resection was planned.

	Study type	**Study cohort (adenoma)**	**Age, Mean, years Sex, Male:Female**	**Gross Total Resection***	**Complications**	**Other**
Barkhoudarian *et al* (2013)	Retrospective cohort (Level 3)	2D: 95 pts (60 adenoma; 35 other)	50.3 M:F 1:1.3	Not reported	6 (4 CSF leak; 2 DI)	Reduced operating time in the 3D group (148 vs. 174 minutes; p = 0.03)
		3D: 65 pts (55 adenoma; 10 other)	49.1 M:F 1:1.3	Not reported	3 (1 CSF leak; 1 DI; 1 Visual)	
Kari *et al* (2010)	Retrospective cohort (Level 3)	2D: 32 pts (all adenoma)	50.1 M:F 1:1.7	Not reported	16 (11 CSF leak; 3 DI; 2 Visual)	
		3D: 26 pts (all adenoma)	48.6 M:F 1:2.7	Not reported	12 (7 CSF leak; 5 DI)	
Tabaee *et al* (2009)	Case-control (Level 4)	2D: 13 pts (11 adenoma; 2 other)	57.3 M:F 1:1.6	9 (90%)	Not reported	
		3D: 13 pts (10 adenoma; 3 other)	55.5 M:F 1:2.2	10 (100%)	Not reported	

5.1.4 Discussion

5.1.4.1 Principal findings

At present, there is limited and low quality data on the comparative effectiveness and safety of 3D versus 2D endoscopy in skull base surgery. Only 3 studies met the inclusion criteria, and none demonstrated any strong evidence in favour of 3D endoscopy.

The included clinical cohort and case-control studies generally failed to demonstrate a significant difference in effectiveness or safety between the 2D and 3D groups. Barkhoudarian *et al* found that in the subset of patients undergoing pituitary adenoma surgery, the operating time was significantly lower in the 3D compared to the 2D group, though this was likely to be a post hoc analysis[197].

All of the studies included reported subjectively improved depth perception. This finding is supported by several non-comparative case reports and case series'[200-202]. In using 3D endoscopy for resection of an adenocarcinoma of the left nasal fossa eroding the skull base, Castelnuovo *et al* felt that this imaging modality improved visualisation irrespective of lower quality resolution[200]. Cadaver studies were also identified that undertook endonasal and transcranial skull base approaches with both 2D and 3D endoscopes[46, 47]. Authors of these studies acknowledged benefits of 3D endoscopes, particularly for improved perception of complex anatomical spatial relationships within the brain.

5.1.4.2 Limitations

The present systematic review has a number of limitations. First, the scarcity and heterogeneity of the available clinical data makes it difficult to draw any firm conclusions; the analysis may simply be underpowered. Second, the included clinical studies all compared 3D SD and 2D HD endoscopy. Higher image quality may allow for improved depth perception using monocular cues, confounding interpretation of these studies. Finally, the included clinical studies reported the outcomes of expert surgeons. Previous studies on 3D endoscopy in other surgical specialties have generally determined that the greatest value of the technology is during training, as

experience can mitigate the loss of binocular depth cues. The impact of 3D endoscopes on the surgeon learning curve warrants further research. Low-volume centres may preferentially benefit if naive residents acquire skills more efficiently.

5.1.4.3 Conclusions

At present, there is limited and low quality data to support 3D compared to 2D endoscopy in skull base surgery. Further larger-scale prospective clinical studies comparing 3D and 2D are warranted to determine the extent to which subjective improvements in perception lead to objective improvements in patient outcome. The introduction of 3D HD endoscopes may allow for such studies to better control for image quality as a confounder. Future studies should also control for surgeon experience, and the learning curve.

5.2 Comparative effectiveness of 3-Dimensional versus 2-Dimensional and High-Definition versus Standard-Definition endoscopy: A preclinical randomised crossover study

5.2.1 Introduction

Although the potential benefits of 3-Dimensional (3D) versus 2-Dimensional (2D), and High-Definition (HD) versus Standard-Definition (SD) endoscopic visualisation have long been recognised in other surgical fields, such endoscopes are generally considered too large and bulky for use within the brain[203-207]. The recent development of 3D and HD endoscopes may therefore bring improved depth perception, better appreciation of anatomical details and improved surgical performance, compared to conventional endoscopy[23, 43-45]. These benefits must be balanced, however, against the higher cost, larger size, and greater weight of HD endoscopes. Moreover, the human visual system is exquisitely sensitive to stereoscopic cues, and although stereo fusion can tolerate quite major artefacts, symptoms such as diplopia and nausea have been described with prolonged use of 3D endoscopy systems[199].

Previous studies have sought to assess the impact of either 3D or HD endoscopy on surgical performance, with mixed findings[43-47, 198-200]. A major limitation of all these studies, as outlined in the systematic review above, is that they do not allow comparison of the effectiveness of 3D *and* HD endoscopy. It remains unclear whether, for example, HD endoscopy provides sufficient monocular cues to obviate the need for true 3D endoscopy. The aim of this study was therefore to compare simultaneously the effectiveness of 3D versus 2D, and HD versus SD endoscopy.

5.2.2 Materials and Methods

The trial protocol was approved by the Imperial College Joint Research Compliance Office (JRCO). The Consolidated Standards of Reporting Trials (CONSORT) statement was used in the preparation of this manuscript.

5.2.2.1 Participants and study settings

Ten novice endoscopic neurosurgeons were recruited from one university hospital. Participants were deemed suitable for inclusion if they had no earlier experience of

endoscopic neurosurgery (performed zero). Informed consent was obtained from all participants.

5.2.2.2 Trial design

A preclinical randomised crossover study design was adopted, comparing 3D versus 2D, and HD versus SD endoscopy.

A sawbone skull and brain (Sawbone Pacific Research Lab, Washington, USA), with an accompanying circle of Willis including an anterior communicating artery aneurysm, was utilised. A 25mm x 15mm left supraorbital craniotomy was fashioned, and five collared targets were placed around the surgical field approximately 30mm in diameter, and 30-60mm in depth.

A VisionSense III endoscopy system (VisionSense, Petach Tikva, Israel) was used for visualisation. The SD 0-degree rigid VisionSense endoscope was 4.9mm in diameter, and 20cm in length, providing a resolution of 640 x 480 pixels. The HD 0 degree rigid VisionSense endoscope was 4mm in diameter, and 18cm in length, providing a resolution of 1920 x 1200 pixels. Images were displayed using a 24" stereoscopic flat screen system, and switched between 3D and 2D (left eye) using the system's toggle.

Participants were randomly allocated using a computer-generated sequence into groups to determine the order in which 2DSD, 3DSD, 2DHD, or 3DHD endoscopy were utilised. Blocked randomisation was used to ensure that an equal number of participants began with 3D versus 2D, and HD versus SD endoscopy.

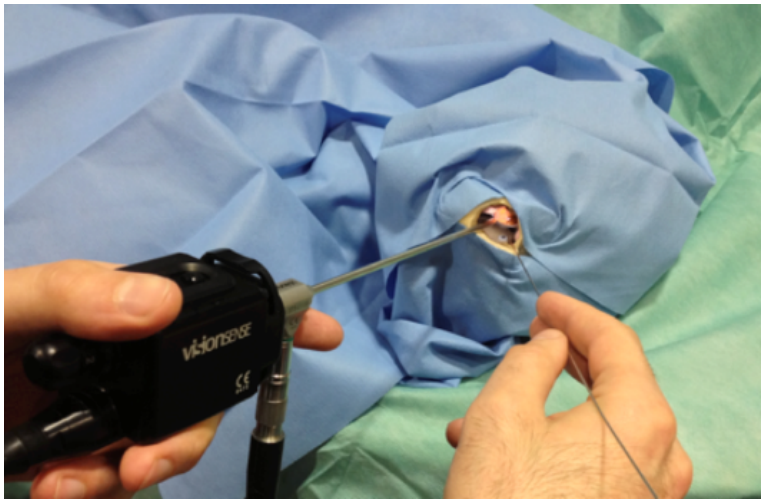


Figure 5.2. Photograph illustrating experimental set up, with the endoscope (left hand) used to guide the probe (right hand) to collared targets through a left supraorbital keyhole craniotomy (draped with only surgical field exposed).

Each participant was asked to place a probe on targets in a predetermined random sequence of ten colours (Figure 5.2). Participants were instructed to be both quick and accurate, placing the probe as close to the centre of the collared targets as possible. This process was repeated on three occasions with each endoscope configuration.

5.2.2.3 Outcomes

The primary outcomes were time to task completion (seconds), and accuracy with which probes were placed on targets (score). To determine accuracy, all recorded videos were reviewed and scored independently by two observers on how closely each probe was to the centre of the collared targets; participants were scored 3 points if they directly made contact with the 1mm collared target, 2 points if they made contact with the surrounding 1mm black line, 1 point if they made contact with the surrounding 2mm white line, and zero points if they missed the target entirely (Figure 5.3). Whereas participants were aware of the endoscope they were using, the data analysts were partially blinded to the allocation (to 3D versus 2D, but not HD versus SD).



Figure 5.3. Endoscope image illustrating a typical target. Participants were scored 3 points if they contacted the 1mm collared target, 2 points if they made contact with the surrounding 1mm black line, 1 point if they made contact with the surrounding 2mm white line, and zero points if they missed the target entirely.

The secondary outcomes were perceived task workload using the NASA Task Load Index (NASA-TLX)[208], and subjective impressions of the endoscopes using a 5-point Likert scale. Participants were asked after using each endoscope to what extent they considered the system provided high-quality images, allowed high fidelity depth perception, and they would like to use the visualisation modality again.

5.2.2.4 Statistical analysis

The sample size was calculated on the basis of recently published work[7]. It was estimated that to detect a reduction in time to task completion from 90 to 66 seconds (SD 30 seconds), with a two-sided 5% significance level and a power of 80%, a sample size of 10 participants was necessary.

Data was analysed with SPSS v 20.0 (Illinois, USA). Cronbach's α was used to assess the inter-rater reliability of accuracy scores. The median and interquartile ranges were calculated for all outcome measures, and nonparametric tests performed, with a value of $p < 0.05$ considered statistically significant. 2DSD, 3DSD, 2DHD, and 3DHD endoscopy were compared using the Kruskal-Wallis one-way analysis of variance. Subsequently, if a significant difference was identified, the Mann-Whitney U test was used to compare 3D versus 2D, and HD versus SD endoscopy, with the Bonferroni correction. A post-hoc analysis was also performed comparing the data from the two

novice endoscopic neurosurgeons with extensive laparoscopic experience against the other participants, to determine whether there was a significant difference in performance.

5.2.3 Results

5.2.3.1 Baseline demographic data

The demographics of the ten participants are summarised in Table 5.2. All participants completed the study, and no losses occurred after randomisation. Two of the subjects had considerable experience with laparoscopic surgery (performed >50 cases), but had no experience with endoscopic neurosurgery, and were included nonetheless; post-hoc analysis confirmed no significant difference in performance.

Age, Median (range), years	29.5 (25-43)
Sex, Male:Female	7:3
Handedness, Right:Left	8:2

Table 5.2. Participant demographics.

5.2.3.2 Primary outcomes

Cronbach's α demonstrated excellent inter-rater reliability when scoring the accuracy of probe placement ($\alpha = 0.925$). The median and interquartile ranges of the primary outcomes are summarised in Table 5.3. The time to task completion and accuracy of probe placement with different endoscopes were significantly different ($p = 0.005$ and $p = 0.021$ respectively); they are illustrated in Figure 5.4 and Figure 5.5.

The median and interquartile ranges of the primary outcome data stratified according to 3D versus 2D, and HD versus SD endoscopy are summarised in Table 5.4 and Table 5.5 respectively. Post-hoc statistical analysis suggested that time to completion was significantly shorter when using 3D versus 2D endoscopy ($p = 0.001$), and accuracy of probe placement was significantly greater when using HD versus SD endoscopy ($p = 0.009$).

5.2.3.3 Secondary outcomes

The median and interquartile ranges of the secondary outcome data are summarised in Table 5.3. The subjective impressions of the endoscopes using a 5-point Likert scale varied significantly ($p < 0.001$), but the perceived task workload according to the NASA-TLX did not reach statistical significance ($p = 0.161$).

The median and interquartile ranges of the secondary outcome data stratified according to 3D versus 2D, and HD versus SD, endoscopy are summarised in Table 5.4 and Table 5.5 respectively. Post-hoc statistical analysis suggested that 3D endoscopy significantly improved perceived depth perception ($p < 0.001$), HD endoscopy significantly improved perceived image quality ($p < 0.001$), and both improved the overall likelihood participants would use again ($p < 0.001$). As the Kruskal-Wallis analysis failed to demonstrate a significant difference in the cognitive workload with different endoscopes no further analysis was performed.

		2DSD	3DSD	2DHD	3DHD	p
Time seconds*		69.5 (59.3 – 80.5)	53.5 (42.0 – 73.5)	58.5 (50.0 – 84)	51 (43.3 – 65.8)	0.005*
Accuracy*		14.5 (12.1 – 17.1)	15.3 (14.0 – 18.5)	16.3 (14.1 – 20.5)	18.0 (14.9 – 23.0)	0.021*
NASA-TLX		42.9 (36.4 – 62.0)	32.0 (26.5 – 43.3)	35.0 (29.1 – 52.8)	26.8 (22.4 – 37.9)	0.161
Likert scale	Quality*	2.0 (1.3 – 2.0)	3.0 (2.3 – 4.0)	4.0 (4.0 – 5.0)	5.0 (5.0 – 5.0)	<0.001*
	Depth*	2.0 (2.0 – 2.0)	4.0 (4.0 – 4.0)	3.0 (2.3 – 3.0)	4.0 (4.0 – 5.0)	<0.001*
	Overall*	2.5 (2.0 – 3.0)	3.0 (3.0 – 4.0)	4.0 (3.3 – 4.0)	5.0 (5.0 – 5.0)	<0.001*

Table 5.3. Summary of results according to endoscope used. Likert scale: 5 = High quality, excellent depth perception and overall would use again. 1 = Low quality, poor depth perception, and overall would not use again. Median (interquartile range) reported.

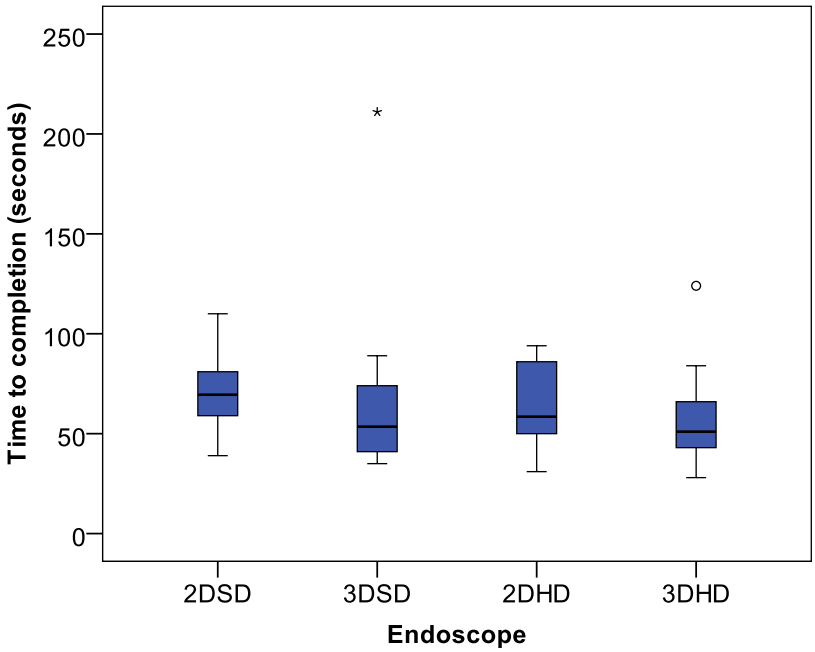


Figure 5.4. Graph illustrating time to completion with different endoscopes. Points represent outliers (circle greater than 1.5 times the interquartile range; star greater than 3 times the interquartile range)

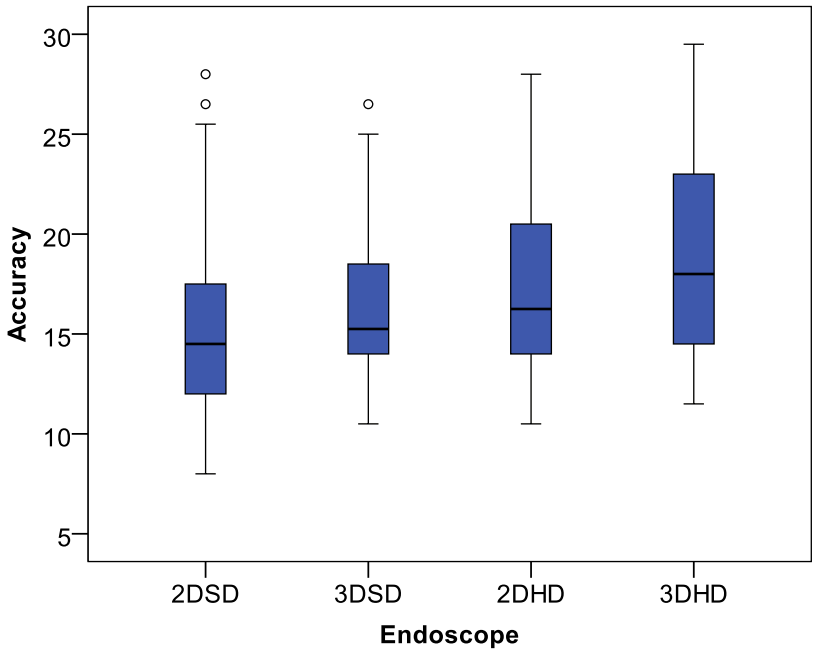


Figure 5.5. Graph illustrating accuracy of probe placement with different endoscopes. Points represent outliers (circle greater than 1.5 times the interquartile range)

		2D (2DSD and 2DHD)	3D (3DSD and 3DHD)	p
Time seconds		67.5 (52.0 – 81.3)	52.0 (42.5 – 68.3)	0.001*
Accuracy		15.5 (12.9 – 19.4)	17.0 (14.0 – 21.3)	0.085
NASA-TLX		39.7 (31.2 – 53.4)	28.9 (24.2 – 43.3)	N.A.
Likert scale	Quality	3.5 (2.0 – 4.0)	4.0 (3.0 – 5.0)	0.460
	Depth	2.0 (2.0 – 3.0)	4.0 (4.0 – 4.0)	<0.001*
	Overall	3.0 (2.8 – 4.0)	4.0 (4.0 – 5.0)	0.001*

Table 5.4. Summary of results stratified into 3D versus 2D. Median (interquartile range). Likert scale: 5 = High quality, excellent depth perception and overall would use again. 1 = Low quality, poor depth perception, and overall would not use again.

		SD (2DSD and 3DSD)	HD (2DHD and 3DHD)	p
Time seconds		63.0 (49.0 – 76.5)	54.0 (45.8 – 69.5)	0.110
Accuracy		14.8 (13.0 – 18.1)	17.5 (14.5 – 22.6)	0.009*
NASA-TLX		39.7 (27.5 – 47.8)	31.5 (22.6 – 45.5)	N.A.
Likert scale	Quality	2.0 (2.0 – 3.0)	5.0 (4.0 – 5.0)	<0.001*
	Depth	3.0 (2.0 – 4.0)	4.0 (3.0 – 4.3)	0.060
	Overall	3.0 (2.8 – 4.0)	4.0 (4.0 – 5.0)	<0.001*

Table 5.5. Summary of results stratified into SD versus HD. Median (interquartile range). Likert scale: 5 = High quality, excellent depth perception and overall would use again. 1 = Low quality, poor depth perception, and overall would not use again.

5.2.4 Discussion

5.2.4.1 Principal findings

The advantages of 3D and HD endoscopy have been demonstrated in other surgical fields but until recently the large size of such endoscopes restricted their use within the brain[203-207]. This preclinical randomised crossover study is the first to compare simultaneously the effectiveness of 3D versus 2D, and HD versus SD endoscopy. Interestingly, the effects of 3D and HD endoscopy appear to be distinct and complementary; the use of 3D versus 2D endoscopy led to a significant reduction in the time to task completion and a subjective improvement in depth perception, while the use of HD versus SD endoscopy led to a significant increase in the accuracy of probe placement and a subjective improvement in image quality.

5.2.4.2 Comparison with other studies

While no previous studies have addressed the influence of both 3D and HD endoscopy, similar studies have assessed their impact individually with varying results. The above systematic review summarised the limited and inconclusive clinical studies comparing 3D and 2D endoscopy. In addition, several preclinical studies have been performed[44, 209]. In the most widely cited of these, Fraser *et al* utilised the VisionSense II system (VisionSense, Petach Tikva, Israel) to compare 3D versus 2D endoscopy in a model simulating the transnasal transsphenoidal approach to the pituitary[44]. In all, 33 participants with varying levels of experience were asked to use a rongeur to remove the sellar floor, and then take 4 small pituitary biopsies. Although 3D endoscopy resulted in improved cutting efficiency ($p = 0.04$) and was subjectively the user preference, it was not associated with a significant difference in other primary outcomes such as time to completion or error rates.

Studies have also assessed the impact HD versus SD endoscopy on surgical performance. Schroeder *et al* reported higher image resolution and colour fidelity with HD endoscopy, particularly when discriminating tumour from neighbouring tissue during transnasal transsphenoidal approaches[45]. Conrad *et al* captured a series of images during endoscopic approaches and found significantly improved recognition of anatomical landmarks by surgeons when using HD versus SD cameras

(84.4% versus 63.0%; p = 0.012)[43]. The clinical significance of HD visualisation has not yet been ascertained, though it is commonly assumed.

The major limitation of all the above studies is that they address the effects of either 3D or HD endoscopy, rather than both, making it difficult to tease apart their relative importance, and the extent to which each can compensate for the other. It is well recognised, for example, that a number of monocular cues can contribute to depth perception such as motion parallax, the kinetic depth effect and pictorial cues (such as size, perspective, texture, interposition, lighting and shadow)[210-214]. It has been suggested that HD endoscopy, by allowing for improved recognition of these monocular cues, might obviate the need for stereoscopy[215]. The present study provides firm evidence that while 3D and HD endoscopy do individually improve surgical performance, they do so in different ways, and neither can fully compensate for lack of the other.

5.2.4.3 Limitations

It should be noted that this study has a number of limitations. First, although all participants were novices in endoscopic neurosurgery, two had substantial experience in laparoscopic surgery. Post-hoc analysis failed to demonstrate a significant difference between these two surgeons and the remaining participants, but it remains likely that this influenced their performance (albeit with a trend towards reduced time to task completion, and improved accuracy of probe placement). Second, while the task was based around similar externally validated measures of surgical performance, it has not itself been validated[216]. Moreover, the duration of the task may not have been long enough for participants to experience symptoms such as diplopia and nausea that have been described with prolonged use of 3D endoscopy. Third, while use of 3D endoscopes that were toggled to 2D, rather than dedicated 2D endoscopes, allowed control of the video capture and display hardware, it might have led to a somewhat lower image quality. Finally, an inherent limitation of the methodology was that video was captured using the endoscope being assessed and the accuracy of probe placement was therefore only partially blinded, with researchers able to distinguish HD versus SD, but not 3D versus 2D. Unfortunately, the small size of the

keyhole supraorbital craniotomy made it difficult to place a further endoscope or camera without obstructing access.

5.2.4.4 Conclusions

In conclusion, the results of this study may have considerable implications on endoscopic neurosurgical approaches. Importantly, the fact that 3D versus 2D and HD versus SD endoscopy had differing but complementary effects suggests that neither 3D nor HD alone can completely compensate for lack of the other. There is therefore strong preclinical evidence for the development and use of next generation 3D HD endoscopes, particularly for inexperienced surgeons, or when performing complex surgery. Further studies are merited to confirm that no side effects or adverse reactions occur with prolonged use, and that these findings are translated into improved surgical performance in a clinical setting.

Clearly the generalisability of these findings is likely to depend on several factors. In this study, only novice endoscopic neurosurgeons were included, in part because of the difficulty in recruiting sufficient numbers of experienced neurosurgeons (particularly as the sample size would have to be substantially larger to detect a presumably smaller effect on performance). The general surgical literature suggests that the influence of 3D versus 2D endoscopy on surgical performance is reduced or negated with experience, as surgeons learn to use monocular cues to judge distance[217]. The relative influence of 3D and HD endoscopy is also likely to vary depending on the nature of the surgical task performed. It is speculated that complex procedures such as neurovascular dissection would be far more influenced by the nature of the endoscope used than relatively straightforward procedures.

CHAPTER 6 TISSUE MANIPULATION: ROBOTIC ARTICULATED INSTRUMENTS*

*Content from this chapter was published or submitted as:

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Marcus HJ, Hughes-Hallett A, Pratt P, Clark J, Nandi D, Darzi A, and Yang GZ. Operating working spaces in keyhole neurosurgery; an MRI study. Hamlyn Symposium, London. June 2013

6.1 Tube-shaft and articulated instruments: A literature review

6.1.1 Introduction

There has been a steady evolution in neurosurgical instruments. At the inception of modern neurosurgery, large instruments designed for general surgery were routinely utilised through an extended craniotomy. With the advent of microsurgery, a set of smaller, and more precise, microinstruments were developed for use with a minicraniotomy. More recently, tube-shaft instruments have been increasingly utilised allowing for greater movement through keyhole craniotomies[26]. Alongside these advances in the overall instrument design, there has also been a corresponding expansion in the range of tools available, from generic instruments, to those tailored for specific procedures such as Endoscopic Third Ventriculostomy (ETV)[218]. Here, recent developments in both instrument design, and tools available, for endoscopic neurosurgery, are reviewed.

6.1.2 Search strategy

The Cochrane Central Register of Controlled Trials (CENTRAL), PubMed and EMBASE databases were searched between January 1990 and December 2014. Relevant combinations of free-text search terms [(instrument*)] AND [(endoscop*) OR (keyhole)] AND [(neurosurg*)]. An English language restriction was applied. Reference lists of selected papers were also reviewed and expert opinions sought to identify any missing manuscripts.

6.1.3 Tools

The majority of tube-shaft instruments used in keyhole neurosurgery are derived from general-purpose surgical instruments such as forceps, scissors, and dissectors[219] (Table 6.1). The development of electrocautery in 1928 was among the most important innovations in neurosurgery, allowing for controlled and precise haemostasis[220]. Bipolar electrocautery devices adapted for keyhole neurosurgery have been described in the literature[220-222]. Although early devices were needle electrodes, modern devices combine bipolar electrocautery with forceps and scissors, allowing for multifunctionality comparable to existing microsurgical instruments, and reducing the need for frequent instrument exchange[220, 221].

Novel instruments for endoscopic neurosurgery have also been developed to aid tissue manipulation. Water dissection has long been used for blunt dissection in the brain, and dedicated water jet devices have been successfully applied to cranial neurosurgery for almost 20 years[223]. Several of these water jet devices have been modified for use in endoscopic neurosurgery[224]. Oertel *et al* reported the use of a specially designed water jet device in four patients with obstructive hydrocephalus and concluded the instrument was safe, and may have helped reduce bleeding[224].

Ultrasonic aspirators are routinely used for brain tumour resection, but until recently have generally been considered too bulky for use in endoscopic neurosurgery. Selvanathan *et al* reported the use of a Micro ENP Ultrasonic Hand Piece (Soring GmbH, Quickborn, Germany) to debulk an intraventricular benign glioneuronal tumour[225]. Although the procedure was considered successful, the authors noted that visibility was transiently obscured by an air bubble caused by the aspirator; this raises important safety concerns that must be addressed before widespread dissemination.

The NICO Myriad (NICO, IN, USA) is another device that may be used for brain tumour resection. The device has a unique design, combining a high-speed reciprocating inner cannula within a stationary outer cannula, and controlled variable suction, to provide side-cutting aspiration[226]. In two recent case series' the device was found to be safe and effective in transcranial endoscopic approaches[226, 227].

Procedure-specific devices have also been applied to endoscopic neurosurgery (Table 6.1). Endoscopic Third Ventriculostomy (ETV), as one of the most commonly performed endoscopic procedures, has been the target of many such devices[228-230]. Multiple methods have described to facilitate dilatation of the floor of the third ventricle. Arguably the simplest technique is to simply push the endoscope itself against the floor of the ventricle until it is perforated. Alternatives to this blunt technique include the use of single or double-balloon catheters[230], or grasping forceps[229].

Name and company	Type	Features	Function	Selected Studies
XS Micro Instruments (Aesculap BBraun, Tuttlingen, Germany)	General purpose	6 Fr or 9 Fr shaft Replacement of components	Scissors and forceps	Cristante, 1999
Bipolar Microforceps (Erbe GmbH, Tubingen, Germany)	General purpose	4 Fr shaft Bipolar forceps	Bipolar electrocautery Forceps	Riegel, 2002
Bipolar Microscissors (Shanghai Second Medical University, Shanghai, China)	General purpose	Diameter of shaft unknown Combines bipolar and scissors	Bipolar electrocautery Scissors	Qiu, 2004
Pulsed Ho:YAG Laser-Induced Liquid Jet (Tohoku University, Sendai, Japan)	General purpose	4 Fr shaft Water jet	Dissection	Ohki, 2004
Helix Hydro-Jet (Erbe GmbH, Tubingen, Germany)	General purpose	8 Fr shaft Water jet	Dissection	Oertel, 2006
Monoshaft Bipolar Cautery (Nagoya University, Aichi, Japan)	General purpose	9 Fr shaft Bipolar electrocautery	Bipolar electrocautery	Nagasaka, 2011
Haemostatic Agent Delivery (University of Malaya, Kuala Lumpur, Malaysia)	General purpose	Diameter of shaft unknown	Delivery of haemostatic agents	Waran, 2011
NICO Myriad (NICO, IN, USA)	General purpose	6 Fr shaft Mechanical oscillation	Resection	Dlouhy, 2011; Garcia-Navarro, 2011

Name and company	Type	Features	Function	Selected Studies
Micro ENP Ultrasonic Hand Piece (Soring GmbH, Quickborn, Germany)	General purpose	9 Fr shaft Ultrasonic aspiration	Resection	Selvanathan, 2013
Atlas Wire Stone Extractor (Cook Medical, IN, USA)	Procedure specific	3 Fr shaft Urological basket retriever	Facilitates dilatation of the floor of the third ventricle	Wong, 1996
Modified grasping Forceps (Hopital Henri Mondor, Creteil, France)	Procedure specific	3 Fr shaft Grasping forceps	Facilitates dilatation of the floor of the third ventricle	Decq, 2000
Detachable Silicone Balloon (A. Manzoni Hospital, Lecco, Italy)	Procedure specific	2 Fr shaft Detachable silicone balloon	Treatment of CSF leak	Alfieri, 2002
Nitinol Stone Retrieval Basket (Boston Scientific, MA, USA)	Procedure specific	3 Fr shaft Urological basket retriever	Retrieval of resected intraventricular tumours	Schirmer, 2011
Gemini Paired Wire Helical Basket (Boston Scientific, MA, USA)	Procedure specific	3 Fr shaft Urological basket retriever	Retrieval of resected intraventricular tumours	Carr, 2013
NeuroBalloon (Integra, NJ, USA)	Procedure specific	4 Fr shaft Double barrel balloon	Facilitates dilatation of the floor of the third ventricle	Guzman, 2013

Table 6.1. Summary of existing tube-shaft instruments and their features. Fr = French.

6.1.4 Instrument design

Endoscopic neurosurgical approaches are characterised by keyhole craniotomies with narrow surgical trajectories to deep targets. Standard microsurgical instruments are ill suited to such approaches because their large size results in frequent clashing against the craniotomy edges, or each other[25, 26]. To this end, Axel Perneczky developed a range of tube-shaft instruments (Figure 6.1)[219]. These purpose-designed instruments represent an important advance in keyhole neurosurgical technique, allowing for more dextrous manipulation through keyhole craniotomies. While no studies have directly compared the use of tube-shaft and standard microsurgical instruments in keyhole neurosurgery, several case series' have reported their utility in such approaches[155, 231].



Figure 6.1. Pernecsky tube-shaft forceps (Aesculap AG, Tuttlingen, Germany).

Despite the aforementioned advantages, tube-shaft instruments continue to carry drawbacks. Most surgeons rest tube-shaft instruments against the edge of the craniotomy to minimise their physiological tremor, but this leads to a "fulcram effect" in which instrument tips move in the opposite direction to that of the surgeons hands; this phenomenon is well recognised in laparoscopic surgery, and can be overcome with training[232]. The use of long tube-shaft instruments may also be associated with reduced proprioceptive feedback, which is a considerable limitation when handling

the delicate neurovascular tissue of the brain. The forces exerted during sharp arachnoid dissection are often less than 0.01N, approaching a level many surgeons already find imperceptible[233, 234]; the corollary is that surgeons must learn to rely instead on visual cues such as tissue deformation. Arguably the greatest limitation of tube-shaft instruments, however, is the difficulty of triangulating through a single long and narrow surgical corridor, and within deep intracranial cisterns that may only be a few cm^3 in volume[235]. To this end, the control of instruments in keyhole neurosurgical approaches is almost co-axial, making relatively complex surgical manoeuvres such as suturing impossible even in expert hands[236].

Articulated instruments offer a theoretical advantage over standard tube-shaft instruments in allowing for improved triangulation through a single-port. Although at present no manual articulated instruments are available for keyhole neurosurgery, several instruments have been designed for use in Single Incision Laparoscopic Surgery (SILS), such as the 5-mm Roticulator set (Covidien, Dublin, Ireland), and the Handheld Autonomy Laparo-Angle Instruments (Cambridge Endo, Massachusetts, USA)[237, 238]. A major limitation with all these instruments is that they are non-ergonomic to handle, and carry a significant learning curve[239].

Advances in robotic surgery may mitigate or negate some of these limitations of manual articulated instruments, and also allow for reduction of physiological tremor and motion scaling[23, 218, 240]. The remaining work in this chapter seeks to better define the general and specific requirements for such robotic articulated instruments, culminating in a feasibility study of devices currently under development.

6.2 Comparative performance of single-port versus multi-port surgery, and small versus large operative working spaces, using existing instruments: A preclinical randomised study

6.2.1 Introduction

Minimally invasive surgery (MIS) is arguably the greatest innovation in surgery of the last 30 years[58, 241]. Although most surgeons can perform the majority of multi-port adult laparoscopic surgery safely and effectively, the clinical penetration of MIS in other specialties has been variable (Table 6.2).

Single-port laparoscopic surgery has been suggested as a less invasive alternative to standard multi-port laparoscopic surgery, but is more technically challenging, principally due to the difficulty triangulating standard instruments[242-245]. Paediatric laparoscopic surgery may also be more technically challenging than standard adult laparoscopic surgery because of the difficulty manipulating instruments within small operative working spaces[246]. Surgical approaches incorporating the smallest operative working spaces, and are necessarily single-port, such as transcranial endoscopic microsurgery, are particularly demanding, and have not been widely adopted by their respective surgical communities[26, 247, 248].

To date, several studies have compared surgical performance in single-port versus multi-port approaches[232, 243, 244], but few have compared performance in small versus large working spaces[246], and no previous studies have evaluated the influence of both variables simultaneously. The primary aim of this study was therefore to compare simultaneously surgical performance in single-port versus multi-port approaches, and small versus large working spaces. The secondary aim was to validate modified tasks and a custom training box to simulate single-port surgical approaches in the smallest operative working spaces.

Working space	Multiple Ports	Single Port
Large 34,225 cm^3 (Fundamentals of Laparoscopic Surgery box trainer)	Adult laparoscopy	Single Incision Laparoscopic Surgery (SILS)
Intermediate 1620 cm^3 (Paediatric Laparoscopic Surgery box trainer)	Paediatric laparoscopic surgery	Paediatric Single Incision Laparoscopic Surgery
Small 81cm^3		Transanal Endoscopic Microsurgery Transoral Endoscopic Microsurgery Transcranial Endoscopic Microsurgery

Table 6.2. Examples of multi-port versus single-port surgery, in large, intermediate and small working spaces.

6.2.2 Materials and Methods

6.2.2.1 Participants and study settings

Ten novice (<10 laparoscopic procedures per year), and five intermediate or expert (10-50, and >50 laparoscopic procedures performed per year respectively) surgeons, were recruited from one university hospital. Informed consent was obtained from all participants. It was decided *a priori* that intermediate and experts surgeons would be combined for subsequent analysis.

All participants underwent a single training session to familiarise themselves with the instruments and tasks. A total of 5 repetitions were performed in each of the trial conditions (see trial design below); previous studies have demonstrated that such practice is usually sufficient to overcome the initial learning phase[249].

6.2.2.2 Trial design

A preclinical randomised crossover study design was implemented, comparing performance under the following conditions: (1) multi-port approach and large working space, (2) multi-port approach and intermediate working space, (3) single-port approach and large working space, (4) single-port approach and intermediate working space, and (5) single-port approach and small working space.

An Adult Fundamentals of Laparoscopic Surgery (FLS) trainer box, with internal dimensions 180 x 100 x 90mm, and a volume of 34,225cm^3, was used for the large working space (Figure 6.2). A Paediatric Laparoscopic Surgery (PLS) trainer box, with internal dimensions 500 x 370 x 185mm, and a volume of 1620cm^3 (reduced by a factor of 20), was used for the intermediate working space. A custom cuboid with dimensions 30 x 30 x 90mm, and a volume of 81cm^3 (reduced by a further factor of 20), was used for the small working space; this is representative of, for example, transcranial approaches[157, 250, 251]. In multi-port approaches, the endoscope port was located at the top centre of the adjacent face of the cuboid, with instruments ports on either side. In single-port approaches, a SILS^{TM} port (Covidien, Massachusetts, USA) was located at the top centre of the adjacent face of the cuboid. The tasks were placed

on a base such that the manipulation angle was 45º, allowing for optimal ergonomics[252].



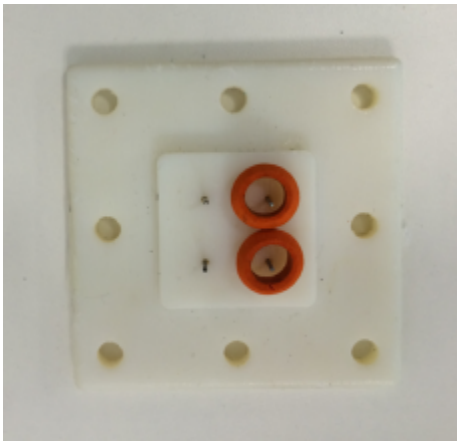
Figure 6.2. Adult FLS trainer box (left), paediatric PLS trainer box (centre), and custom box (right), representing large, intermediate, and small working spaces respectively.

The peg transfer and pattern cutting drills were selected from the McGill Inanimate System for Training and Evaluation of Laparoscopic Skills (MISTELS)[216], to represent simple and complex tasks respectively. The drills were modified so as to fit within all the working spaces, including the 30mm cuboid. The peg transfer drill requires that rings on the left side of the pegboard are grasped with the instrument in the left hand, lifted off the peg, transferred to the instrument in the right hand, and then placed on the right side of the pegboard. After all the pegs are transferred, the process is reversed. The size of the rings were reduced by approximately a factor of 4 compared to the adult drill (height 4mm versus 19mm), and the number of rings transferred reduced to 2. The cutting drill was chosen because it requires considerable dexterity[157] and, unlike suturing, cutting is performed in most MIS procedures[253]. The pattern cutting drill requires participants use scissors to cut a 20mm diameter circular pattern from a square piece of gauze. The diameter of the circular pattern was also be reduced by a factor of 2 compared to the adult drill (20mm versus 40mm). The use of smaller peg transfer and pattern cutting tasks with single and multi-port approaches have been previously validated in paediatric laparoscopic surgery simulators[246]. Novices, intermediates, and experts, were also recruited for further evidence of construct validity.

Conventional 5mm rigid laparoscopic graspers and scissors (Ethicon Endo-Surgery™, Ohio, USA) were used for manipulation. A VisionSense III endoscopy system (VisionSense, Petach Tikva, Israel) was used for visualisation. The HD 0 degree rigid endoscope is 4mm in diameter, and 18cm in length, providing a resolution of 1920 x 1200 pixels. Images were displayed using a 24" stereoscopic screen.

Participants were randomly allocated using a computer-generated sequence to determine the order of the experimental conditions in which they performed the drills. Each participant was asked to perform the drills once in each condition, with participants given a maximum of 100 seconds to perform the peg transfer task, and 300 seconds to perform the pattern cutting task.

a.



b.

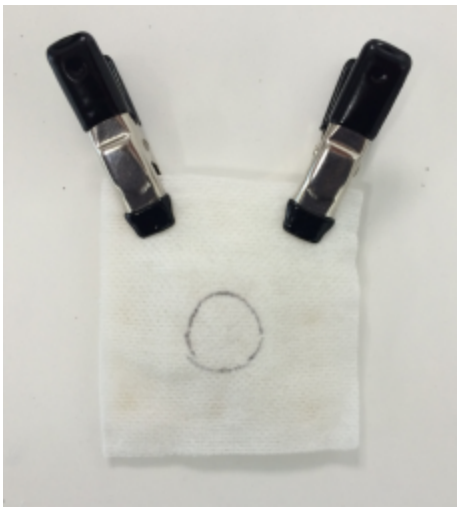


Figure 6.3. Modified (a) peg transfer and (b) pattern cutting tasks.

6.2.2.3 Outcomes

The primary outcome was the total score (non-normalised MISTELS based criteria[216]). For the peg transfer drill: timing score = 100 seconds minus task completion time (seconds); penalty score = percentage of pegs dropped outside the field of view, or outside of reach; total score = timing score minus penalty score. For the pattern cutting drill: timing score = 300 seconds minus time to complete the exercise (seconds); penalty score = percentage area of deviation from a perfect circle; total score = timing score minus penalty score.

Whereas participants were aware of the instruments they are using, the data analysts were blinded to their allocation.

6.2.2.4 Statistical analysis

The sample size was calculated on the basis of recently published work that reported the total score of novices performing the pattern cutting drill using standard instruments was 52 ± 16[246], and on a pilot study using the above methadology. It was estimated that to detect a 50% increase in total score in experts, with a two-sided 5% significance level and a power of 80%, a sample size of at least 8 novice surgeons, and 4 intermediate-expert surgeons, was necessary.

Data were analysed with SPSS v 20.0 (IBM, Illinois, USA). A value of $P < 0.05$ was considered statistically significant. The median and interquartile ranges (Q1-Q3) were calculated for the primary outcome measures. The Mann-Whitney *U* test was used to compare performance between novices and intermediates-experts in each of the study conditions to evaluate construct validity. Performance was then compared in the different study conditions using the Kruskal-Wallis one-way analysis of variance. If a significant difference was identified, the following groups were then directly compared, with the Bonferroni correction ($n = 5$; $p < 0.01$): any multiple ports versus any single port; multiple ports with large working space versus medium working space; single port with large working space versus medium working space; single port with large working space versus small working space; and single port with medium working space versus small working space.

6.2.3 Results

6.2.3.1 Baseline demographic data

The demographics of the participants are summarised in Table 6.3. The expert surgeon had experience with both standard multi-port surgery and single-port surgery (including approximately 50 TEMS procedures). All participants that were enrolled completed the study, and no losses occurred after randomisation.

	Age, Median (range), years	**Sex, Male:Female**	**Handedness, Right:Left**
Novice (n = 10)	27.5 (22-33)	7:3	10:0
Intermediate (n = 4)	31 (29-33)	4:0	4:0
Expert (n = 1)	34	1:0	1:0
Overall (n = 15)	28 (22-33)	12:3	15:0

Table 6.3. Participant demographics.

6.2.3.2 Outcomes

The median and interquartile ranges of performance for the modified peg transfer and pattern cutting tasks are summarised in Table 6.4 and Table 6.5 respectively. The intermediate-experts performed significantly better than novices in all conditions, confirming construct validity of the modified tasks and custom box trainer ($p < 0.05$; Table 6.4 and Table 6.5).

Working space	Multiple ports		Single port	
	N	I-E	N	I-E
Large	57 (42.5 – 63.8)	71 (70 – 76)	-7.5 (-42.5 – 1.5)	52 (40 – 55)
	p = 0.004		p = 0.007	
Medium	49 (45.8 – 54.8)	73 (71 – 76)	28.5 (2.5 – 45.5)	67 (60 – 70)
	p = 0.022		p = 0.047	
Small			38 (16 – 47.5)	63 (60 – 66)
			p = 0.019	

Table 6.4. Performance of the modified peg transfer task. Probabilities represent comparison between novice and intermediate-expert performance. N = Novice, I-E = Intermediate-Expert.

Working space	Multiple ports		Single port	
	N	**I-E**	**N**	**I-E**
Large	152.5 (117.5 – 174.5)	215 (202 – 223)	-35 (-100 – 47.5)	120 (115 – 121)
	p = 0.003		p = 0.014	
Medium	150 (125.3 – 168.8)	188 (176 – 199)	69.5 (-7 – 140.8)	155 (154 – 195)
	p = 0.024		p = 0.050	
Small			75.5 (6 – 97.3)	167 (135 – 195)
			p = 0.010	

Table 6.5. Performance of the modified pattern cutting task by novices and intermediates-experts. Probabilities represent comparison between novice and intermediate-expert performance. N = Novice, I-E = Intermediate-Expert.

6.2.3.2.1 Peg transfer

The Kruskal-Wallis one-way analysis of variance demonstrated significant variation in the performance of novices in the different study conditions ($p < 0.001$; Figure 6.4). Performance in single-port surgery was significantly worse than multi-port surgery ($p < 0.001$). Performance with multi-port surgery and a large working space was not significantly different to a medium working space ($p > 0.1$). Performance with single-port surgery and a large working space was worse than a medium or small working space, approaching significance ($p = 0.089$ and $p = 0.011$ respectively).

The Kruskal-Wallis one-way analysis of variance also demonstrated significant variation in the performance of intermediates-experts in the different study conditions ($p < 0.001$). Performance in single-port surgery was significantly worse than multi-port surgery ($p = 0.001$). Working space did not significantly influence the performance of experts ($p > 0.1$).

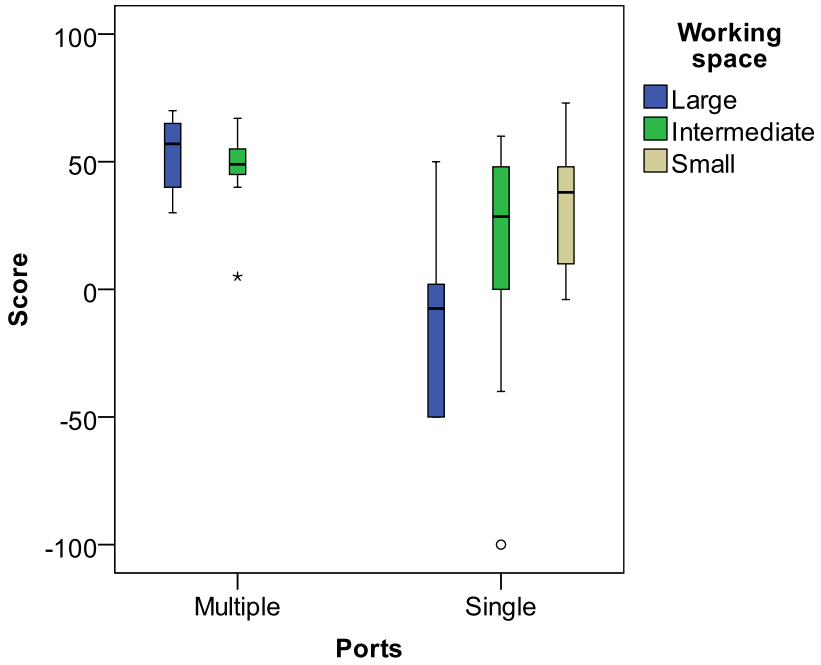


Figure 6.4. Performance of the modified peg transfer tasks by novices in different experimental arrangements. Points represent outliers (circle greater than 1.5 times the interquartile range; star greater than 3 times the interquartile range).

6.2.3.2.2 Pattern cutting

The findings for the pattern cutting task were comparable to the peg transfer task. The Kruskal-Wallis one-way analysis of variance demonstrated significant variation in the performance of novices in the different study conditions ($p < 0.001$; Figure 6.5). Performance in single-port surgery was significantly worse than multi-port surgery ($p < 0.001$). Performance with multi-port surgery and a large working space was not significantly different to a medium working space ($p > 0.1$). Performance with single-port surgery and a large working space was worse than a medium or small working space, approaching significance ($p = 0.075$ and $p = 0.026$ respectively).

The Kruskal-Wallis one-way analysis of variance also demonstrated significant variation in the performance of intermediates-experts in the different study conditions ($p < 0.001$). Performance in single-port surgery was significantly worse than multi-port surgery ($p = 0.004$). Working space did not significantly influence performance in experts ($p > 0.1$).

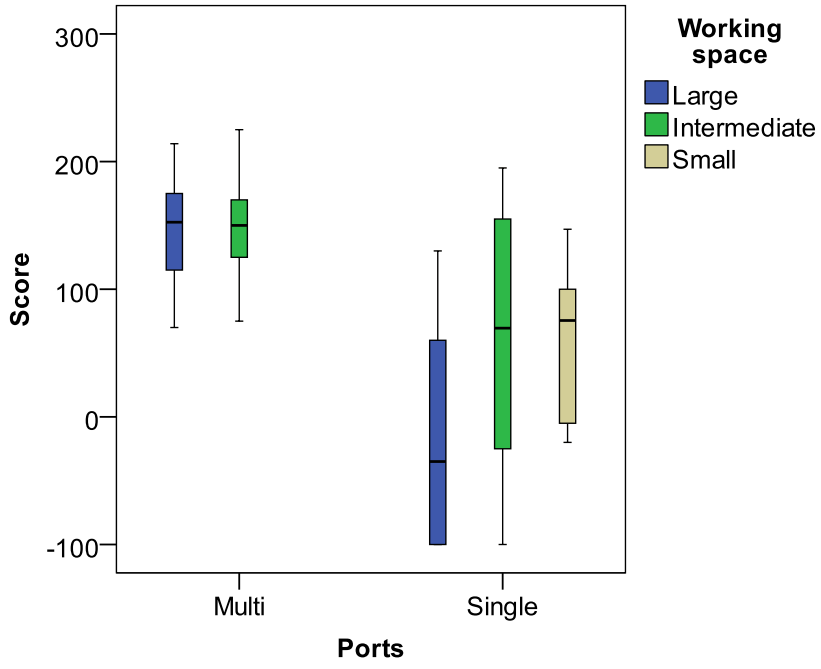


Figure 6.5. Performance of the modified pattern cutting tasks by novices in different experimental arrangements.

6.2.4 Discussion

6.2.4.1 Principal findings

This study has successfully validated modified tasks and a custom training box to simulate single-port surgical approaches in the smallest operative working spaces. Moreover, this study has compared simultaneously performance in single-port versus multi-port approaches, and small versus large working spaces. In keeping with previous studies, single-port approaches were found to be significantly more technically challenging than multi-port approaches, irrespective of the level of experience of the surgeon, or the nature of the surgical task performed, reflecting loss of instrument triangulation[243, 244]. Interestingly, the influence of working space on surgical performance was variable. In multi-port approaches, there was a non-significant trend towards worsened performance in smaller working spaces, perhaps resulting from reduced triangulation, as the instrument ports were necessarily placed closer together. In single-port approaches, in which triangulation was no longer a factor, performance in large working spaces was, surprisingly, worse than in intermediate and small working spaces.

6.2.4.2 Comparison with other studies

Several studies have previously compared the performance of surgeons when performing laparoscopic tasks through single-port versus multi-port access. Cox *et al* randomised 40 medical students into two groups, using single-port and multi-port access[244]. Both groups were trained in four basic laparoscopic drills (including peg transfer and pattern cutting), before being crossed over to the alternate approach. Participants in the single-port group took more time to reach proficiency (178.0 ± 93.4 versus 119.1 ± 69.7 min; $p = 0.058$), with significantly greater repetitions (118.8 ± 54.3 versus 77.6 ± 42.6; $p = 0.027$). Santos *et al* and Lewis *et al* performed similar randomised crossover studies, confirming these findings in novice surgeons, and also suggesting that experience can mitigate, at least to some extent, the technical barriers associated with loss of triangulation in single-port surgery[243, 245].

Few studies have looked at the affect of working space on performance of laparoscopic surgery; though many surgeons have argued that operating within

smaller working spaces such as the paediatric abdomen is inherently more technically challenging than standard laparoscopy[246]. Azzie *et al* developed and validated the Pediatric Laparoscopic Surgery (PLS) box trainer simulator used in the present study, and found that the revised total PLS scores in their simulator were considerably worse than in the adult FLS trainer box[246]. The present study also trended towards worsened performance in multi-port approaches in the PLS trainer box, compared to the adult FLS trainer box. However, in contrast to the aforementioned multi-port approaches, there was a trend towards *improved* performance in single-port approaches in smaller working spaces. It is speculated that this may be the result of instruments being more frequently lost outside the operative field when performing tasks through single-port approaches and large working spaces, particularly in the hands of novices. Nonetheless, no previous studies have previously assessed the impact of smaller working spaces in single-port approaches, and further investigation is merited to confirm and extend these findings.

6.2.4.3 Limitations

It should be noted that this study has limitations. Intermediate and expert surgeons were combined for analysis due to lack of experts familiar with uncommon and difficult single-port approaches in the smallest operative working spaces. Nonetheless, the significant difference in performance between novices and intermediates-expert surgeons supports use of modified tasks and a custom box trainer.

The sizes of the tasks themselves, while appropriate in the small custom and intermediate paediatric training boxes, may have been mismatched in the large adult FLS training box. While this does not in itself invalidate the findings of this study, it suggests that it is not the physical constraints of the operating working space *per se* but rather the size of the tasks themselves that may be particularly important in determining operative performance. This may, at least to some extent, explain the reason that performance in smaller working spaces was not significantly worse and, in single-port approaches, actually better than in larger working spaces, despite an abundance of anecdotal evidence to the contrary.

6.2.4.4 Conclusions

The generalisability of this study is likely to depend on several other factors including the experience of the surgeon with a particular approach, the instruments and endoscopes used, and the size and complexity of the surgical task performed. Nonetheless, the finding that instrument triangulation is perhaps the most critical determinant of surgical performance is likely to hold true, and has been corroborated by other groups comparing multi-port and single-port approaches[242-245]. This general insight supports efforts to improve the performance of surgeons in single-port approaches through robotic articulated instruments. The following three studies in this chapter quantify the working spaces, forces, and instruments, used in microneurosurgery, in order to provide detailed specifications for such instruments.

6.3 Operative working spaces: An MRI study

6.3.1 Introduction

The central dogma of keyhole neurosurgery is the minimisation of intraparenchymal dissection and reduction of exposure and retraction of unaffected brain tissue in order to reduce approach related morbidity. The next generation of progress in this field would seek to further exploit the natural anatomical corridors and cerebrospinal fluid (CSF) pathways within the brain. The latter have already been extensively used for conventional microneurosurgery. The challenge lies in the difficulty of triangulating rigid tube-shaft instruments and performing fine dissection of delicate neurovascular structures through a narrow working channel. The construction of robotic platforms with articulated instruments may allow improved manipulation through keyhole approaches. A necessary prerequisite for these platforms is knowledge of the microsurgical anatomy of these working spaces.

The aim of the present study was to anatomically define and measure the intracranial cisterns utilised during keyhole neurosurgical approaches in a high-resolution Magnetic Resonance Imaging (MRI) brain atlas.

6.3.2 Materials and Methods

A literature search was performed to define the working spaces of the suprasellar, quadrigeminal and cerebellopontine cisterns[254]. The SRI24 multichannel atlas of normal human brain structure was used as a reference system[255]. The SRI24 atlas was recently developed using template-free registration of 3T MRI images of 24 normal control volunteers (12 male and 12 female; 12 young and 12 elderly), and is unique in being well suited to both spatial normalisation and label propagation (atlas-based segmentation).

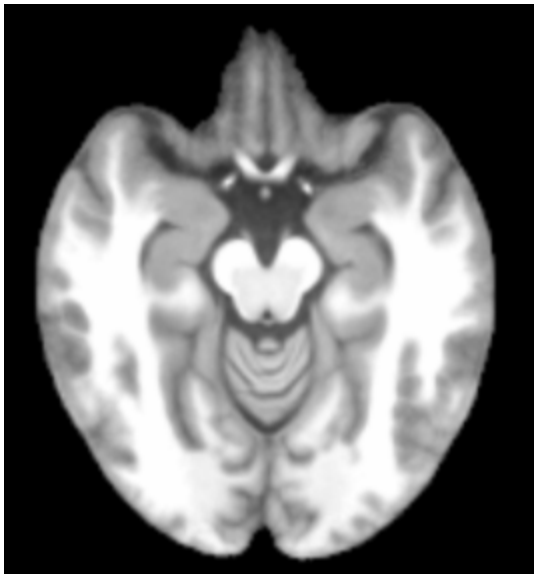


Figure 6.6. SRI24 Axial T1-weighted MRI illustrating the suprasellar cistern bordered by gyrus rectus of the frontal lobes anteriorly, uncus of the temporal lobes laterally, cerebral peduncles posterolaterally, and the interpeduncular cistern posteriorly.

Atlas files were converted to DICOM using MedCon v0.12.0. Two independent observers measured distances on T1-weighted MRI using the OsiriX Imaging Software v5.6 (Figure 6.6), and segmented and measured volumes using itk-SNAP v2.4.0[192]. Mean values for distances and volumes were calculated, and the concordance correlation coefficient between the two observers determined.

6.3.3 Results

The SRI24 atlas was crisp enough for region definition, allowing precise atlas-based segmentation. Distances and volumes are summarised in Table 6.6.

Cistern	A-P	S-I	Lat	Volume
Suprasellar	25mm	18mm	20mm	6525mm^3
Quadrigeminal	17mm	16mm	20mm	2953mm^3
Cerebellopontine	20mm	19mm	15mm	3428mm^3

Table 6.6. Dimensions of the suprasellar, quadrigeminal and cerebellopontine cisterns. A-P = Anterior-Posterior; S-I = Superior-Inferior; Lat = Lateral.

The concordance correlation coefficient was: ρ (precision) = 0.97, C_b (accuracy) = 0.99, and $\rho_c = 0.96$.

6.3.4 Discussion

This study has successfully extracted information on the deep cisterns that are utilised in keyhole neurosurgical approaches using a novel MRI atlas that incorporates data from multiple volunteers while maintaining salient anatomical features. The suprasellar cistern was the largest of those assessed; supporting the use of the keyhole supraorbital approach as an index procedure for putative robotic platforms.

A limitation of this study is that the cistern volumes may be altered intra-operatively by numerous factors. However, it is likely that during actual operations the working spaces encountered will be greater as CSF is drained, and instruments are used dynamically retract tissue.

6.4 Forces exerted: A cadaver study

6.4.1 Introduction

The evolution of neurosurgery has been towards increasingly delicate and safe surgical technique. Surgical robotics, which has the ability to eliminate tremor, and scale movements, has the potential to greatly enhance surgical performance. A prerequisite for the successful design and use of such robots is knowledge of the surgical instrument forces exerted by surgeons during neurosurgical procedures. The advent of surgical robotics may in turn allow, for the first time, the forces exerted during neurosurgical procedures to be routinely recorded[48, 256-258]. The corollary is that expert performances might be analysed to determine the optimal force ranges utilised when performing robot-assisted neurosurgical procedures, providing quantitative feedback to trainees to further their development, and allowing for the possibility of force limits to be set to improve surgical safety[258].

Despite an abundance of anecdotal data on the instrument forces exerted during neurosurgical procedures, there remains a lack of quantitative data in the field. To date, the majority of studies addressing the forces necessary to manipulate brain tissue are either non-penetrating indentation studies designed to estimate the elastic properties of the brain[259-263], or penetration studies designed to estimate the forces required for probe insertion[264-267]. No studies have yet assessed the forces exerted during cranial microsurgery such as arachnoid dissection. To this end, the aim of the present study was to measure the surgical instrument forces exerted during robot-assisted microneurosurgery by performing a human cadaver study.

6.4.2 Materials and Methods

An experimental apparatus was set up consisting of a platform for brain specimens, a Leica microscope (Leica Microsystems GmbH, Wetzlar, Germany) to provide illumination and magnification, and a Quanser 6 Degrees-Of-Freedom (DOF) Telepresence System (Quanser Inc, Ontario, Canada) for tissue manipulation and force measurements (Figure 6.7). The robotic master-slave setup included a DENSO VP Series 6-Axis Articulated Robot and the control module (DENSO Robotics, Aichi, Japan), Gamma Multi-Axis ATI Force/Torque Sensor (ATI Industrial Automation,

North Carolina, USA) equipped with a 16-Bit Data Acquisition Board (National Instruments, Texas, USA) for force/torque measurements, and a High-Definition Haptic Device (HD^2) with the capability of providing 6 DOF force/torque feedback to the operator; this configuration allowed for a continuous force feedback. The robot utilised an open-architecture interface with the QuaRC 2.2 (Quanser Real-time Control) Denso Robot block-set, alongside Simulink® (Mathworks, Massachusetts, USA), Matlab® (Mathworks, Massachusetts, USA) and Windows® (Microsoft, Washington, USA). The force/torque sensor was located between the DENSO Robot's end-effector and tool holder and measured 6 DOF force/torque with a capacity of 32N and a resolution of 0.01N. There were no force or position scaling involved and the ratio of force/torque feedback from the robot sensor to the haptic controller was set to 1:1. Calibration was independently verified using a Chatillon Diital Force Gauge (AMETEK, Florida, USA) with a capacity of 10N and accuracy of 0.01N.

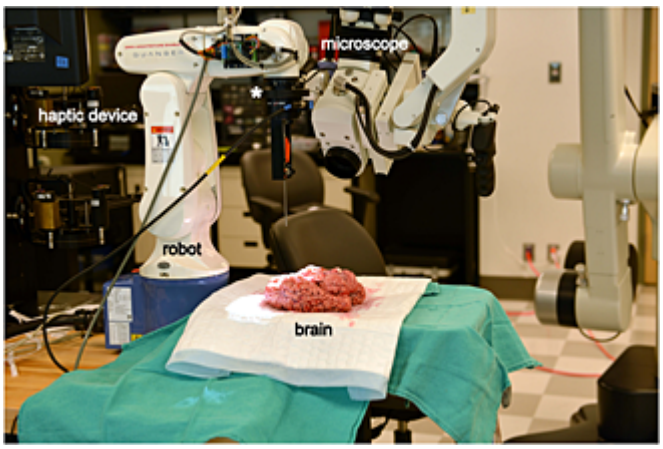


Figure 6.7. Experimental rig consisting of a platform for brain specimens, a Leica microscope, and a Quanser 6 DOF Teleoperation system. White star = location of the force/torque sensor between the DENSO Robot's end-effector and the tool-holder.

Two fresh brain specimens were utilised for the study (Body Donation Program, Department of Anatomy, University of Calgary, Alberta, Canada). Brains were removed from their respective cranial cavities and dural sacs, leaving the brain, arachnoid and pia. In each specimen, a neurosurgical trainee was asked to coagulate the brain surface using bipolar electrocautery on the 15W setting and then perform a sequence of simple procedures: (1) a Beaver Mini-Blade was used to incise the

coagulated area, (2) the Mini-Blade was used to carry the incision to a length of approximately 30mm, and (3) a No 6 Rhoton spatula dissector with a 1.1mm tip was inserted to a depth of approximately 5mm and used to retract the brain approximately 5mm. These manoeuvres were carried out in the cerebrum (gyrus rectus, middle frontal gyrus, inferior temporal gyrus), cerebellum (hemispheres, vermis) and brainstem (midbrain, pons, medulla); and each was repeated twice on each side of the brain, unless it was too technically difficult to do so. In addition, the forces required to perform a corpus callosotomy and perforate the floor of the third ventricle were also measured.

The Beaver Mini-Blade and No 6 Rhoton dissector were also used to perform sharp and blunt dissection of the Circle of Willis respectively. An observer carefully took note of iatrogenic injury to neurovascular structures during dissection (such as injury to tearing of small perforators). In cases of uncertainty, injury was recorded as having occurred.

Force vector data was produced each 0.2ms (5 KHz). A Matlab® program was developed and used to extract data each 10ms (100 Hz) and record in an Excel spreadsheet, and force vectors were summated. Statistical software (SPSS 20.0.0; IBM, New York, USA) was then used to calculate the median, interquartile range and maximal forces during individual procedures. The Mann-Whitney U test was used to compare the surgical instrument forces exerted in each brain specimen, and on the left- and right-side of the brain. The Kruskal-Wallis test was used to compare the forces exerted when performing different procedures, and between different brain regions; if significance was demonstrated post-hoc analysis was performed using the Mann-Whitney U test, with the Bonferroni correction. The Mann-Whitney U test was then used to compare the forces exerted when performing sharp and blunt dissection, and the manoeuvres that resulted in iatrogenic injury against those that did not. The threshold for significance was set at 5%.

6.4.3 Results

In all, there was no significant difference in forces exerted between the two brain specimens, and between the left- and right-sides of the brains ($p > 0.1$). The median

and interquartile ranges of forces exerted when performing different procedures in different brain regions are summarised in Table 6.7. The median force exerted when performing different procedures was significantly different ($p < 0.0001$); performing stab incisions (0.01N) required significantly less force than carrying incisions (0.05N; $p < 0.0001$) or retracting brain tissue (0.08N; $p < 0.0001$). The median force exerted when manipulating different regions of the brain was also significantly different ($p = 0.016$); manipulating the brainstem (0.05N) required significantly greater force than manipulating the cerebellum (0.02N; $p = 0.022$) or cerebrum (0.03N; $p = 0.013$).

Illustrative examples of the forces exerted over time during individual manoeuvres are shown in Figure 6.8. The median, interquartile ranges, and maximal forces exerted when performing sharp and blunt arachnoid dissection around the Circle of Willis are summarised in Table 6.8 and Figure 6.9; manoeuvres are stratified according to whether they did or didn't result in iatrogenic injury. The median force exerted during blunt dissection (0.22N) and sharp dissection (0.03N) was significantly different ($p = 0.001$). When performing sharp dissection the median force during manoeuvres in which iatrogenic injury occurred (0.28N) and those in which it did not (0.02N) was significantly different ($p = 0.011$). When performing blunt dissection the median force during manoeuvres in which iatrogenic injury occurred (0.60N) and those in which it did not (0.11N) was also significantly different ($p = 0.004$).

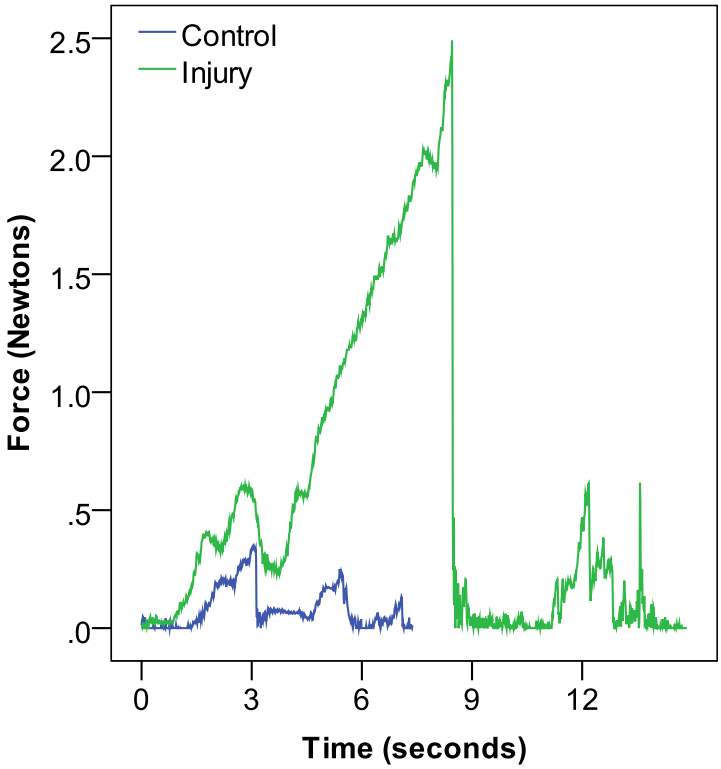
		Median (interquartile range)		
		Stab Incision	**Carrying Incision**	**Retraction**
Cerebrum (n = 24)	Gyrus rectus (n = 8)	<0.01 (0.00 – 0.03)	0.02 (0.01 – 0.03)	0.03 (0.03 – 0.05)
	Inferior temporal gyrus (n = 8)	<0.01 (0.00 – 0.01)	0.02 (0.00 – 0.03)	0.07 (0.06 – 0.09)
	Middle frontal gyrus (n = 8)	<0.01 (0.00 – 0.01)	0.15 (0.12 – 0.18)	0.08 (0.06 – 0.10)
Cerebellum (n = 12)	Cerebellar hemisphere (n = 8)	0.01 (0.00 – 0.01)	0.03 (0.02 – 0.04)	0.08 (0.02 – 0.13)
	Cerebellar vermis (n = 4)	0.02 (0.01 – 0.02)	0.12 (0.12 – 0.12)	N.A.
Brainstem (n = 22)	Midbrain (n = 6)	0.01 (0.00 – 0.01)	0.11 (0.04 – 0.26)	0.15 (0.13 – 0.20)
	Pons (n = 8)	<0.01 (0.00 – 0.01)	0.05 (0.04 – 0.06)	0.18 (0.12 – 0.21)
	Medulla (n = 8)	0.01 (0.01 – 0.03)	0.09 (0.06 – 0.16)	0.09 (0.06 – 0.11)
Other (n = 8)	Corpus callosum (n = 4)	0.01 (0.00 – 0.03)	0.23 (0.09 – 0.43)	N.A.
	Perforating floor of 3rd ventricle (n = 4)	<0.01 (0.00 – 0.01)	N.A.	N.A.

Table 6.7. The median (interquartile range) of forces exerted (Newtons) when performing simple procedures in different brain regions. N.A. = Not Applicable.

		No injury (n = 32)	Injury (n = 6)
Sharp arachnoid dissection (n = 28)	Median (interquartile range)	0.02 (0.01 – 0.13)	0.28 (0.26 – 0.31)
	Maximum	1.33	2.49
Blunt arachnoid dissection (n = 12)	Median (interquartile range)	0.11 (0.08 – 0.18)	0.60 (0.53 – 0.75)
	Maximum	2.04	4.28

Table 6.8. The median (interquartile range) and maximum forces (Newtons) exerted when performing sharp and blunt dissection of the Circle of Willis.

a.



b.

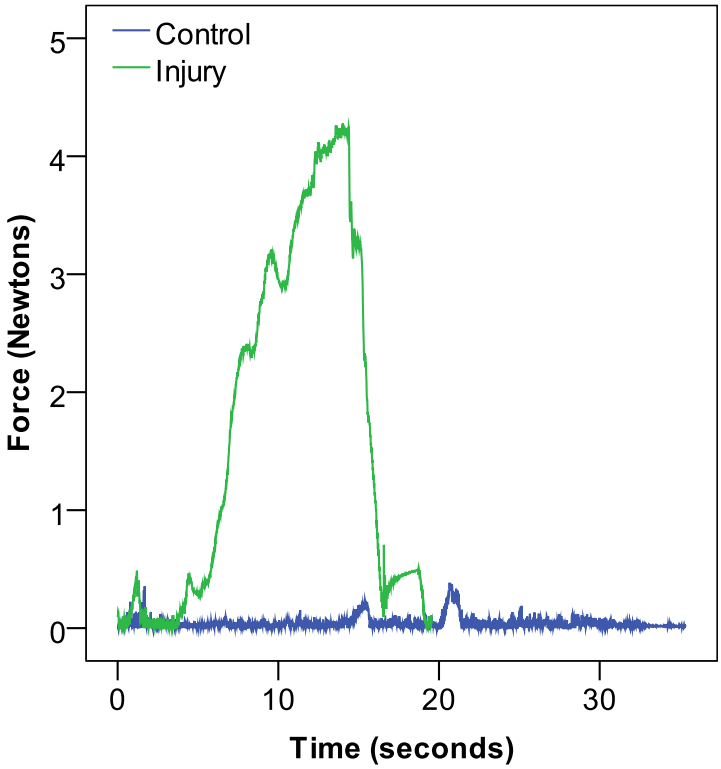


Figure 6.8. Illustrative examples of the forces exerted over time when performing individual manoeuvres, stratified according to whether they did or didn't result in iatrogenic injury, during (a) sharp dissection and (b) blunt dissection.

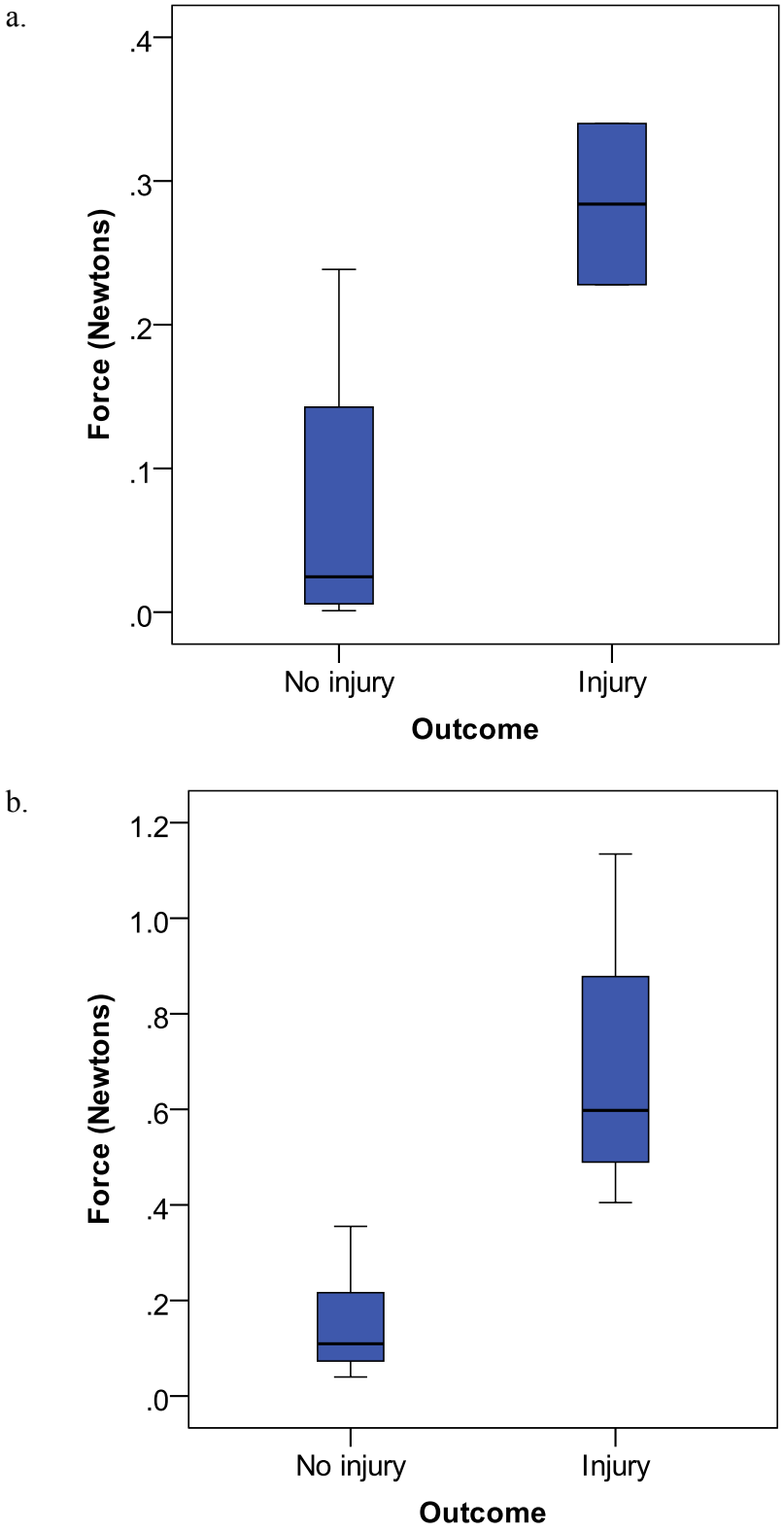


Figure 6.9. Box plot illustrating the median forces exerted (Newtons) during (a) sharp and (b) blunt dissection around the circle of Willis, stratified according to whether they did or didn't result in iatrogenic injury.

6.4.4 Discussion

6.4.4.1 Principal findings

In this study the surgical instrument forces exerted during a number of procedures on fresh cadaver brains were successfully determined. The measured forces varied depending on the region of the brain and the manoeuvre performed. Significantly greater force was exerted when manipulating the brainstem (0.05N) than the cerebellum (0.02N; $p = 0.022$) or cerebrum (0.03N; $p = 0.013$), and significantly less force was exerted when performing stab incisions (0.01N) than carrying incisions (0.05N; $p < 0.0001$) or retracting brain tissue (0.08N; $p < 0.0001$). Moreover, blunt arachnoid dissection with a Rhoton No 6 dissector was associated with greater force exertion than sharp dissection with a Beaver Mini-Blade.

6.4.4.2 Comparison with other studies

Existing literature on the forces exerted during neurosurgical procedures is sparse. Several studies have evaluated the mechanical properties of the brain itself through non-penetrating indentation experiments[259-263]. As early as 1976, Walsh *et al* measured the elastic response of brain tissue in dogs using a diaphragm-type pressure sensor mounted co-linear with a displacement transducer, and described a nonlinear response[259]. Miller et al conducted a study on an exposed porcine brain and reported that approximately 0.3N was required for up to 4mm of brain displacement, slightly greater than predicted by their hyper-viscoelastic constitutive model[261]. Gefen *et al* performed a similar non-penetrating indentation study on exposed porcine brains, comparing the forces required to deform brain tissue during *in vivo*, *in situ*, and *in vitro* experiments, and demonstrating that most of the brain's mechanical properties are unaffected by perfusion pressure, and can therefore be examined *in vitro*[263]. These findings are broadly comparable to those of the present study; the median forces to retract brain tissue 5mm varied from 0.03N in the cerebrum to 0.18N in the brainstem.

Alongside the aforementioned studies evaluating the mechanical properties of the brain, a number of studies have utilised penetration experiments to estimate the forces required to insert probes of various characteristics into neural tissue. Howard *et al* measured the penetration forces on 2.5mm spheres and the drag forces on a 3mm

ventricular catheter advanced 20-30mm deep into the brain tissue of patients undergoing temporal lobectomy, and reported forces of 0.08N and 0.03N respectively[265]. Chen *et al* measured the forces exerted when placing a 3mm ventricular catheter into a porcine brain during validation of an agarose gel phantom, and reported a typical penetration force of less than 0.1N[267]. Sharp *et al* addressed micrometer-scale penetration dynamics, assessing the influence of probe size and geometry, and also reported that low forces were required[264]. When utilising a 200μm diameter flat punch probe, for example, a maximum of 0.03N force was exerted. In the current study, the forces exerted to penetrate brain tissue were very low, varying from <0.01N to 0.02N, though greater forces were required to extend the incision. It is speculated that the very low forces observed in our study are the result of its distinct methodology; to better reflect standard operative neurosurgical practice the brain surface was coagulated with bipolar electrocautery prior to any manoeuvres, and a sharp beaver mini-blade instrument used to incise the brain.

Cranial microsurgery, such as aneurysm clipping or tumour resection, is characterised by precise and delicate complex manoeuvres such as dissection around critical neurovascular structures, rather than simple brain tissue retraction and penetration. To date, no previous studies have reported the forces actually exerted during such neurosurgical procedures. In other surgical disciplines, the forces exerted during, for example, laparoscopic cholecystectomy was reported to be approximately 17N[268]. In comparison, the instrument forces measured during sharp and blunt arachnoid dissection were an order of magnitude less, and with median forces typically less than 1N.

6.4.4.3 Limitations

The present study has several limitations. First, although forces were measured carefully using an externally calibrated system, the penetration forces detected were surprisingly low compared to other studies in the literature, with several readings falling below the 0.01N resolution of the experimental configuration. Nonetheless, the fact that such low forces were observed was in itself an important finding, and other readings such as microsurgical dissection were well within the operating range of the force sensor. Second, the cadaver brains utilised undoubtedly had different tissue

properties to living brain tissue. While animal studies might have allowed for *in vivo* measurements, the gross size and structure of, for example, porcine brains differ considerably from their human counterparts. Fresh cadaver brains were used to ameliorate this as they are anatomically accurate and previous studies have suggested that there is in fact little difference in the mechanical properties of living and cadaver brain tissues[263]. Third, although arachnoid dissection with a Beaver Mini-Blade or No 6 Rhoton dissector is almost certainly a far better reflection of in-vivo microneurosurgery than previous studies, it still does not reflect the full spectrum of instruments available to neurosurgeons, the complex and varied technical manoeuvres of actual neurosurgical operations, and the range of speeds with which such manoeuvres may be performed. Procedures such as microanastomosis, for example, may utilise a considerably different range of forces. Fourth, a single surgical trainee performed the manoeuvres. While the forces exerted during simple procedures such as retraction are likely to be relatively independent of the operator, the surgical forces exerted during microsurgery are known to be greater in novices than experts[269], and the forces applied by the neurosurgical trainee in this study are therefore likely to be higher than if experienced consultants had performed it. Although not explored in the present study, additional factors such as surgeon fatigue and perhaps the nature of the case (e.g. emergency craniotomy) could also influence technical performance, and therefore forces exerted[270].

6.4.4.4 Conclusions

The present study suggests that the instrument forces exerted during microsurgical arachnoid dissection are relatively low, with median forces less than 1N, and maximum forces less than 5N. Nonetheless, in-vivo forces are likely to vary depending on a number of factors including the patient's particular brain characteristics, the nature of their pathology (such as tumour consistency), the experience of the operating surgeon, and surgical procedure performed. In the future, widespread adoption of surgical robots into mainstream practice might allow for quantification of surgical forces on a routine basis, enhancing not only the precision, accuracy, and safety of cranial microsurgery, but also providing valuable feedback to neurosurgical trainees.

6.5 Instrument use: A time-motion study

6.5.1 Introduction

A greater understanding of the clinical efficiency and functionality of instruments is an essential prerequisite for the development of improved surgical tools. Ideally, the number of instrument exchanges should be minimised to reduce the risk of iatrogenic injury, and improve the operative workflow.

In this study time-motion analysis of an expert surgeon performing microneurosurgery is used to quantitatively explore the use of instruments in these approaches, assessing both the sequence of instrument use and the relative functionality of different instruments.

6.5.2 Materials and Methods

An objective coding system was developed to define the instruments and distinct surgical manoeuvres encountered during these microsurgical approaches (Table 6.9).

Five microsurgical approaches were performed by the senior surgeon. The intra-dural components of the procedures were recorded using the Carl Zeiss Surgical Microscope. An observer reviewed and coded the videos (Figure 6.10). Instruments were considered inserted when they entered the surgical field. Manoeuvres were considered as beginning when instruments made contact with tissue. If a single instrument performed several manoeuvres simultaneously, such as suction and retraction, all these manoeuvres were noted. Idle time was recorded when instruments had been removed from the patient, or when they were inactive for more than 30 seconds.

Clinical efficiency of instruments was determined by the duration of their use, and the relative frequencies of different instrument exchanges. Instrument functionality was evaluated by determining the number of unique manoeuvres that each performed.

Manoeuvre	Definition
Retraction without grasping	Manoeuvring tissue while not within the jaws of an instrument
Retraction with grasping	Manoeuvring tissue within the jaws of an instrument
Dissecting	Separating tissue planes using the blunt end of an instrument
Cutting	Cutting tissue or sutures using sharp scissors or mini-blade
Coagulation	Cauterising a vessel
Specimen or material placement or removal	Placing or removing tissue or surgical material from the surgical field
Suction	Clearing the surgical field using suction
Irrigation	Clearing the surgical field using irrigation
Endoscopy	Insertion of an endoscope for improved visualisation
Image guidance	Insertion of an image guidance probe for surgical orientation

Table 6.9. Coding system to define surgical manoeuvres.



Figure 6.10. Image captured during microvascular decompression illustrating use of sucker and bipolar forceps.

6.5.3 Results

A total of 5 microneurosurgical approaches were reviewed including resection of high-grade glioma (n = 2), resection of meningioma (n = 2), and microvascular decompression for trigeminal neuralgia (n = 1).

Overall, 478 minutes of video footage was reviewed. Idle time was 19 minutes (3.9%) for the left (non-dominant) hand, and 26 minutes (5.4%) for the right (dominant) hand. Instrument use is summarised in Table 6.10. The left hand exclusively used the sucker. The right hand most commonly carried bipolar forceps (57.9%), scissors (17.4%) or dissectors (10.3%). The most common instrument cycles were: bipolar forceps → scissors (72 complete cycles); and bipolar forceps → dissector (22 complete cycles).

Individual instruments were analysed for the number of distinct manoeuvres they were involved with. Most of the instruments had several overlapping functions. The left hand almost always simultaneously performed suction (98.4%) and retraction without grasping (87.5%). The right hand most commonly performed retraction without grasping (80.5%), in conjunction with the placement or removal of material such as cottonoid patties, coagulation, and cutting.

The bipolar forceps was the most multifunctional instrument (Table 6.11). Although designed primarily for haemostasis, it was used to perform five distinct manoeuvres.

Left (non-dominant) hand	Right (dominant) hand
Sucker (459.5 minutes; 100%)	Bipolar forceps (261.5 minutes; 57.9%)
	Scissors (78.5 minutes; 17.4%)
	Dissectors (46.5 minutes; 10.3%)
	Forceps (37 minutes; 8.2%)
	Image guidance (14 minutes; 3.1%)
	Endoscopy (8 minutes; 1.8%)
	Irrigation (4 minutes; 0.9%)

Table 6.10. Instrument use (excludes idle time).

Instrument (number of functions)	Functions
Bipolar forceps (5)	Retraction without grasping; Retraction with grasping; Dissecting; Coagulation; Specimen or material placement or removal
Forceps (4)	Retraction without grasping; Retraction with grasping; Dissecting; Specimen or material placement or removal
Scissors (3)	Retraction without grasping; Dissecting; Cutting
Sucker (3)	Retraction without grasping; Specimen or material placement or removal; Suction
Dissector (2)	Retraction without grasping; Dissecting
Irrigation (1)	Irrigation
Endoscope (1)	Endoscopy
Image guidance (1)	Image guidance

Table 6.11. Instrument multifunctionality.

6.5.4 Discussion

In this study it has been demonstrated, for the first time, that expert neurosurgeons utilise relatively few instruments, each with multifunctionality. In this way, the number of instrument exchanges is minimised, improving safety and reducing operating time. Mehta *et al* performed an analysis of instrument use in laparoscopic surgery and also found that instruments were often used to perform a variety of manoeuvres in addition to their primary function[253].

Important limitations of this study include the small number of cases analysed, and the fact that all procedures were performed by a single expert surgeon. Nonetheless, the finding that the most frequently used combination of instruments, a sucker and bipolar forceps, allows up to six distinct manoeuvres, is likely to remain valid. New surgical tools, should seek to maintain and build on the multifunctionality of existing microsurgical instruments.

6.6 Novel robotic articulated instruments for single-port surgery in small operative working spaces: A feasibility study

6.6.1 Introduction

The above data on operating working spaces, instrument forces exerted, and surgical manoeuvres performed, were used to develop a range of robotic articulated instruments better suited to single-port surgery in small operative working spaces. These instruments are in a process of continuous refinement and the present study represents an early feasibility study on their use in a peg transfer task.

6.6.2 Materials and Methods

6.6.2.1 Participants and study settings

A team from a University Hospital comprising a trainee surgeon and engineer involved in the development of the robotic articulated instruments participated in the study.

6.6.2.2 Trial design

A feasibility study design was adopted to determine whether the robotic articulated instruments could be used to perform the modified peg transfer task in the simulation of a single-port approach and small working space.

The previously described custom cuboid with dimensions 30 x 30 x 90mm, and a volume of 81cm^3 was used to simulate the small working space; this is representative of, for example, transanal and transcranial approaches[157, 250, 251] The cuboid was placed on a base such that the manipulation angle was 45º, allowing for optimal ergonomics[252].

The peg transfer was selected from the McGill Inanimate System for Training and Evaluation of Laparoscopic Skills (MISTELS)[216], to represent a simple task for this initial feasibility study. Construct validity of this task was confirmed in work earlier in this chapter; intermediates-experts scored significantly higher than novices (63 vs. 38 respectively; $p = 0.019$).



Figure 6.11. Computer Aided Design of a robotic articulated instrument illustrating the delivery shaft, elbow joint, and wrist joint.

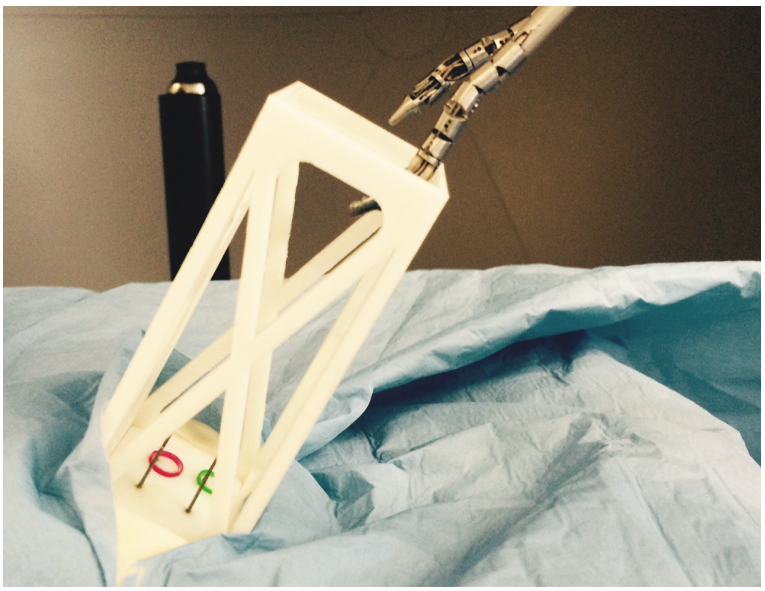


Figure 6.12. Arrangement of the robotic articulated instruments.

Two prototype robotic articulated graspers 5mm in diameter were used for manipulation (Figure 6.11 and Figure 6.12). These graspers were tendon-driven, and each had a total of 7 degrees of freedom (2 degrees of freedom at the delivery shaft, 2 degrees of freedom at the elbow joint, and 3 degrees of freedom at the wrist joint including grasping). An Olympus EndoEye Flex 3D HD system (Olympus, Tokyo, Japan) was used for visualisation. The 0 degree endoscope is 10mm in diameter, 37cm in length, and has a flexible neck.

Control of the instruments was using omega.7 interfaces (Force Dimension, Nyon, Switzerland) (Figure 6.13). The telesurgical system eliminated the fulcrum effect, and allowed for motion scaling and tremor filtering. Images were displayed using a 24" stereoscopic screen.

The task was performed a total of three times. In this feasibility study, there was no maximum time limit to perform the task.

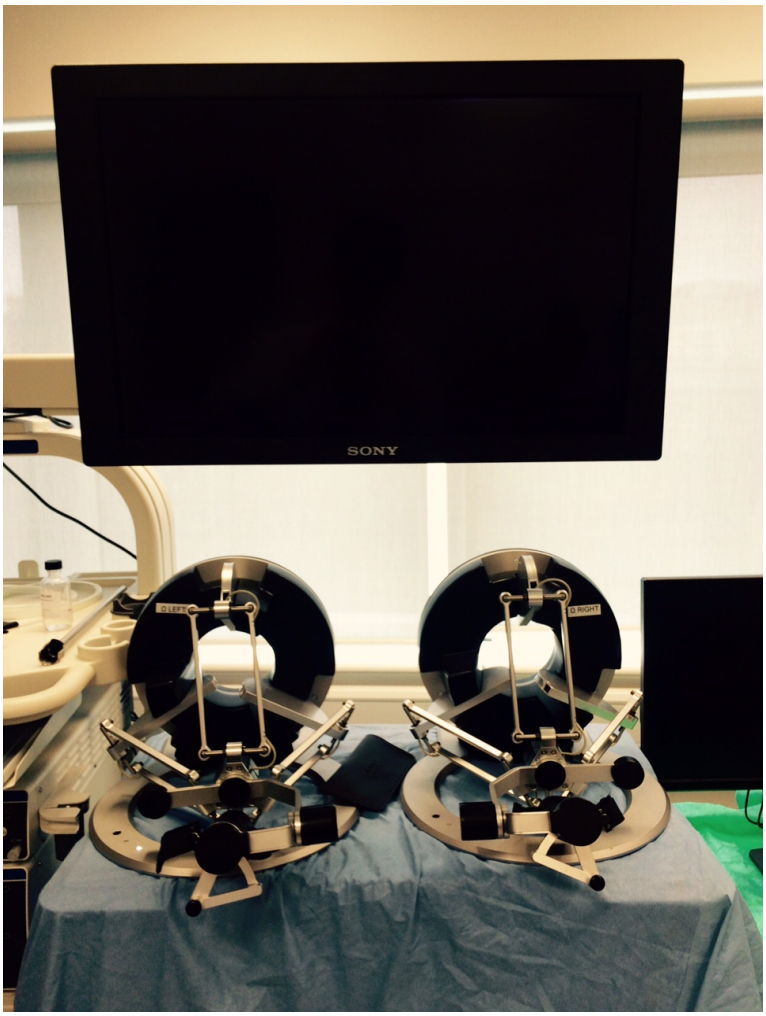


Figure 6.13. Arrangement of the master console.

6.6.2.3 Outcomes

The primary outcome was the total score (non-normalised MISTELS based criteria[216]): timing score = 100 seconds minus task completion time (seconds); penalty

score = percentage of pegs dropped outside the field of view, or outside of reach; total score = timing score minus penalty score.

Throughout the study detailed feedback was obtained, including images of the operating room arrangement, and of the endoscope feed.

6.6.3 Results

The participants were an average age of 34 years, both male, and right-handed. The median task duration was 100 seconds (range 96 to 149 seconds), and the median total score was -46 points (range -50 to -9 points).

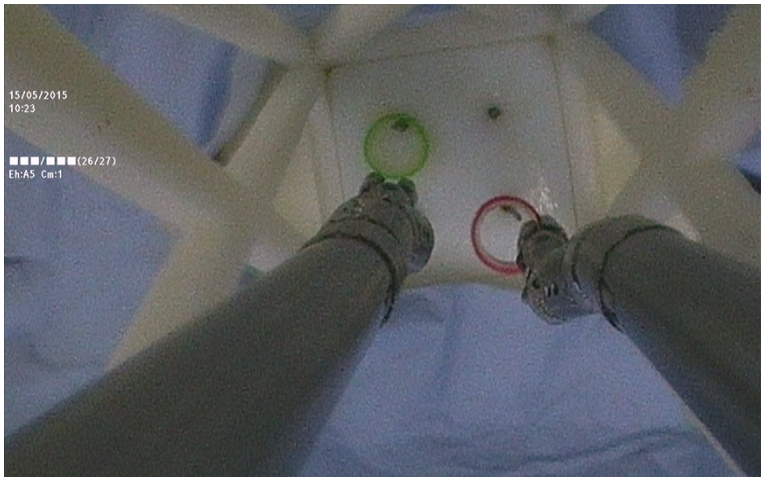


Figure 6.14. Endoscopic view during peg transfer task.

The instrument tips were able to reach the entire working space of the peg board. Force delivery was considered sufficient, though the grip of the graspers loosened considerably during the course of the study making it increasingly difficult to pick and place the rings.

The participants appreciated the greater dexterity provided by the robotic articulated instruments (Figure 6.14). However, the kinematic control of the instruments was unsatisfactory; the instruments responded unpredictably and erratically to command.

6.6.4 Discussion

In this study it was demonstrated that the use of the prototype robotic articulated instruments in single port approaches and small working spaces is feasible. However, at present their poor kinematic control limits their effectiveness compared to standard rigid instruments; the median score using robotic articulated instruments was -46 points (range -50 to -9 points), compared to 48 (range 34.5 to 62) using standard rigid instruments. Possible causes for the poor kinematic control observed include loss of tendon tension, tendon twisting, friction between tendons, backlash, and redundant kinematic degrees of freedom.

Few other studies have sought to evaluate the role of robotics in single port approaches and small working spaces. Thakre *et al* described the use of the da Vinci™ platform to perform MISTELS tasks in increasingly small workspaces, and found that a cube had to be at least 60mm in size to do so without significant collision between the instruments[157]. In a related preclinical randomised crossover study, Cundy *et al* found that performance with the da Vinci™ platform in spatially constrained operative workspaces was considerably worse than non-robotic instruments, and argued for the development of new robotic instruments better suited to such approaches[271].

The adoption of a feasibility study design was necessary given that the robotic articulated instruments remain early prototypes, but inherently limits the generalisability of this study. Nonetheless, work is currently underway to improve the design and control of the instruments, with a plan to then perform a more rigorous preclinical randomised controlled trial to evaluate their comparative effectiveness.

CHAPTER 7 AN INTEGRATED ROBOTIC PLATFORM FOR IMAGE GUIDED ENDOSCOPIC MICROSURGERY AND CLINICAL TRANSLATION*

*Content from this chapter was published or submitted as:

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*Content from this chapter was presented as:

Marcus HJ. A robotic platform for keyhole transcranial endoscopic microsurgery: Development and preclinical studies. Annual Meeting of the German Society of Neurosurgery (DGNC), Karlsruhe, Germany. June 2015.

7.1 An integrated robotic platform for image guided endoscopic microsurgery: Technical specifications

7.1.1 Introduction

The prototype micro-IGES robot has a master-slave configuration in which the surgeon sits at a console (master) and remotely controls the robots actions (slave) (Figure 7.1). The three chief components of the integrated platform are augmented reality, 3D HD endoscopy, and robotic articulated instruments.

7.1.2 Augmented reality

A custom on-demand inverse realism augmented reality system is used to assist with surgical approach as described in CHAPTER 4. An NDI Polaris Optical Tracking System (Northern Digital Inc., Ontario, Canada) is used to track the endoscope with respect to a reference frame. Rigid registration of surface fiducials is used to relate the head and CT scan coordinate frames. Manual alignment of a reference object is then used to determine the hand-eye transformation from the camera tracking frame to the camera frame defining the projection to display coordinates. Concatenated together, the results of these calibrations are used to map renderings of CT segmentations onto captured images.

7.1.3 3-Dimensional High-Definition endoscopy

Following work in CHAPTER 5, an Olympus EndoEye Flex 3D HD system (Olympus, Tokyo, Japan) is used for visualisation. The 0 degree endoscope is 10mm in diameter and 37cm in length. The endoscope also features a flexible neck that allows for optimisation of the view. Images are displayed using a 24” stereoscopic screen.

7.1.4 Robotic articulated instruments

Two custom robotic articulated graspers 5mm in diameter are used for manipulation as described in Chapter 6. These graspers each had a total of 7 degrees of freedom (2 degrees of freedom at the delivery shaft, 2 degrees of freedom at the elbow joint, and 3 degrees of freedom at the wrist joint including grasping). The instruments are controlled by a pair of omega.7 interfaces (Force Dimension, Nyon, Switzerland).

7.2 Preclinical evaluation of the integrated robotic platform: A feasibility study using the MARTYN head

7.2.1 Introduction

In the preceding chapters, the effectiveness of augmented reality, 3-Dimensional High-Definition (3D HD) endoscopy, and robotic articulated instruments, were independently evaluated against their respective gold standards using validated models. The micro-IGES platform is a surgical robot under development by Guang-Zhong Yang *et al* at Imperial College London that integrates these technologies. Although initially conceived for transanal endoscopic microsurgery, the robot is well suited to all operations that utilise a single-port approach and a small working space. In this study, the use of the micro-IGES robot in keyhole neurosurgery was assessed using a validated model of the supraorbital approach.

7.2.2 Materials and Methods

7.2.2.1 Participants and study settings

A team from a University Hospital comprising a trainee surgeon and an engineer involved in the development of the robotic platform participated in the study.

7.2.2.2 Trial design

A feasibility study design was adopted to determine whether the micro-IGES platform could be used in the simulation of the keyhole supraorbital approach.

The previously described Modelled Anatomical Replica for Training Young Neurosurgeons (MARTYN) head (Royal College of Surgeons of England, London, UK), with an accompanying circle of Willis including a basilar tip aneurysm, was used.[33] The model consists of a gelatine-based brain, encased within a latex dura, and a polyurethane skull. The validation study described in Chapter 2.3 confirmed the MARTYN head is realistic (face validity), useful (content validity), and able to discriminate between surgeons of different experience (construct validity), with respect to the keyhole supraorbital approach.[191]



Figure 7.1. Arrangement of the robot and the master console.

The model head was fixed in place with a Mayfield clamp and a Budde-halo retractor system attached (Integra, New Jersey, USA). A 25 x 15mm left supraorbital craniotomy was fashioned using a high-speed drill (B. Braun, Melsungen, Germany). The high-speed drill was then used to remove the inner edge of the bone above the orbital rim, and the jugae cerebralia. A simple “C” durotomy was performed, and the flap retracted basally.

The robot was then mounted on a custom passively controlled arm and locked into an appropriate surgical trajectory. The task was to identify a previously placed clip on a basilar tip aneurysm using the robotic articulated instruments, with instructions to minimise their exposure and manipulation of brain tissue. The task was considered complete when users applied either instrument to the aneurysm clip.

Throughout the study detailed feedback was obtained, including images of the operating room arrangement, and of the endoscope feed.

7.2.3 Results

The participants were an average age of 34 years, both male, and right-handed. The robot was able to complete the task without interruption over 139 seconds.

7.2.3.1.1 Augmented reality

The on-demand augmented reality system worked well, allowing for a precise surgical trajectory. The depth of the virtual overlay was easily appreciated, and the metallic robotic articulated instruments combined well with the inverse realism overlay, allowing the salient details of the instruments to be easily recognisable (Figure 7.2).

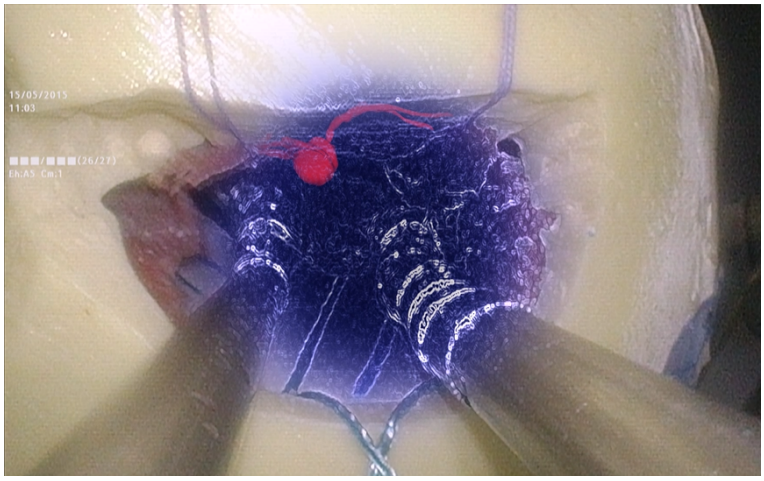


Figure 7.2. Integrated on-demand augmented reality overlay.

7.2.3.1.2 3-Dimensional High-Definition endoscopy

The 3D HD endoscope provided excellent visualisation of the operative field. The ability to flex the neck of the endoscope was especially useful as the robot and endoscope positions were locked.

7.2.3.1.3 Robotic articulated instruments

The robotic articulated instruments allows for considerably greater dexterity than could be achieved with conventional rigid instruments (Figure 7.3). The instrument tips were able to reach the entire operative workspace, and force delivery was sufficient for tissue manipulation.

Several problems were noted, however, that would prohibit their clinical use. Only graspers were available, limiting the tasks that could be performed. Moreover, the kinematic control of the instruments remained unpredictable making it difficult to execute effective surgical manoeuvres, and raising issues over safety.

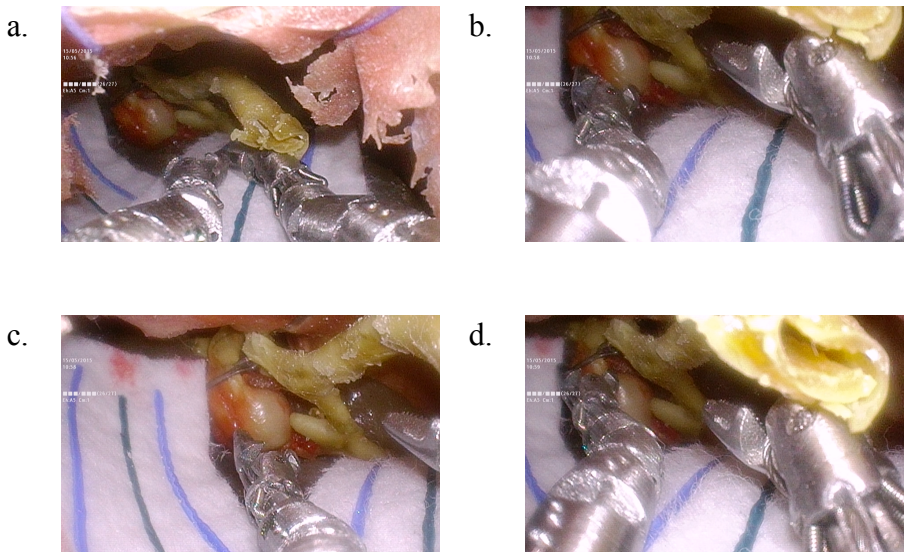


Figure 7.3. Endoscopic views demonstrating the robot-assisted supraorbital approach.

7.2.4 Discussion

In this study it was demonstrated that use of the prototype micro-IGES robot in the supraorbital approach was feasible. The integrated augmented reality system, and 3D HD endoscopy, were both considered to be safe and effective. Kinematic control of the robotic articulated instruments, however, remains unsatisfactory, precluding their use in clinical studies at present.

The prototype micro-IGES robot used in this study represents substantial progress towards an integrated platform better suited to single-port approaches and small working spaces. The combination of augmented reality, 3D HD endoscopy, and robotic articulated instruments, proved synergistic. The use of stereoscopic augmented reality necessitated 3D HD endoscopy. The greater depth perception afforded by 3D HD endoscopy, allowed for the more precise use of the robotic articulated instruments. Finally, the salient details of the robotic articulated

instruments were more easily maintained with the inverse realism augmented reality overlay.

Few telesurgical robotic platforms have been applied to keyhole transcranial endoscopic microsurgery. The cadaver study reported in Chapter 3 demonstrated that the most widely used surgical robot worldwide today, the da Vinci^{TM} platform, is neither safe nor feasible to use in keyhole neurosurgery. The NeuRobot (Shinshu University School of Medicine, Matsumoto, Japan) was the first telesurgical robot designed specifically for keyhole neurosurgery, and includes a 3D endoscope and three sets of micromanipulators, each with 3 DOF (rotation, neck swinging, and forward/backward motion)[141-146]. Although the system was able to perform relatively simple surgical procedures in cadavers and human studies, the authors report the system was limited by lack of manoeuvrability of the micromanipulators and robot itself. Another Japanese group have recently developed a similar Neurosurgical Robot for Brain Tumor Removal (Nagoya Institute of Technology, Nagoya, Japan)[147, 148]. As with NeuRobot the robot incorporates a 3D endoscope, an irrigation system, and a volume control suction tool, with 2 DOF at the instrument tips. The robot has not yet been thoroughly evaluated, but it is likely that, as with NeuRobot, the restricted working space will limit its clinical use.

The adoption of a feasibility study design was necessary given that the robot remains at an early prototype stage, but inherently limits the generalisability of this study. Nonetheless, work is currently underway to improve the design of the robot, particularly the instruments, with a plan to then perform a cadaver study.

7.3 Preclinical evaluation of 3-Dimensional High-Definition endoscopy: A cadaver study

7.3.1 Introduction

Visualisation of the operative field during keyhole neurosurgical approaches is challenging[272]. The laboratory study performed in Chapter 0, and the above feasibility study, demonstrated that 3D HD endoscopes can significantly improve surgical performance, particularly in patients with complex anatomy, or when cases are performed by less experienced surgeons.

The goals of the present cadaver study were to confirm the effectiveness of the 3D HD endoscope in keyhole neurosurgery and to ensure no side effects or adverse reactions occur with prolonged use.

7.3.2 Materials and Methods

Ethical approval was obtained from the Proportionate Review Sub-committee of the National Research Ethics Service. A formalin-fixed cadaver head was obtained from the Department of Anatomy, Imperial College London. An operating microscope (Albert Wetzlar GmbH, Wetzlar, Germany) and high-speed drill (B. Braun, Melsungen, Germany) were used to fashion supraorbital subfrontal, retrosigmoid and supracerebellar infratentorial keyhole craniotomies, each 20-30mm in diameter. In each case, a durotomy was performed and the flap retracted.

A VisionSense III endoscopy system (VisionSense, Petach Tikva, Israel) was used to provide 3D and HD visualisation. The endoscope utilises a proprietary technology with a single chip, and a matrix of microlenses, in a manner analogous to an insect's compound eye. The 0-degree rigid endoscope was 4mm in diameter and 180mm in length. Images were displayed on a 24" stereoscopic screen, at a resolution of 1920 x 1200 pixels.

Dissection was performed towards the deep intracranial cisterns with the endoscope, a micro-sucker, and Perneczky tube-shaft instruments (B. Braun, Melsungen,

Germany). Throughout each procedure, detailed feedback was obtained on depth perception, image quality, and any side effects or adverse reactions.

7.3.3 Results

The 3D HD endoscope had a size and weight comparable to standard endoscopes. The depth perception provided was excellent and image quality generally high (Figure 7.4). However, the lack of an available 30-degree endoscope was a notable limitation. Procedures were carried out uneventfully over 90 minutes. No issues such as nausea or diplopia occurred.

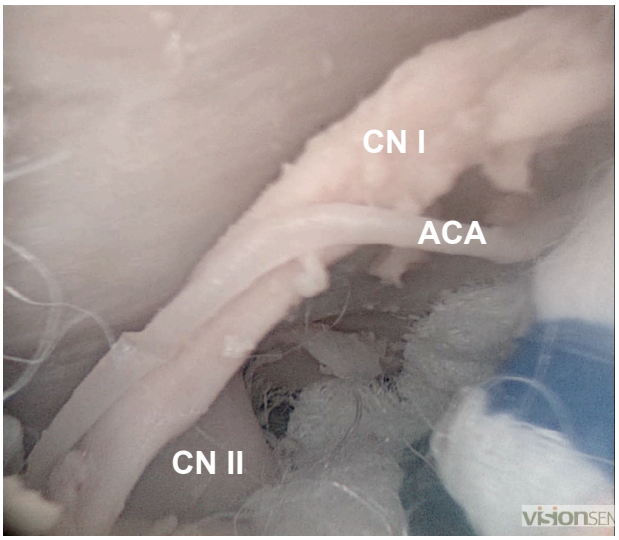


Figure 7.4. Image capture from left supraorbital subfrontal approach demonstrating the olfactory nerve (CN I), optic nerve (CN II), and anterior cerebral artery (ACA).

7.3.4 Discussion

In this cadaver study the VisionSense III endoscopy system was demonstrated to be effective and safe for use in keyhole neurosurgery. The development of a 30-degree endoscope will further enhance visualisation of the operative field.

A limitation of this study was that only one trainee surgeon performed the procedures. Unfortunately, limited availability of the cadaver specimen precluded a more extensive study. It is recognised that a proportion of individuals do suffer from side effects when using 3D endoscopes, limiting the generalisability of this study[199].

7.4 Early clinical evaluation of 3-Dimensional High-Definition endoscopy: First-in-human study

7.4.1 Introduction

Although 3D endoscopes have been used in neurosurgery, they have generally been limited to Standard Definition (SD), compromising image quality[197-199]. This study describes the endoscope-assisted microsurgical resection of a cerebral metastasis using the first commercially available 3D and High-Definition (HD) endoscope.

7.4.2 Case report

A 78-year-old right-handed male smoker presented with a several month history of increasing headache and memory loss. Their past medical history included adenocarcinoma of the prostate and transitional cell carcinoma of the bladder two years prior, for which they underwent surgical resection. Neurological examination was unremarkable.

Magnetic Resonance Imaging (MRI) demonstrated a left parietal ring-enhancing space-occupying lesion with associated cerebral oedema and mass-effect (Figure 7.5). Concomitant whole body Computed Tomography (CT) did not reveal any recurrence or metastases affecting his chest, abdomen, or pelvis.

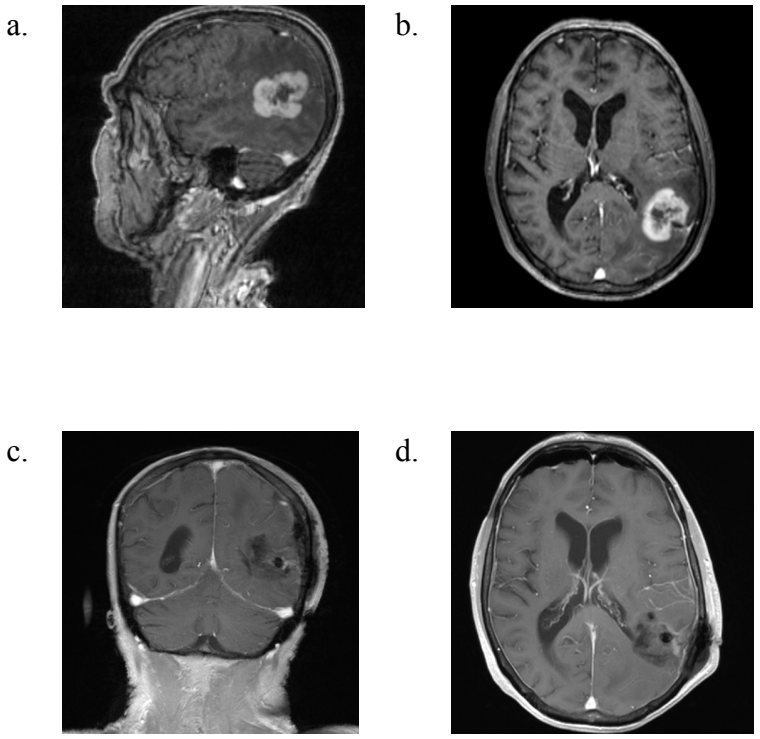


Figure 7.5. Pre-operative (a) axial and (b) sagittal MRI head with contrast demonstrating a left parietal ring-enhancing space-occupying lesion. Post-operative (c) coronal and (d) axial MRI head with contrast demonstrating complete resection.

The patient subsequently underwent endoscope-assisted microsurgical resection of the lesion. They were positioned supine with their head rotated to the right. A sandbag was placed under the left shoulder, and care was taken to ensure that all pressure points were padded. The approach was planned using neuronavigation (Sonowand, Trondheim, Norway) with special attention paid to avoiding the post-central, supramarginal, and angular gyri. A linear parietal scalp incision was made, a minicraniotomy fashioned, and a cruciate durotomy was performed (Figure 7.6A-C).

Intra-operative ultrasound was used to confirm the tumour location, and a limited corticotomy made. Microsurgical dissection then proceeded along the plane between the tumour and brain. The bulk of the tumour was subsequently removed en-bloc (Figure 7.6D-F).

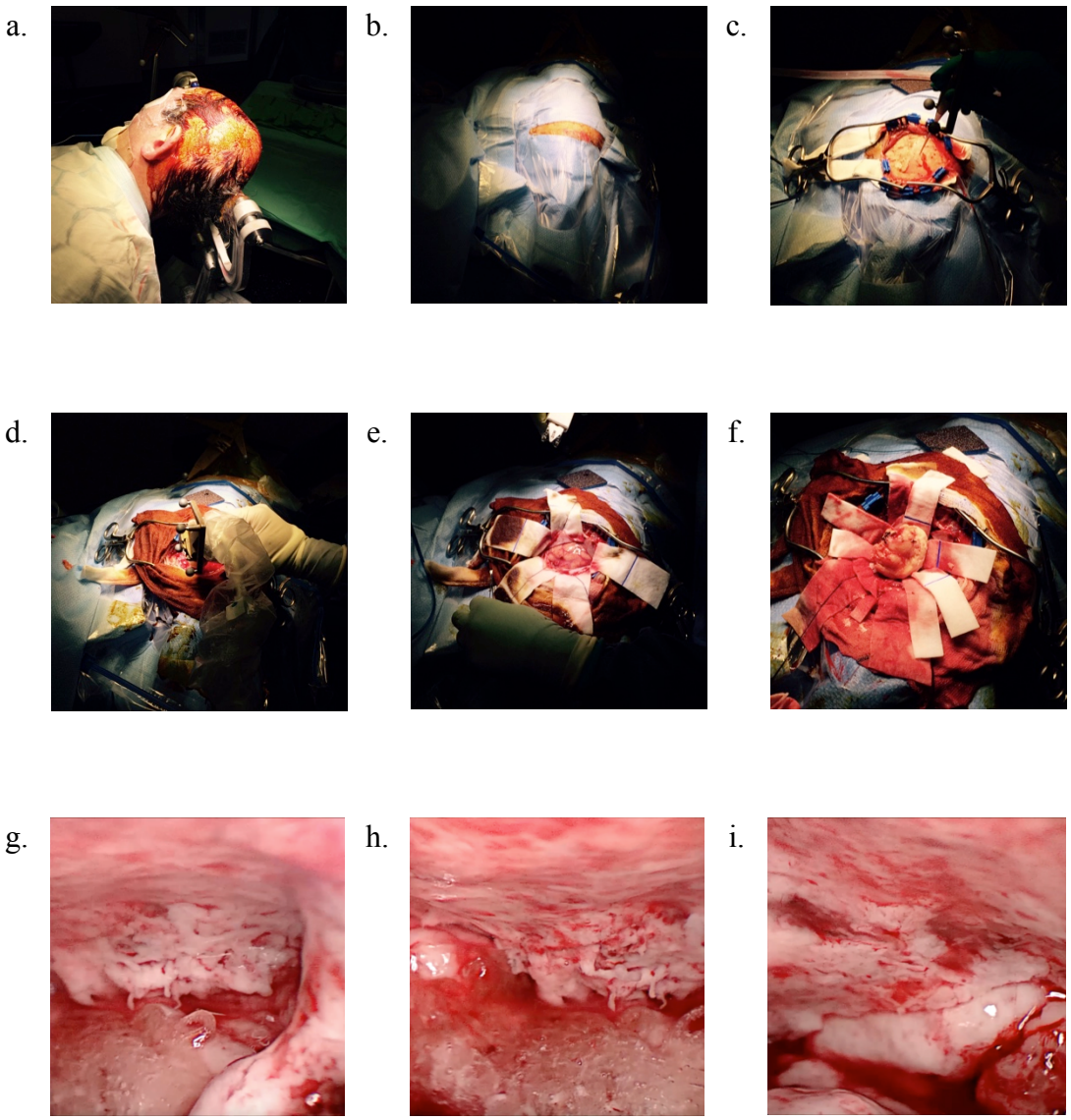


Figure 7.6. (a-c) the patient was positioned supine with their head turned, a linear incision was made, a parietal minicraniotomy fashioned, and a cruciate durotomy performed, (d-f) intra-operative ultrasound was used to confirm the tumour location, a limited corticotomy was made, and the tumour removed en-bloc, (g-i) an endoscope was used to visualise the resection cavity and remove any residual tumour tissue.

A novel 3D HD VisionSense III endoscope (VisionSense, Petach Tikva, Israel) was used to assess the resection cavity for residual tumour tissue (Figure 7.6G-I). The 0° rigid endoscope was 4mm in diameter and 20cm in length, providing a resolution of 1920 x 1200 pixels. Images were displayed on a 24-inch flat screen monitor, and surgeons wore polarised glasses. Overall, the endoscope was found to be useful, with surgeons appreciating the improved depth perception and greater image quality. There was an area of gliotic brain in the tumour bed where it was not definitively clear

under the microscope if there was any tumour remnant. The use of the endoscope made visualisation of this region much clearer and it was felt no residual tumour was present. This was a crucial intervention by the endoscope as the tumour was in an eloquent location in the dominant hemisphere and the added clarity helped to avoid unnecessary further dissection. No side effects were associated with prolonged use. However, the endoscope was observed to be relatively bulky, making it awkward to drape, and difficult to manoeuvre. Moreover, the viewing angle was somewhat restricted.

After endoscope-assisted tumour resection was completed, the durotomy was re-approximated with sutures, the bone flap replaced with Craniofix (Aesculap AG, Tuttlingen, Germany), and a subgaleal wound drain inserted. Histopathology confirmed the diagnosis of cerebral metastasis. The patient had an uneventful recovery. Post-operative MRI demonstrated complete resection (Figure 7.5C-D).

7.4.3 Discussion

Advances in endoscopy represent among the most important technological innovations in neurosurgery over the last 50 years[273]. Endoscopes have been used in neurosurgery since Victor l'Espinasse, an American urologist, operated on a neonate with hydrocephalus over a century ago. However, endoscope technology at that time was very rudimentary, and enthusiasm waned following the advent of cerebrospinal fluid shunts to treat hydrocephalus, and the emergence of the operating microscope. In the late 1980's the introduction of the SELFOC© lens, Charge-Coupled Device (CCD), and fibre-optic light sources, allowed for endoscopes with a wider viewing angle, higher image quality, and greater illumination[62]. Endoscopic procedures such as Endoscopic Third Ventriculostomy (ETV) and endoscopic transsphenoidal hypophysectomy are now widely accepted as alternatives to standard surgery in selected cases[38, 39, 274].

The development of 3D endoscopes suitable for use within the brain may signify a further paradigm shift in their technological trajectory. The systematic review in Chapter 5.1 demonstrated that there is limited and low quality evidence to support 3D compared to 2D endoscopy in neurosurgery. Notably, all existing clinical studies have

compared 3D SD and 2D HD endoscopy[197-199]. The subsequent preclinical study in Chapter 5.2 concluded that 3D and HD endoscopy have differing but complementary effects on surgical performance, suggesting that neither alone completely compensate for the lack of the other[275]. To this end, the VisionSense III endoscope described in this report is the first commercially available 3D HD endoscope suitable for neurosurgery.

The present report confirms the effectiveness and safety of the VisionSense III endoscope; in neurosurgery it provided excellent depth perception, high image quality, and was not associated with any untoward side effects. However, several limitations were noted. The current design is considerably larger and less ergonomic than standard endoscopes. The viewing angle was also comparatively smaller than standard endoscopes, as described in previous studies[276]. Nonetheless, the VisionSense III endoscope represents an important advance, and justifies work towards next-generation endoscopes. Future comparative clinical studies are warranted.

7.5 Clinical translation of technological innovation: An observational study

7.5.1 Introduction

In an attempt to better understand the process by which advances such as those outlined above are adopted into the wider clinical arena, this chapter concludes with a study on the process of clinical translation. New technologies have preceded many of the major advances in clinical practice[58]. The advancement of a technological innovation has been described as a continuum of activities that constitute the translation of a technological innovation from "bench to bedside". This translation is punctuated by several well defined chasms[277]: the translation of basic science to humans, with preclinical studies and proposal of a potential medical application (T1); the translation to clinical treatment, with clinical trials to evaluate safety and efficacy (T2); and the translation to practice, with implementation and adoption by clinicians (T3).

Although translation has been discussed for more than 40 years[278], the process has only recently become the subject of considerable biomedical research[277, 279-283]. The majority of such studies have focused on the latter translational barriers (T2 and T3), and on pharmaceutical innovations[281]. The rate and extent of early translation (T1 and T2) of technological innovations has not, to date, been quantitatively evaluated.

Device innovations hold particular importance to the field of surgery. The development and refinement of laparoscopic instruments, for example, heralded the emergence of minimally invasive surgery, which represented a paradigm shift in surgical practice[58]. Several economic-, clinical- and research-related factors may influence the early translation of such device innovations, though the degree to which these variables do so remains unclear[48].

The aims of the present study were therefore two-fold: first, to quantitatively evaluate the rate and extent of clinical translation of technological innovation, using surgical device innovation as an exemplar; and second, to evaluate the factors that influence such clinical translation.

7.5.2 Materials and Methods

An observational study was performed of surgical device innovations described in the biomedical engineering literature, and the extent to which such devices were clinically translated.

7.5.2.1 Device innovation

All biomedical engineering journals were identified using the earliest available ISI Web of Knowledge Journal Citation Report 1997 (Thompson-Reuters, New York, USA).

Previous reviews have suggested that the lag between initial publication and clinical adoption is approximately 17 years[284]. Two authors independently searched the NCBI PubMed (NCBI, Maryland, USA) and IEEE Xplore (IEEE, New York, USA) databases between 1993 and 1995 using the Boolean search term "surgery OR surgical OR surgeon", to identify publications describing innovative surgical devices. Devices were defined according to the US Food and Drug Administration as *"...products which do not achieve their primary intended purposes through chemical actions within or on the body of man or other animals and which are not dependent upon being metabolized for the achievement of any of their primary intended purposes"*[285].

In cases in which multiple publications were identified that described the same surgical device, the earliest publication was used for subsequent analysis.

Two authors independently collected data on the factors that might influence clinical translation, including: the journal; the year of publication; the country of origin of the corresponding author; the extent of clinical involvement (author affiliation, acknowledgement, or none reported); the extent of industry involvement (author affiliation, financial support, provision of technology, or none reported); the technology type (instrument, active implant, passive implant, or other); and the target of potential application (single disease, or broader disease category).

7.5.2.2 Clinical translation

The progress of a device innovation through the chief translational barriers was determined in a stepwise fashion by two authors, blinded to the factors influencing translation: a first-in-human study was taken to represent translation to humans (T1); a license for use to represent device safety and efficacy (T2); and a plateau in the number of units sold per year to represent clinical penetration (T3).

7.5.2.2.1 T1

Publications were used to identify first-in-human studies associated with device innovations. A publication was considered to describe the clinical translation of a particular device innovation, if the device was clearly referenced in the manuscript, and an uninterrupted citation chain could be identified.

For each device innovation, a search was performed through all citations to the corresponding article using the Web of Science (Thompson-Reuters, New York, USA). A recursive search strategy was utilised: all citations to an article were sorted according to date of publication (oldest first) and screened to identify the first clinical publication using the device; if no clinical publications were identified, citations were then screened to identify articles by any of the original authors describing subsequent development of the device and, if found, the process repeated.

7.5.2.2.2 T2

In cases in which device innovations resulted in first-in-human studies, a further search was then performed to determine whether they were licensed for clinical use. A US Food and Drug Administration (FDA) 510(k) premarket notification relevant to the device was considered to describe clinical translation.

The FDA medical database (FDA, Maryland, USA) was searched for 510(k) premarket notifications relevant to the device. The keywords used during each search were drawn from the title and abstract of the initial publication describing the surgical device.

7.5.2.2.3 T3

Applicants for licenses were contacted to provide data on the number of units sold year-on-year. Previous studies have suggested that the dissemination of new surgical devices follows Diffusion of Innovations theory[58]. To this end, a plateau in the number of units sold per year was taken to represent clinical market saturation.

At all stages of the above methodology, disputes were resolved by consensus, and by discussion with the senior author. Corresponding authors were also contacted to provide supplemental information as appropriate.

7.5.2.3 Statistical analysis

Data were analysed with Statistical Package for the Social Sciences (SPSS) v 22.0 (Illinois, USA). Kaplan-Meier curves were constructed for the time first-in-human studies. Factors influencing translation were evaluated using Cox proportional hazards models.

7.5.3 Results

7.5.3.1 Device innovation

In all, 9,295 articles were published between 1993 and 1995 in the 41 biomedical engineering journals searched, of which 132 (1.4%) described surgical device innovations and were included in subsequent analysis (Figure 7.7).

The original articles identified were most commonly published in the ASAIO journal (48; 36.4%), Artificial Organs (36; 27.3%), and Biomaterials (8; 6.1%). The majority of the corresponding authors were located in Japan (42; 31.8%), the USA (37; 28.0%), and Germany (11; 8.3%) (Table 7.1).

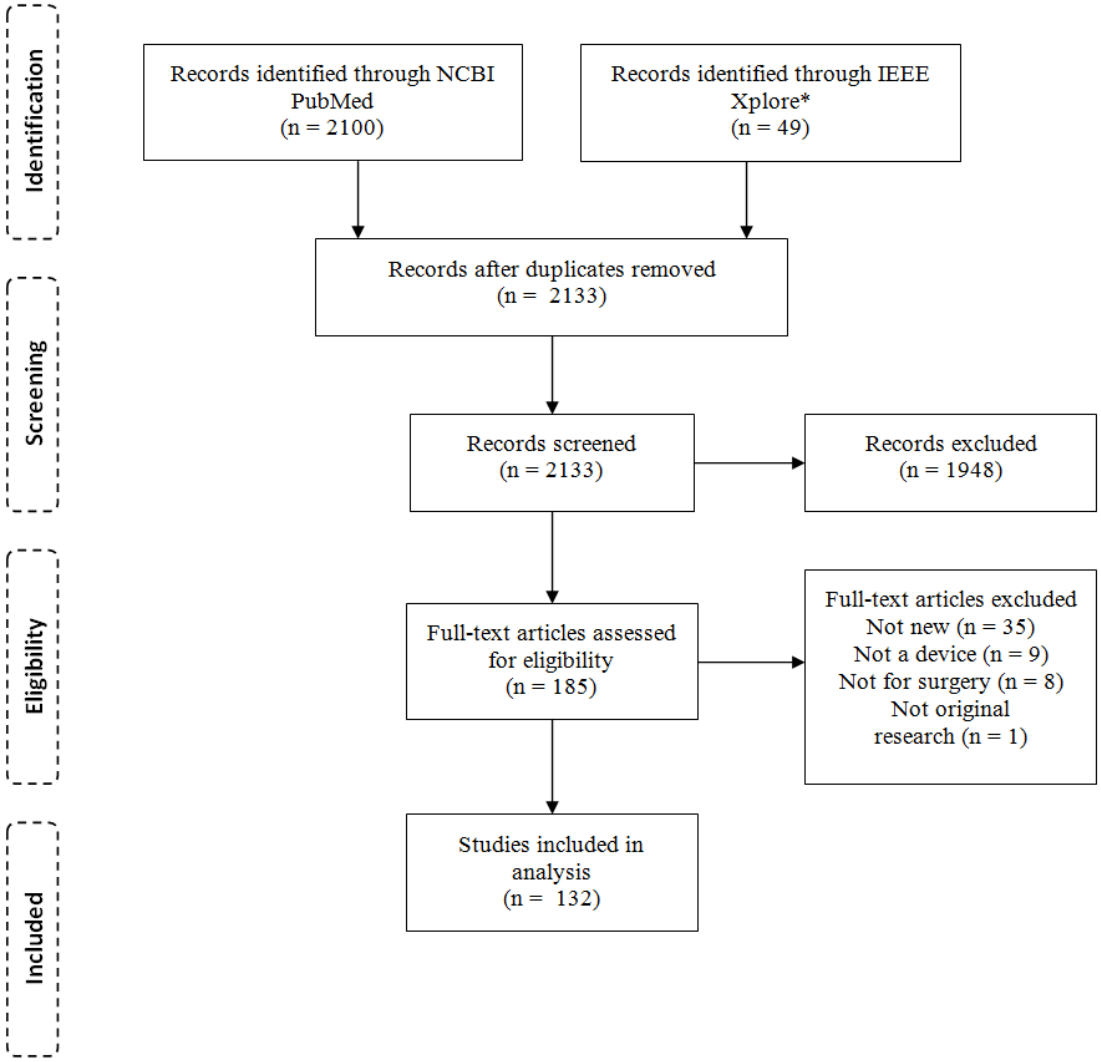


Figure 7.7. Selection of publications describing innovative surgical devices.

	Total (n = 132)	First-in-human (n = 18)	License (n = 6)
Journal:			
ASAIO J	48	3 (6.3%)	1 (2.1%)
Art Organs	36	5 (13.9%)	2 (5.6%)
Biomaterials	8	2 (25.0%)	0 (0.0%)
IEEE Eng Med Bio Mag	6	3 (50.0%)	1 (16.7%)
Med Eng Phys	5	1 (20.0%)	1 (20.0%)
J Appl Biomat	5	0 (0.0%)	0 (0.0%)
Other	24	4 (16.7%)	1 (4.2%)
Year:			
1993	42	4 (9.5%)	1 (2.4%)
1994	36	6 (16.7%)	2 (5.6%)
1995	54	9 (16.7%)	3 (5.6%)
Country of origin:			
Japan	42	4 (9.5%)	0 (0.0%)
USA	37	4 (10.8%)	3 (8.1%)
Germany	11	3 (27.3%)	2 (18.2%)
UK	9	3 (33.3%)	0 (0.0%)
Canada	6	0 (0.0%)	0 (0.0%)
France	6	1 (16.7%)	0 (0.0%)
Other	21	3 (14.3%)	1 (4.8%)
Clinician involvement:			
Author affiliation	99	13 (13.1%)	4 (4.0%)
Acknowledgement	6	4 (16.7%)	1 (16.7%)
None reported	27	1 (3.7%)	1 (3.7%)
Industry involvement:			
Author affiliation	33	5 (15.2%)	2 (6.1%)
Financial support	4	0 (0.0%)	0 (0.0%)
Provision of technology	7	0 (0.0%)	0 (0.0%)
None reported	88	13 (14.8%)	4 (4.5%)

	Total (n = 132)	First-in-human (n = 18)	License (n = 6)
Technology type:			
Instrument	31	7 (22.6%)	1 (3.2%)
Active implant	61	7 (11.5%)	4 (6.6%)
Passive implant	36	4 (11.1%)	1 (2.8%)
Other	4	0 (0.0%)	0 (0.0%)
Target of application:			
Single disease	120	17 (14.2%)	6 (5.0%)
Broader category	12	1 (8.3%)	0 (0.0%)

Table 7.1. Characteristics of included bioengineering publications, and whether they resulted in a first-in-human study and FDA license for use.

Most original articles involved clinicians (105; 79.5%), but only a third involved industry (44; 33.3%). Devices were generally implants (97; 73.5%) and constructed for a specific disease or application (120; 90.9%).

7.5.3.2 Clinical translation

In all, few devices described were translated; 18 (13.6%) of innovative devices resulted in a first-in-human study, and 6 (4.5%) were licensed for use (Table 7.2). The most common type of device that was clinically translated was ventricular assist devices, accounting for 5 (27.8%) first-in-human studies, and 3 (50.0%) FDA licenses for use.

The probability of a first-in-human study at 5, 10, and 20 years after the publication was 7.6%, 10.6%, and 13.6% respectively (Figure 7.8). The probability of an FDA license at 5, 10, and 20 years after the publication was 0.8%, 3.0%, and 4.5% respectively.

Of the six devices that received an FDA license, only the applicant for the Meithke DualSwitch^{TM} valve (B Braun, Melsungen, Germany) provided data on the number of units sold year-on-year. A plateau of 868 units sold per year was achieved in 2004,

approximately 10 years after the original publication. Two of the remaining device manufacturers provided data to suggest at least partial clinical penetration (Table 7.2).

7.5.3.3 Statistical analysis

The type of device and extent of clinical involvement approached significance using the Cox proportional hazards model ($p = 0.06$ and 0.08 respectively). Instruments were almost three times more likely to be translated than implants, and devices developed with early clinical collaboration over six times more likely to be translated than those without (Table 7.3; Figure 7.9 and Figure 7.11). Other variables, including the potential target of devices, and industry involvement, were not significantly associated with translation ($p > 0.1$ in all cases; Figure 7.10 and Figure 7.12).

	Original article (Year)	First-in-human (Year)	License (Year)	Dissemination
A new valve for the treatment of hydrocephalus	1994	1996	2002	> 7,000 cases
Concept, realization, and first in vitro testing of an intraarterial microaxial blood pump	1995	2004	2008	No data available
Oxygenator with built-in hemoconcentrator: a new concept	1995	2011	*	**
Design, manufacturing, and testing of a paracorporeal pulsatile ventricular assist device: Sao Paulo Heart Institute VAD	1995	2007	*	**
In vitro performance of the Baylor/NASA axial flow pump	1993	2000	*	**
A seal-less centrifugal pump (Baylor Gyro Pump) for application to long-term circulatory support	1993	1995	1998	No data available
In-vitro efficacy of an antibiotic releasing silicone ventricle catheter to prevent shunt infection	1994	2003	*	**
Re-freeze dried bilayer artificial skin	1993	1995	*	**
Thermal diffusion probe and instrument system for tissue blood flow measurements: validation in phantoms and in vivo organs	1994	1994	*	**
An integrated system for cementless hip replacement	1995	2000	2008	>30,000 cases
Robot assisted knee surgery	1995	2003	*	**
Stereotactic brain surgery	1995	1995	*	**

	Original article (Year)	First-in-human (Year)	License (Year)	Dissemination
An automatic technique for micro-drilling a stapedotomy in the flexible stapes footplate	1995	2007	*	**
Detachable clamps for minimal access surgery	1995	1995	*	**
Modified fabrication techniques lead to improved centrifugal blood pump performance	1994	1998	2000	>3,000 cases
Development and clinical application of a next generation implantable echocardiography probe for monitoring cardiac function under assisted circulation after open heart surgery	1994	1994	*	**
A new tracheal prosthesis made from collagen grafted mesh	1993	2005	*	**
Indentation instrument for the measurement of cartilage stiffness under arthroscopic control.	1995	1999	2001	No data available

Table 7.2. Articles that led to a first-in-human study and FDA license for use *No FDA license **No dissemination

	Rate ratio (95% confidence interval)*	
	First-in-human (n = 18)	**License (n = 6)**
Clinician involvement (Yes or No)	6.5 (0.8 – 53)	1.8 (0.2 – 19.3)
Industry involvement (Yes or No)	0.5 (0.2 – 1.4)	0.9 (0.2 – 5.4)
Technology type (Instrument or Implant)	2.7 (1.0 – 7.8)	0.6 (0.05 – 5.7)
Target of application (Broad disease or Single disease)	1.0 (0.1 – 8.8)	**

Table 7.3. Factors associated with publication of a first-in-human study and FDA license for use. *A rate ratio >1 indicates a faster publication **None of the devices proposed for a broad disease category were subsequently licensed for use

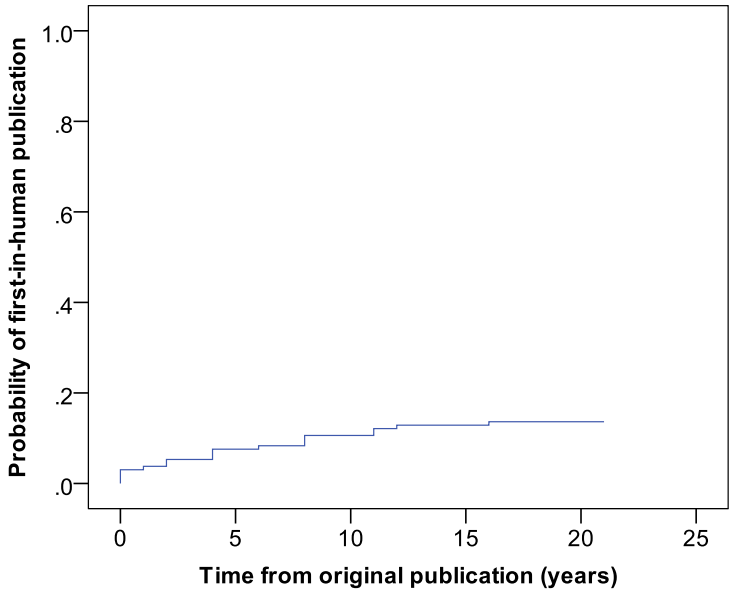


Figure 7.8. Kaplan-Meier graph illustrating the probability of a first-in-human publication over time.

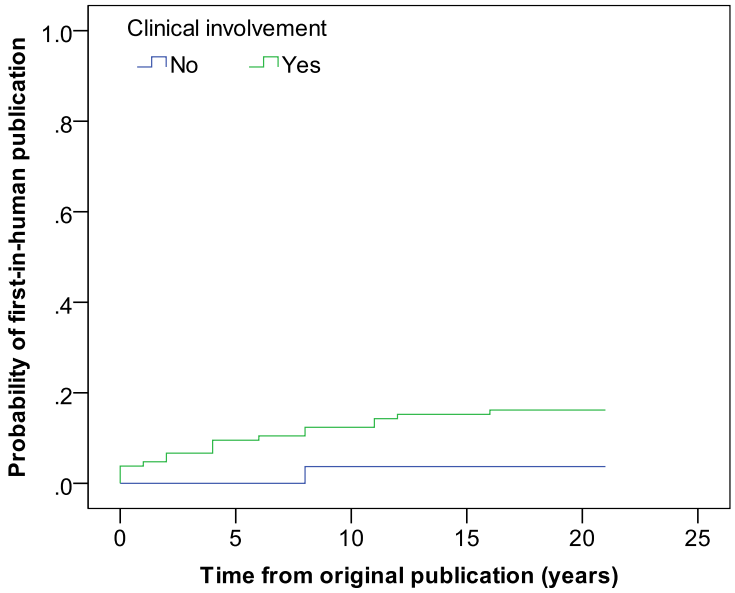


Figure 7.9. Kaplan-Meier graph illustrating the probability of a first-in-human publication over time stratified according whether there was clinical involvement or not.

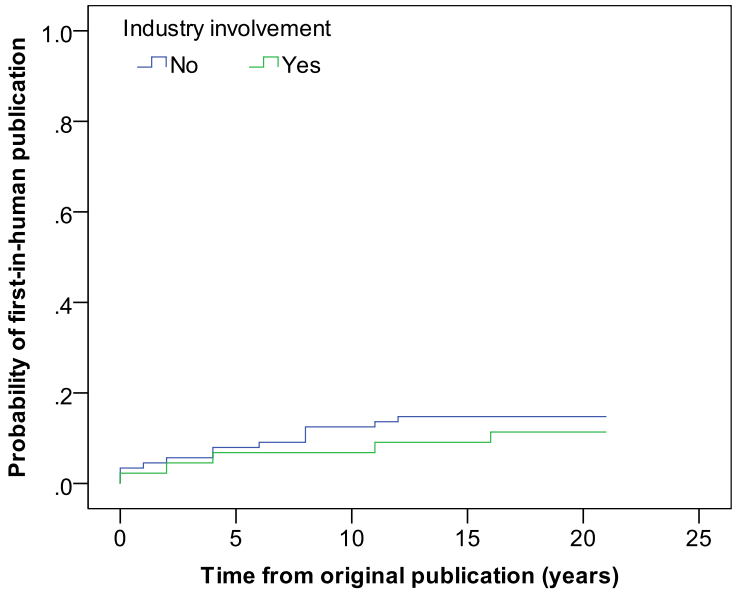


Figure 7.10. Kaplan-Meier graph illustrating the probability of a first-in-human publication over time stratified according whether there was industry involvement or not.

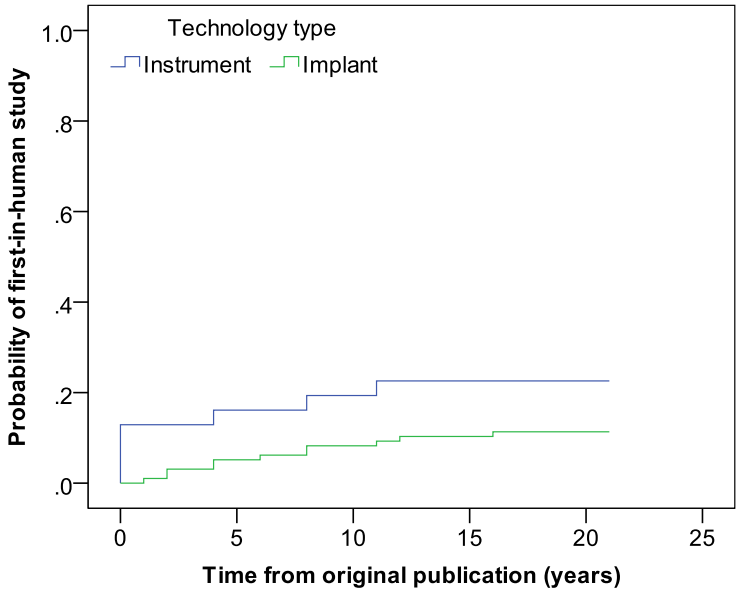


Figure 7.11. Kaplan-Meier graph illustrating the probability of a first-in-human publication over time stratified according whether the device was an implant or an instrument.

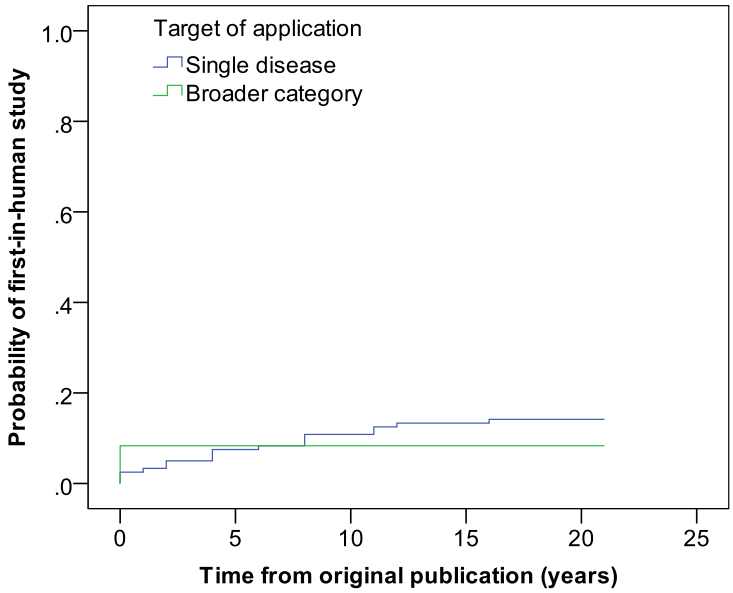


Figure 7.12. Kaplan-Meier graph illustrating the probability of a first-in-human publication over time stratified according whether the device was for a broad disease category or a single disease.

7.5.4 Discussion

7.5.4.1 Principal findings

For the first time, this study has quantitatively evaluated the clinical translation of technological innovation, using surgical device innovation as an exemplar. The early barriers to translation were considerable; only 13.6% of devices described in the literature resulted in first-in-human studies (T1), and 4.5% were ultimately licensed for use in patients (T2). The data on the late dissemination of devices (T3) was more sparse, but corroborates previous estimates that the lag between the initial description of a device and its widespread adoption by clinicians over a decade[280, 284]. Instruments were three times more likely to be translated than implants, and devices developed with clinical collaboration six times more likely to be translated than those without.

7.5.4.2 Comparison with other studies

Contopoulos-Ionnidis *et al* evaluated the translation of promising basic science research but, unlike the present study, they included work that had already been used in man, and focused on medicinal rather than device innovation [281]. They concluded that even the most promising basic science research, published in journals with the highest impact factors, were rarely translated; 5.0% of innovations were licensed for clinical use, and 1.0% were widely disseminated. In the present study, the leap from initial device description to first-in-human study (T1) represented a major barrier. The fact that Contopoulos-Ionnidis *et al* observed a similarly low rate of translation despite including early nonrandomised human studies, may reflect the more stringent requirements for licensing drugs compared to devices[286, 287].

In recent years, there have been several initiatives to increase translation through improved interactions between basic, translational and clinical researchers[283]. The present study is the first to provide quantitative evidence to support the idea that clinical collaboration is associated with more rapid and extensive translation. Interestingly, and in contrast to previous studies, industry collaboration was not associated with increased translation[281]. It is speculated that the reason for this disparity lies in the varying role of clinical and industry collaboration through the continuum of translation. Early translation (T1 and T2) may be more reliant on

clinicians to drive first-in-human and early clinical studies, while later translation (T2 and T3) may be more reliant on industry to navigate the complex and costly licensing pathway, and market devices to the wider clinical community.

7.5.4.3 Limitations

Several limitations to the present study must be acknowledged. First, this study made the implicit assumption that research groups publishing a first-in-human study would cite their initial description of the device, or subsequent developments of the device. Preliminary searches through the bibliographies of first-in-human studies suggested this was invariably the case. Second, the use of FDA approval to represent device safety and efficacy, did not account for devices developed and used elsewhere. The Acrobot®, for example, had received CE approval but not FDA approval[288]. The reason for selecting approval by the FDA, rather than other licensing authorities, was the availability of a search engine for the FDA medical database (FDA, Maryland, USA), allowing for a systematic search strategy. Third, the evaluation of dissemination relied on device manufacturers providing data on the number of units sold year-on-year. In many cases no valid contact details could be found and, if such details were available, manufacturers were rarely forthcoming. Fourth, the use of publications rather than patents, which are rarely cited in the literature, largely limited this study to the translation of technological innovations developed at academic institutions rather than industry. This may have favoured the more disruptive, and higher risk, innovations conceived by academia compared to the incremental innovations made by industry. Finally, in order to allow sufficient time for translation to have occurred, the devices evaluated in this study were initially described over 20 years ago. The environment in which these innovations were developed and translated is likely to be different from the complex ecosystem of today.

7.5.4.4 Conclusions

In conclusion this study has, uniquely, demonstrated quantitatively the considerable barriers to the translation of technological innovation. Moreover, this study suggests that clinical collaboration may be associated with greater translation. Nonetheless, a fundamental drawback of this analysis relates to the concept of translation itself. In this study a narrow definition of translation was necessarily adopted but it is

recognised that basic science research can indirectly have far more wide-reaching effects[279]. The inventors of the da Vinci™ robot (Intuitive Surgical, California, USA), for example, acknowledge earlier work captured in this study by Taylor *et al* that would not otherwise have been credited as having contributed towards clinical translation[289, 290]. To this end, future studies may investigate translation with greater granularity.

CHAPTER 8 CONCLUSIONS AND FUTURE WORK*

*Content from this chapter was published or submitted as:

Marcus HJ, Nandi D, Darzi A, and Yang GZ. Surgical Robotics through a Keyhole: from Today's Translational Barriers to Tomorrow's 'Disappearing' Robots. IEEE Trans Biomed Eng. 2013; 60: 674-681

8.1 Achievements

At the commencement of this thesis, few studies had specifically addressed the application of robotics to keyhole transcranial endoscopic microsurgery. To this end, this thesis has carefully identified the unique technical challenges of keyhole neurosurgery, systematically evaluated the potential technological solutions, and then integrated these technologies into a prototype robotic platform.

Chapter 2 described the supraorbital approach through an eyebrow incision as an exemplar of the keyhole concept in the brain. The Modelled Anatomical Replica for Training Young Neurosurgeons (MARTYN) was modified to simulate the supraorbital approach, and a validation study was performed, which confirmed that the model had face, content, and construct validity. This model was developed with a view to evaluating the technologies described in subsequent chapters (see below), but it is hoped it may also be helpful for education and training.

Chapter 3 was a clinical needs assessment and technological gap analysis. A qualitative survey of neurosurgeons was performed to determine the technical challenges of keyhole neurosurgery, and an emergent theme analysis identified three major areas for research: first, surgical approach and better integration with image guidance systems; second, intra-operative visualisation and improvements in endoscopes; and third, surgical manipulation and improvements in instruments. A novel methodology was then used to quantitatively evaluate technological innovation in neurosurgery using patents and publications as metrics of technology development and translation respectively. Image guidance devices and endoscopes were among the top-performing technology clusters, providing empirical evidence for their development and use. A community survey suggested that master-slave and handheld robotic platforms incorporating these technologies would be acceptable to patients and their relatives. Chapter 3 then critically appraised existing surgical robots against these requirements. The literature review represents the most extensive summation of the literature that has been undertaken to date. The chapter concluded with a cadaver study that demonstrated that the most widely used surgical robot worldwide today, the da Vinci™ platform, is neither safe nor feasible to use in keyhole neurosurgery.

Chapter 4 addressed surgical approach and image guidance. A narrative review summarised the various image display modalities used by image guidance platforms including standard triplanar display, and various augmented reality overlays. A laboratory-based randomised study using the MARTYN head compared the efficacy and safety of these platforms. All forms of image guidance significantly improved surgical performance, with augmented reality overlays found to be superior to triplanar display. An unexpected finding was that all image display modalities, including triplanar display, carried a risk of inattentional blindness. The use of on-demand inverse realism or wireframe overlays may represent an optimal solution, allowing for improved effectiveness, while maintaining a safety profile comparable to triplanar display. Nonetheless, this supports the need for less experienced surgeons using image guidance systems, particularly when undertaking complex approaches, to be carefully supervised by experts that are less cognitively loaded and better able to identify potential complications.

Chapter 5 addressed intra-operative visualisation and endoscopy. The systematic review represents the first and only effort at data synthesis of comparative data on 3D versus 2D endoscopy in neurosurgery. The review concluded that at present there is limited and low quality data to support 3D compared to 2D endoscopy. A notable limitation was that all studies compared 3D SD and 2D HD endoscopy. Higher image quality may allow for improved depth perception using monocular cues, confounding interpretation of these studies. Chapter 5 therefore evaluated the first commercially available 3D HD endoscope designed for brain surgery. A laboratory-based randomised crossover study was performed comparing simultaneously the effectiveness of 3D versus 2D, and HD versus SD. Interestingly, 3D and HD endoscopy led to differing but complementary improvements in surgical performance, suggesting that neither alone can completely compensate for the lack of the other.

Chapter 6 addressed surgical manipulation and improvements in instruments. A narrative review summarised the various tools available in endoscopic neurosurgery, and discussed more generally the evolution of instrument design. The loss of triangulation with use of tube-shaft instruments through a single keyhole, and the small operative working spaces within the brain, represent considerable technical barriers to keyhole neurosurgery. To investigate this, a laboratory-based randomised

crossover study comparing the performance in single-port versus multi-port surgery and small versus large operative working spaces was performed. The findings of this study suggested that instrument triangulation, rather than operative working space, is the most critical determinant of surgical performance. The study also validated a modified peg transfer and pattern cutting task in a small cuboid training box that is representative of transcranial approaches, which was used in subsequent technology evaluation. Recognising that robotic articulated instruments may allow for improved triangulation, Chapter 6 then sought to provide detailed specifications for such instruments: an MRI study found the volume of the suprasellar cistern to be approximately 6.5cm^3; a cadaver study found the forces exerted in microsurgical dissection to be typically less than 0.3N; and a time-motion video demonstrated that a sucker and bipolar forceps were the most common tools used. This data was used to develop prototype robotic articulated instruments. A pilot laboratory study showed the use of these instruments was feasible. However, at present their poor kinematic control limits their effectiveness compared to standard rigid instruments.

Lastly, Chapter 7 described the micro-IGES platform; a prototype robot that integrates on-demand augmented reality, 3D HD endoscopy, and robotic articulated instruments. A pilot laboratory study showed the use of this platform in keyhole neurosurgery is feasible, and that many of the incorporated technologies were synergistic. A cadaver and early clinical study of the 3D HD endoscope was also performed, demonstrating that the technology had promise. The chapter concluded by taking an overarching view of the process of translation, with an observational study on the rate and extent of translation of technological innovation, and the factors that affect it. Although significant barriers exist – only 13.6% of devices described in the literature resulted in first-in-human studies – clinical collaboration was found to be associated with improved translation; this has clear policy implications.

8.2 Future work

Area	Advances
Surgical approach	Augmented reality Compensation for intra-operative shift Flexible access with hyper-redundant (e.g. snake like) robot platforms
Intra-operative visualisation	Integrated 3D HD endoscopy Macroscopic endoscopic imaging - Photodynamic diagnosis - Narrow band imaging Microscopic endoscopic imaging - Optical coherence tomography - Confocal microendoscopy
Tissue manipulation	Robotic articulated instruments Miniaturisation Novel instruments Delivery of custom therapies
Integrated robotic platforms and the human-machine interface	Ergonomic console Haptic feedback Seamless human-robot interaction and perceptual docking

Table 8.1. Areas of research in robotic transcranial endoscopic microsurgery (underlined are topics covered in the present thesis).

8.2.1 Surgical approach

Although image guidance systems are frequently used in contemporary neurosurgical practice to plan the scalp incision and craniotomy, the shift of structures intra-operatively has restricted their use later in the course of surgical procedures. Intra-operative imaging can be used to account for the movement of structures during surgery, and therefore provide real-time information on the location of pathology[291-293]. Intra-operative ultrasound, CT and MRI systems have all been used in this way, each with their own strengths and weaknesses. Intra-operative ultrasound, for example, is relatively inexpensive but produces images of relatively low contrast and

low resolution. Conversely, intra-operative CT and MRI offer high contrast and high resolution images, but the former utilises ionising radiation, and the latter requires non-ferromagnetic instruments. In recent years, progress has been made towards addressing all these issues including the development of high-quality ultrasound, low-dose CT, and low-field MRI systems. Indeed, several MRI-compatible robotic systems have already been developed, some of which are currently under evaluation in clinical trials[294]. The integration of image guidance systems that combine intra-operative imaging and augmented reality into surgical robots will permit surgeons to quickly and exactly define their operative approach.

A potential extension of these advances in image-guidance technology is the concept of "flexible access surgery", allowing a safe approach to lesions even if they do not lie directly within a rigid surgical trajectory. While flexible endoscopes do in principle allow for flexible access their passive kinematic design often leads to them veering off a planned course, and makes them unsuitable for neurosurgery. Flexible access robotic platforms with greater structural stability are currently under development and may have a role in selected cases, such as the biopsy of deep-sited brain lesions[119, 295, 296]. In these instances, surgeons might use pre-operative imaging to identify the entry-point, target-point, and no-go regions that must be avoided such as critical vasculature or eloquent neural structures, and an optimal curvilinear path followed.

8.2.2 Intra-operative visualisation

Improved macroscopic visualisation techniques such as photodynamic diagnosis and narrow band imaging are already now utilised in some cases to better distinguish between cancerous and unaffected tissue[297, 298]. These techniques are particularly valuable in fields such as neurosurgery where it is important to preserve normal tissue and wide resection margins are not feasible. In photodynamic diagnosis, a protoporphyrin analogue such as 5-Aminolevulinic acid (5-ALA) is administered, and selectively accumulates in cancer cells. During surgery a blue light source (375-440nm) is used and stimulates tumour cells to fluoresce and appear red. In a well publicised randomised controlled multicenter phase III trial of patients with intrinsic brain cancers undergoing surgery, complete resection was achieved in 65% of patients

when using 5-ALA, compared to 36% of patients using white light alone[298]. In narrow band imaging improved visualisation of tumour and normal tissue is accomplished without the use of exogenous contrast agents. Instead, a light source is used that filters white light into two wavelengths (415 and 540nm) that are strongly absorbed by haemoglobin, therefore enhancing the contrast between the more vascular cancerous tissue and the surrounding benign tissue[297]. The drawback of this approach is that identification may be more subjective than photodynamic diagnosis. Moreover, bleeding intra-operatively decreases overall illumination and further impairs surgical recognition of tumour tissue.

While photodynamic diagnosis and narrow band imaging offer improved macroscopic visualisation, several novel technologies are being developed with the goal of providing real-time in-vivo microscopic imaging, and the capacity for superior discrimination of tumour and non-tumour tissue. Optical coherence tomography operates in a manner analogous to ultrasound but utilises the scattering of light rather than sound to provide high-resolution cross sectional imaging of tissue[297]. Confocal microendoscopy combines the principles of confocal microscopy with fibre-optics to visualise tissue at even higher resolutions in-situ. Fluorescent agents are generally administered and video-sequences then acquired of tissues using the technique, revealing cellular morphology and micro-architecture in a way previously only possible by cytological or histological analysis respectively[297, 299, 300]. In an animal study using thirty mice implanted with GL261-luc cells, the use of indocyanine green (ICG) with near-infrared laser confocal microendoscopy was able to effectively visualise the infiltrating tumour boundary and also identify satellite cancer cells within the surrounding tissue[300]. More recently, a total of 15 fresh specimens from patients undergoing surgical resection were analysed ex-vivo using confocal microendoscopy after being incubated with acruavine or fluorescein for 3-5 minutes at room temperature. Healthy brain, glioblastoma, meningioma, and metastases, were all readily visualised using the technique[299]. The development and integration of these promising new optical imaging technologies into robotic systems may further improve the detection, characterisation and resection of tumours. Robot-assisted in-vivo confocal endomicroscopy may, for instance, allow the maintenance of constant force and contact between the probe and tissue, which is critical for large area

surveillance and acquiring high quality images[301]. This will also help to assemble images into large mosaics[302].

8.2.3 Tissue manipulation

Novel instruments under development will add further tools to the robotic armoury. In parallel to the development of minimally invasive neurosurgical approaches, great advances are being made in the field of molecular biology. The suppression of endogenous gene expression, and delivery of exogenous genetic material, has the ability to transform the treatment of neurological disease by, for example, enabling the selective eradication of infiltrating tumour cells, or the regeneration of damaged tissues[303]. The presence of the blood-brain barrier, and the relative immune privilege of the brain, limits the escape and eradication of viral vectors respectively, making the brain an ideal target for molecular surgery. Several techniques of gene delivery to the brain have been described. Simple injection of viral vectors into the brain parenchyma or ventricular system does not appear to be very effective, with a range of no more than a few hundred micrometers from the needle-point. Instead, several groups have reported the use of convection-enhanced delivery (CED). Here, very fine catheters are inserted into the brain and vectors infused at a slow-rate, enabling their controlled homogeneous distribution over many centimetres. The use of robotic systems to accurately and precisely position catheter tips may allow for the compartmentalisation of viral vectors, and other drugs, into discrete anatomical regions, thus reducing the risk of toxicity.

8.2.4 Integrated robotic platforms and the human-machine interface

Suitable human-robot interfaces are an essential prerequisite to the utilisation of all surgical robots, but are particularly important in complex systems with multiple degrees of freedom. In robotic systems with redundancy, such as articulated flexible access platforms, the use of human hands alone is insufficient, and additional degrees of freedom must therefore be controlled independently. In these instances the recently introduced concept of perceptual docking may be applied[304]. In short, in-situ sensing is used to determine operator-specific visuomotor behaviour, which can in turn be used to provide more seamless robotic control. For example, during neurosurgical procedures the brain may be seen to visibly pulsate with cardiac-induced variations in

intracranial pressure (ICP), which can make delicate surgical dissection more hazardous. A gaze-contingent perceptual docking paradigm could use binocular eye-tracking to provide information on a surgeon's gaze, allowing motion compensation and visual stabilisation on the pulsating brain.

The provision of haptic feedback in robot-assisted surgery has proved difficult but in recent years considerable progress has been made towards this goal too, with commercially available robots such as neuroArm integrating optical force sensors and transmitting information to the surgical workstation and hand controllers[294]. Such systems hold the prospect of a more immersive surgical environment.

8.3 Conclusion

Alongside these improvements in surgical approach, intra-operative visualisation, and tissue manipulation, technological progress will see robots evolving towards smaller, more powerful, and less costly units in a way analogous to digital computing over the last half-century. The Colossus computers, which were used to assist with cryptanalysis during World War II, were perhaps the world's first programmable digital computers. Each of the ten Colossus computers that were built weighed approximately a ton, and occupied their own large room[305]. Over the subsequent half-century incremental advances led to the development and popularisation of personal digital computers that bore little resemblance to their predecessors. Within the last decade further miniaturisation has led to the integration of digital computing into everyday "smart" devices such as mobile phones. Paradoxically, the rapid expansion of pervasive computing has resulted in digital computers increasingly disappearing into the background of people's professional and personal lives.

Although lagging several decades behind digital computing, there is evidence that surgical robotics is already moving along a similar trajectory. While the robots in use today remain large and imposing, a range of smaller robotic systems is being constructed. Technological progress will almost certainly see the relatively high cost of robotic systems drop. Furthermore, with multiple robots available, and more competition between the manufacturers of these robots, it is likely that their price will further fall. Eventually a tipping point will be reached, and their purchase will become a realistic prospect for most hospital managers; thus overcoming a major barrier to their utilisation[307].

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