Innovation in neurosurgery: Evaluation of neurosurgical innovation, related ethics, and solutions

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For my mother

Non viribus aut velocitate aut celeritate corporum res magnae geruntur, sed consilio auctoritate sententia
(It is not by muscle, speed, or physical dexterity that great things are achieved, but by reflection, force of character, and judgement)

Marcus Tulius Cicero (*De Senectute* 17)

Contents

Preface

Neurosurgery has come a long way during the past century as a result of continuous innovation. The quality of care provided by neurosurgeons today is the result of previous innovative neurosurgeons, including pioneers such as Dr. Harvey Cushing and Dr. Gazi Yaşargil, that wanted to provide better outcomes for their patients.[5, 8] There are endless examples of how neurosurgical innovation has resulted in improved patients' outcomes. These include microsurgical aneurysm clipping, awake resections, and epileptic surgery.[2, 3, 10, 13] These innovations are not limited to strictly surgical innovations and also include revolutions in imaging, new pharmaceuticals, radiation, and perioperative care.[1, 12, 14] As a result, neurosurgery in its current form would be unrecognizable to neurosurgeons a hundred years ago. Nevertheless, outcomes of many neurosurgical patients, and neuro-oncological patients in particular, remain poor and warrant further improvement.[11] This improvement will require continuous innovation and improvement of the innovation process.

Despite the need for continuous innovation, the manner of introduction of neurosurgical innovations has hardly changed over the last fifty years. Most neurosurgical innovations are introduced as an alteration of previous procedures or as a broadening of indications. Neurosurgeons may also be faced with a challenging case which forces them to innovate when no other options are available. Neurosurgical innovations may also only become apparent in retrospect. This is in stark contrast with pharmaceuticals, which have to be evaluated according to strict guidelines and receive official approval.[15] Not all neurosurgical innovations have been beneficial to patients and some have turned out to be downright detrimental to patients, such as the frontal lobotomy.[7] The manner in which neurosurgical innovation takes place may, therefore, be improved. In this thesis, several neurosurgical innovations, manners of outcome evaluation, related ethics, and potential manners for improvement of innovation are evaluated.

In **part I**, the current status of neurosurgical innovation will be evaluated. Several recent innovations such as the Woven Endobrigde device[6] (**chapter 1**), retreatment for intracranial aneurysms (**chapter 2**), and endoscopic endonasal meningioma resection (**chapter 3**) will be evaluated. **Chapter 4** will evaluate the applicability of randomized control trials (RCT) in neurosurgery as a manner of ethical innovation. This chapter describes what the advantages and disadvantages are of RCTs in neurosurgery.

Part II will focus on the ethical evaluation of neurosurgical innovation. **Chapter 5** describes the ethics related to oversight and regulation of medical devices introduction. Ethics related to conflicts of interest in neurosurgery are discussed in **chapter 6**. **Chapter 7** describes how procedural innovations may be introduced in an ethical manner. **Chapter 8** reviews the implications of the learning curve that comes with innovative surgery. Finally, respect for autonomy in emergency neurosurgery and

innovation in such a scenario is discussed in **chapter 9**.

Part III focuses on the applicability of available frameworks for neurosurgical innovation. **Chapter 10** describes the evaluation of the Idea, Development, Exploration, Assessment, Long-term study (IDEAL) Framework for neurosurgery and discusses how it may be applied in neurosurgery.[9] **Chapter 11** describes the applicability of the learning health systems (LHS) in neurosurgery for potential improvement of the current situation from both a practical and an ethical perspective.[4] This will provide insight into how neurosurgical innovation may be improved in both an ethical and practical manner and thereby improve patients' outcomes.

Ivo S. Muskens
The Hague, February 2021

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I

Part 1: Evaluation of past neurosurgical innovation

1

The Woven Endobridge Device for Treatment of Intracranial Aneurysms: A Systematic Review

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***Introduction**: The Woven Endobridge (WEB) device is an innovative endovascular device for treatment of intracranial aneurysms, especially bifurcation and wide-neck aneurysms. Although not approved by the U.S. Food and Drug Administration, it has been available in Europe since 2011. The aim of this review is to evaluate the outcomes of WEB device use for intracranial aneurysm treatment. **Methods**: A systematic review was conducted with MEDLINE search engines PubMed and Embase from 2011. The search strategy provided 6229 articles, and 19 articles were included. **Results**: A total of 19 papers were identified describing the use of WEB devices in 687 patients with 718 aneurysms. The 2 largest prospective multicenter studies (WEBCAST and the French Observatory Trial) reported successful treatment, defined as complete closure or a neck remnant, in 85% and 79% of aneurysms, respectively. The use of a WEB device in combination with coiling or stenting was described with varying results in multiple small series. Outcomes of WEB device use in ruptured aneurysms in 2 studies showed 94% and 80% adequate treatment. Thromboembolic events were described in 71 patients (10.3% of all patients) and infarctions in 8 patients (1.2% of all patients). **Conclusions**: Despite initial promising results, the WEB device should be used with caution given its potentially large learning curve and because it has primarily been investigated only in*

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wide-neck and bifurcation aneurysms. In addition, currently available prospective studies have short follow-up, and the device has not been directly compared with other treatment modalities.

Introduction

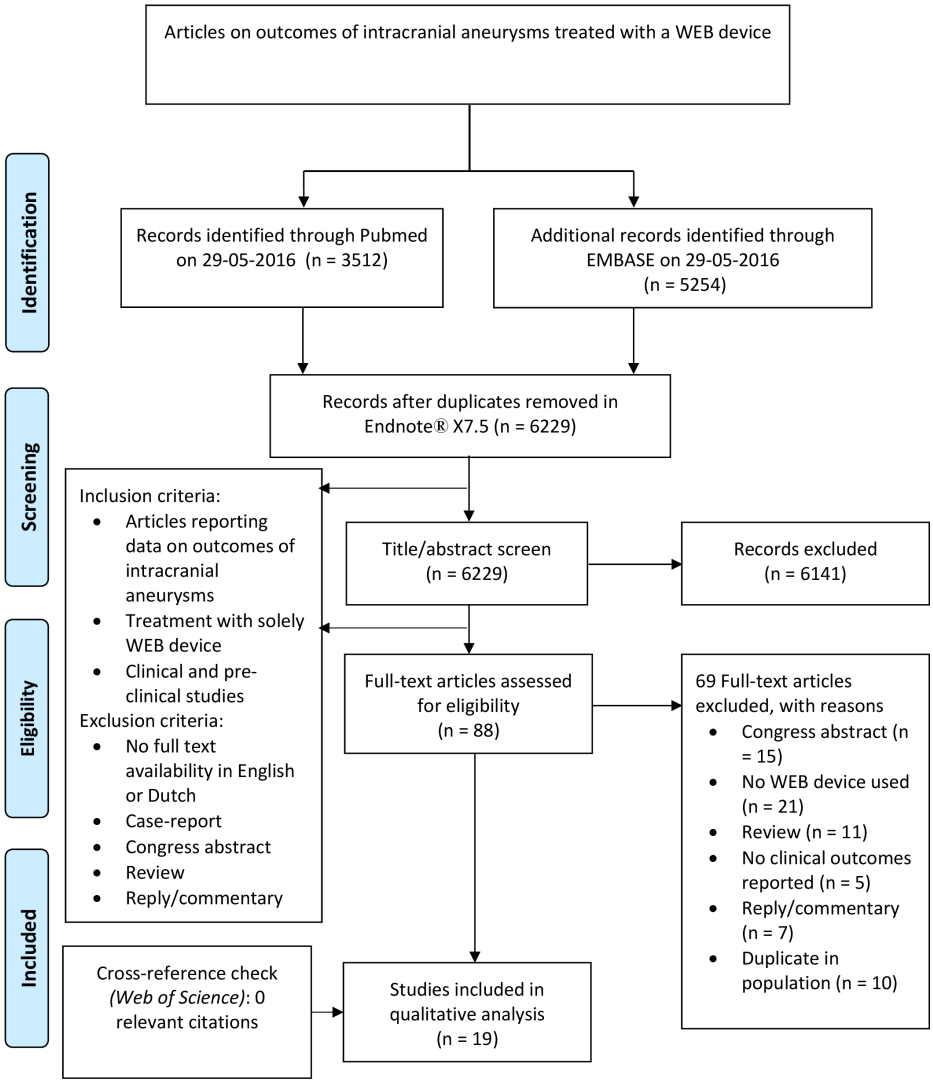
Wide-neck and bifurcation aneurysms, especially of the basilar artery, remain particularly difficult to exclude from the circulation.[1] Indeed, they still confer great morbidity and mortality despite advances in medical technology.[2] As a result, there have been a growing number of options to treat aneurysms using endovascular approaches (e.g. coiling or flow diverters) as opposed to traditional clipping.[3-5] A recently introduced innovative endovascular device, the Woven Endobridge (WEB) device (©Sequent Medical Inc., Aliso Viejo, California, USA), is a self-expanding mesh that can be introduced into intracranial aneurysms.[6] After deployment, the mesh covers the neck of the aneurysm, resulting in flow disruption in the sac of the aneurysm. This subsequently leads to exclusion of the aneurysm from the circulation.[6] This feature makes it ideal for treating wide-neck and bifurcation aneurysms, as it covers the neck of the aneurysm.[6] Since the introduction of the WEB device in 2011, it has become clinically available in Europe, but is currently not FDA (Food and Drug Administration) approved.[6] In this systematic review, the aim is to evaluate outcomes of aneurysms treated with a WEB device.

Methods

Search strategy and paper selection

A systematic review of the current literature was conducted to identify studies reporting on pre-clinical and clinical experience with WEB devices for intracranial aneurysms. To this aim, both PubMed and Embase databases were searched. As the WEB device was introduced in 2011, articles published before that time were excluded from the search.[6] For the search strategy the keywords "WEB device" and "endovascular therapy" with synonyms were used. The search strategy, which was made with help from a librarian, is described in **Supplementary Table 1.3**. The last search was conducted on 5-29-2016. This review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[7] The resulting flowchart is depicted in **Figure 1.1**. After the articles were imported into Endnote X7.5, duplicates were removed. Titles and abstracts were screened by two authors independently (IM and JS) for articles reporting on the use of the WEB device for intracranial aneurysms. For full text screening, articles reporting on outcome of aneurysms treated with a WEB device were included, both clinical and pre-clinical. Only literature in English and Dutch was reviewed. Case reports, congress abstracts, commentaries and reviews were excluded. If there were overlapping cohorts, only the largest cohort was included in the review. Web of Science was consulted for additional papers, and references of selected articles were checked for possible relevant studies.

Figure 1.1: Flowchart



Flowchart of study selection process for articles on the WEBdevice

Data extraction

The following variables were extracted from the full text of each study: study design, number of patients, number of aneurysms treated, aneurysm location, number of ruptured aneurysms, microcatheter size, successful WEB device placement, length of follow-up, complete aneurysm occlusion on angiogram, aneurysm neck remnant, aneurysm remnants, re-treatment, antithrombotic therapy, thromboembolic events, other complications, and re-rupture.

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Table 1.1: Study characteristics

Author (year of publication)	patients (N)	Number unruptured (%)	Trial design	Follow-up (month)	Sort of aneurysm	aneurysm location	anti thrombotic therapy protocol	microcatheter size used (inch)	Thromboembolic event	Other procedural complications reported
Ambrosi et al. (2015)	10	10 (100)	PCS	6	bifurcation	MCA (4), AcomA (5), Basilar Tip (1)	500mg aspirin preoperatively, 75 mg aspirin once daily for one month	0.027	0	
Behme et al. (2015)	52	41 (75)	RCS	3 (44 aneurysms)	Wide neck	MCA (19), AcomA (9), Basilar (10), Pcom (4), ICA (8), superior cerebellar artery (1), ACA (1)	100 mg aspirin and 75 mg Clopidogrel 5 days before treatment. aspirin was continued for 6 weeks post treatment	0.027	4	aneurysm rupture (1) P1 stenosis (1)
Caroff et al. (2014)	6	6 (100)	RCS	6	Wide neck	MCA (3), ACA(3)	none	0.027, 0.025	2	
Caroff et al. (2015)	90	65 (66)	RMCS	Mean 3.3 (54 aneurysms)	not specified	MCA (38), AcomA (21), BA(19) ICA (15)	Varied per hospital, all patient heparinized during the procedure	0.027, 0.033	6	aneurysm rupture (1), parenchymal hemorrhage (7)
Clajus et al. (2016)	108	67 (59)	RCS	mean: 13.4 (90 aneurysms)	87.5% wide neck	MCA (39), ACA (7), AcomA (27), ICA (17), Pcom (7), PCA (1), BA (15), VA (1)	Heparinized during procedure, aspirin 100mg, clopidogrel 75 mg one week prior and for 6 months post procedural	0.021, 0.027, 0.033, 0.038, 0.044	11	Re-bleed (2), infarction from WEB dislocation (2)
Colla et al. (2013)	4	2 (50)	RCS	7	basilar tip	BA (4)	not standardized	not standardized	NR	
Gherasim et al. (2015)	10	10 (100)	RCS	3 - 6	Wide neck	AcomA(10)	none	0.027, 0.038	1	WEB device protrusion with thromboembolic event (1)
Kabbasch et al. (2016)	8	7 (88)	RCS	3.5 - 38 months	large partially thrombosed	AcomA (5), Pcom (1), ICA (1) Basilar (1)	not standardized	NS	NR	
Klisch et al.	2	2	RCS	1.5	bifurcation	Basilar (1) , MCA (1)	heparinized during procedure and aspirin 100mg		0	

Table 1.1: Study characteristics (continued)

(2011)		(100)			and basilar tip		for 6 months postprocedural			
Lawson et al. (2016)	22	3 (14)	RCS	3	wide neck and bifurcation	MCA (5), ICA (3), AcomA (3), Basilar tip (11), Pcom (3)	heparinized during procedure	0.033	3	aneurysm rupture (1), Symptomatic ischemia (1)
Lescher et al. (2016)	22	22 (100)	RCS	mean: 7	NS	MCA (5), AcomA/ACA (4), ICA (I), BA (11), VA (1)	apririn 100 mg 3 months	0.021, 0.027, 0.033, 0.058, 0.072	0	
Liebig et al. (2015)	47	0 (0)	RMCS	Mean 4 (25 aneurysms)	Wide neck	MCA (7), Pcom (1)	not standardized	0.027, 0.033	4	aneurysm perforation (3), WEB device protrusion (4), infarction (2)
Lubicz et al. (2013)	19	19 (100)	PCS	mean: 6 month	Wide neck	MCA (14), AcomA (2), ICA (1), Basilar (2), VA (1)	none	0.027, 0.033	2	infraction (1), intraoperative aneurysm rupture (1)
Papagiannaki et al. (2014)	83	75 (88)	PMCS	Mean 5.3 (65 aneurysms)	NS	MCA (48), basilar (18), AcomA (11), ICA (8)	not standardized	≥ 0.027	9	aneurysm rupture (1)
Pierot et al. (2013)	33	29 (85)	RMCS	mean: 7.2 (30 aneurysm)	Wide neck	MCA (34)	not standardized	≥ 0.027	5	intraoperative rupture (1)
Pierot et al. (2015)	26	24 (92)	RMCS	mean: 27.9 (19 aneurysms)	Wide neck bifurcation	MCA (13), Basilar (8), PICA (1), AcomA (3), ICA (1)	NR	NR	3	
Pierot et al. (2016)	62	56 (89)	PMCS	12 (58 aneurysms)	Wide neck	MCA (32), AcomA(16), Basilar (9), ICA (6)	not standardized	0.027, 0.033	9	intraoperative rupture (1)
Pierot et al. (2016)	51	48 (94)	PMCS	6 months (41 aneurysms)	Wide neck	MCA (29), Basilar (12), ICA (6), AcomA(4)	not standardized	NS	9	
Van Rooij et al. (2016)	32	0 (0)	RCS	3 - 6 months (18 aneurysms)	Ruptured	AcomA(11), MCA (8), Pcom (7), pericallosal (3), superior cerebellar (1), BA (1), ophthalmic (1)	None	0.027, 0.033	3	

Legend: Abbreviations: RCS: retrospective case series, PCS: prospective case series RMCS: retrospective multicenter study, PMCS: prospective multicenter study, MCA: middle cerebral artery, ACA: anterior cerebral artery, AcomA: anterior communicating artery, Pcom: posterior communicating artery, ICA: internal carotid artery, Basilar artery: BA PCA: posterior cerebral artery, VA: vertebral artery, PICA: posterior inferior cerebellar artery, NS: Not specified

Results

After removing duplicates, 6229 articles were identified. After screening for title and abstract, 6141 articles were excluded and the full texts of 88 articles were reviewed. Afterwards, 19 studies were included in the review, with a total of 687 patients with 718 aneurysms.[6,8-25] Study characteristics are reported in **Table 1.1**.

Preclinical results

Two studies reported preclinical results of the WEB device.[26,27] The first study, performed in rabbits, reported complete occlusion of 19, incomplete occlusion of 2, and recanalization of 3 aneurysms at 12-month follow-up (n=24).[26] A different study in 80 rabbits found complete occlusion of 15, neck remnants in 11, proximal recess persistence in 11, and aneurysm remnants in 37 aneurysms based on histology.[27] In this study it was also noted that angiographic adequate occlusion had a sensitivity of 97.7% and a specificity of 64.9% compared to histology with an inter-observer weighted kappa coefficient of 0.76 (95% CI, 0.76 - 0.82).[27] Interestingly, this study was published when the WEB device was already used extensively in European clinics.[12,25]

Clinical results

In 2011, Klisch et al reported the first treatment of intracranial aneurysms using the WEB device.[6] They reported on two patients with unruptured wide-neck bifurcation

aneurysms that were treated successfully, with MRAs showing complete occlusion at eight weeks.[6]

Five studies reported on prospective outcomes. In the "WEB Clinical Assessment of Intrasaccular Aneurysm Therapy" (WEBCAST) European multi-center prospective trial for wide-neck aneurysms, 48 out of 51 (5.9% ruptured) aneurysms were considered treatable with a WEB device. At six-month follow-up with Digital Subtraction Angiography (DSA), complete occlusion was achieved in 23 (56.1%) patients, a neck-remnant was observed in 12 (29.3%), and an aneurysm remnant in 6 (14.6%), with 4 patients requiring additional endovascular intervention.[21] Another study also reports a patient with regrowth of a middle cerebral artery (MCA) aneurysm nine months after placement of a WEB device that was successfully recoiled, but no further follow-up was reported.[28]

In the prospective multi-center French Observatory study for WEB devices, 63 devices were placed in wide-neck bifurcation aneurysms in 62 patients. Of the 58 aneurysms with follow-up, 30 aneurysms were completely occluded, 16 (27.6%) had neck remnants and 12 (20.7%) showed aneurysm remnants at one-year follow-up. Among the aneurysms that showed a remnant, seven required additional endovascular intervention at time of WEB placement, and two required retreatment with a flow diverter.[24] Retreatment was unsuccessful for one of these two patients.[24] In the largest prospective multi-center study, 79 out of 85 WEB placement procedures were successful. Out of 65 aneurysms, there was complete occlusion in 37 (57.0%), neck-remnant in 23 (35.3%), and an aneurysm remnant in 5 (7.7%) at a mean follow-up of 5.3 months.[20]

In another prospective cohort study of 10 patients with bifurcation aneurysms, WEB placement was successful in 8 (80%) cases, with complete occlusion in 2 (25.0%), a neck remnant in 5 (62.5%), and an aneurysm remnant in 1 (12.5%) patient at 6-month follow-up.[8] Similar results were reported in a separate study of 20 wide-neck aneurysms, of which 19 were treated successfully. 19 Of the 14 aneurysms in this study with follow-up, 2 (14.2%) required retreatment, and there was complete occlusion in 0 (0%), neck-remnant in 13 (92.9%), and incomplete occlusion in 1 (7.1%) aneurysms.[19]

In the largest reported single-center experience, 114 aneurysms (41.2% of which were ruptured) were treated in 110 patients. Of the 90 aneurysms with follow-up, complete occlusion or occlusion with a neck remnant was achieved in 68, and 22 (24.4%) aneurysms showed residual filling.[12] A total of 15 (16.7%) aneurysms in this study were retreated with other endovascular procedures.[12] The second largest retrospective multi-center study reported success in 93(94.9%) out of 98 WEB device placement procedures for aneurysms (34% of which were ruptured). At a mean follow-up of 3.3 months, good outcomes were not further specified, although there were eight reported aneurysm remnants.11 Eight other retrospective case series with varying degrees of follow-up and occlusion had similar outcomes, and the results of these studies are depicted in **Table 1.2**.[9,10,13,15-18,22,23]

In terms of complications and adverse events associated with WEB device placement, procedural aneurysm rupture was reported in 10 patients.[9,11,16,18-20,22,24] Thromboembolic events associated with the procedure were reported more frequently with a total of 71 patients (10.3% of all cases) and infarction was seen in 8 cases (1.2% of all

cases).[9,12,14,16,18-23,25] Re-bleeds were only reported in five patients in two studies with mean follow-up of 3.3 and 14.4 months.[11,12]

Ruptured versus unruptured aneurysms

Specific outcomes for ruptured aneurysms were described in two retrospective studies.[18,25] The first study included 52 aneurysms, 20 of which had a mean follow-up of 4 months. Of these 20 aneurysms, 15 (75.0%) were completely occluded, 5 (25.0%) had a neck remnant, and 5 (25.0%) showed a remnant.[18] In the other study, 18 aneurysms of the initial 32 had at least 3 months of follow-up. Of these 18 aneurysms with adequate follow-up, 15 (83.3%) showed complete closure, 2 (11.1%) showed a neck remnant, and 1 (5.6%) showed a remnant.[25]

For unruptured aneurysms, 2 prospective studies reported the outcomes of 10 and 20 bifurcation aneurysms, respectively.[8,19] The first study reported 8 successful WEB device placements in 10 aneurysms. Of these 8 aneurysms with successful placement, 2 (25.0%) showed complete occlusion, 5 (62.5%) showed a neck remnant, and 1 (12.5%) showed an aneurysm remnant at follow-up.[8] In the second study, 14 of 20 aneurysms had follow-up, and of these 13 (92.9%) had a neck remnant and 1 (7.1%) showed an aneurysm remnant.[19] Three other retrospective studies for exclusively unruptured aneurysms also showed low numbers of aneurysm remnants as indicated in **Table 1.2**.[11,14,17]

In studies that reported exclusively ruptured or unruptured aneurysms, overall aneurysm remnant at follow-up was 6 out of 43 (14.0%) for ruptured aneurysms versus 8 out of 59 (13.6%) for unruptured aneurysms at follow-up.[8, 11,14,17-19,25] However, although these outcomes may appear similar, they cannot be adequately compared due to great variation in patient characteristics as indicated in **Table 1.1**.

WEB device in combination with other endovascular treatments

One study reported successful treatment of two patients with two aneurysms that were too big to treat with available WEB device sizes by using a combination of coiling and WEB device placement at the dome, with six months of follow-up in one patient.[29] Another study described eight complex large aneurysms, of which six were thrombosed, that were re-treated with a WEB device at the dome in combination with coiling of the sac of the aneurysm. Interestingly, all thrombosed aneurysms showed regrowth, all requiring additional endovascular treatment with stable occlusion in varying follow-up.[15] In another series of four patients with thrombosed aneurysms, two patients that were only treated with a WEB device suffered fatal rupture as opposed to the other two that were treated with a combination of WEB device placement and stenting.[30] There were 12 other studies describing patients that were primarily treated with a WEB device and another form of endovascular therapy varying from additional coiling to an additional WEB device to stenting, or a combination as depicted in **Table 1.1**.[11-13,17-25] In terms of re-treatment of aneurysm remnants, several studies reported on using either coiling, stenting, or again an additional WEB device, but outcomes were reported inconsistently (**Table 1.1**).[9,12,15-19,21,23,24]

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Table 1.2: Study Outcomes

Author (year of publication)	aneurysms treated (N)	successfull WEB. treatment with additional endovascula	Complete occlusion at placement	Neck remnant at placement	aneurysm remnant at placement	Timing of follow-up imaging	Complete occulsional follow-up	Neck remnant at	aneurysm remnant at follow-up	Re-treatment	successfull re-treATMENt	re-rupture
Ambrosi et al. (2015)	10	8	0	1	1	6	6 months	2	5	1	0	-	0
Behme et al. (2015)	55	51	NS	NR	NR	NR	99 days	15	14	15	15	50% (N = 10)	0
Caroff et al. (2014)	6	6	NS	NR	NR	NR	3 months	2	2	2	NR		0
Caroff et al. (2015)	98	93	12	27	2	67	mean 3.3 months	NS	NS	8	NR		3
Clajus et al. (2016)	114	110	13	87	10	12	mean 14.4	52	16	22	15	NR	2
Colla et al. (2013)	4	4	1	NR	NR	NR	minimal 7 months	NS	NS	NS	0		NR
Gherasim et al. (2015)	10	7	NS	2	4	1	3-7 months	3	3	1	NR		NR
Kabbasch et al. (2016)	8	8	8	4	3	1	3.5 to 38	2	2	4	5	NS	NR
Klisch et al. (2011)	2	2	0	NR	NR	NR	8 weeks	2	0	0	NR		0
Lawson et al. (2016)	25	22	0	4	5	13	3 months	8	5	8	2	NS	0
Lescher et al. (2016)	23	22	8	NR	NR	NR	median 7 months	12	7	3	1	NS	0
Liebig et al. (2015)	52	52	8	20	15	17	mean 4 months	15	5	5	4	NS	0
Lubicz et al. (2013)	20	19	4	1	13	5	6 months	0	13	1	2	2	0
Papagiannaki et al. (2014)	85	79	9	NR	NR	NR	mean 5.3	37	23	5	NR		0
Pierot et al. (2013)	34	33	4	NR	NR	NR	Mean 7.2	8	17	5	NR		0
Pierot et al. (2015)	26	NR	4	NR	NR	NR	mean 27.9	13	3	3	3	NS	0
Pierot et al. (2016)	63	62	7	NR	NR	NR	12 months	30	16	12	2	1	0
Pierot et al. (2016)	51	48	4	4	12	32	6 months	23	12	6	3	NR	0
Van Rooij et al. (2016)	32	31	2	NR	NR	NR	3 to 6 months	15	2	1	0		0

Legend: Abbreviations: NS: not specified, NR: not reported

Discussion

In this review, outcomes of WEB device use for treatment of intracranial aneurysms are described. We identified five prospective studies and fourteen retrospective studies.[6,8-28] Unfortunately, due to great variation of reporting it was not possible to conduct a meta-analysis.

In the two prospective multi-center trials, WEBCAST and French Observatory Trial, the WEB device completely occludes aneurysms in 56% to 52% of cases, respectively.[21,24] For coiling, adequate treatment is traditionally defined as either complete occlusion or a small neck remnant. If that standard is applied to these two prospective trials, the successful treatment rate which would increase to 85% and 79%, respectively.[5,21,24] Whether a neck remnant could be defined as adequate treatment for WEB devices, however, remains to be determined; first, because of a limited follow-up of the WEBCAST and French Observatory trial (6 and 12 months, respectively) and second because of incomplete follow-up (85% and 94% follow-up, respectively).[21,24] As indicated by Lawson et al. a more precise grading system of aneurysm occlusion would be valuable to assess outcome of various treatments, especially since neck remnants seem difficult to define and various types could have different clinical implications.[16] With prospective data, such a grading system, based for instance on aneurysm size and location, could potentially even provide a prediction model to aid clinical decision-making.

WEB device closure rates are lower compared to reported closure rates of endovascular coiling and clipping. ISAT (International Subarachnoid Aneurysm Trial) for instance reports complete occlusion or a neck remnant in 92% and 94% of aneurysms respectively at one year follow-up.[31,32] As wide-neck and bifurcation aneurysms are generally regarded as not suitable for coiling, however, a comparison with the ISAT trial cannot be made as it only included aneurysms treatable with coiling.[31,32] Furthermore, as these trials were for specific types of aneurysms, outcomes in other types of aneurysms may not be similar.[21,24]

Another problem with defining adequate aneurysm closure is the accuracy of DSA after placement of a WEB device. One study showed an accuracy of 82% at treatment and 82% at follow up compared to histology in rabbits.[27] We believe that this misjudging of aneurysm closure in approximately 20% of cases is considerable and could possibly have severe clinical consequences like re-rupture, which was reported in 5.6% and 2.2% of cases in two studies.[11,12] Two other studies also compared MRA to DSA for follow-up after WEB treatment, finding that MRA had low sensitivity (25% and 60%) for detecting an aneurysm remnant.[33,34] In the case of unsuccessful treatment, two studied reported that retreatment was necessary in 7.3% and 3.5% of cases with follow up.[21,24] The largest single-center retrospective study even reported retreatment in 16.7% of cases that were followed up.12 Furthermore, it was even reported that retreatment was only successful in 50% of cases in one study (n=10).[9] The Barrow Ruptured Aneurysm trial reports a similar necessity for retreatment in 10.6% of cases treated by coiling compared to 4.5% treated by clipping at one-year follow up.[35]

Few studies reported on the use of the WEB device for ruptured aneurysms. The WEBCAST and French Observatory Trial primarily investigated unruptured aneurysms, with 89% and 94% of the total aneurysms unruptured, respectively.[21,24]

Two other studies primarily examined WEB devices in ruptured aneurysms, reporting adequate occlusion in 94% (n=18) and 80% (n=20) of aneurysms with three to six month follow-up, respectively, and a mean follow-up of four months.[18,25] In the first study, 26 out of the 32 initial patients were treated on the day of the subarachnoid hemorrhage.[25] Overall, due to small numbers in these studies, more research is necessary to determine the therapeutic value of the WEB device in ruptured aneurysms. Furthermore, it has not been investigated whether ruptured aneurysms have similar outcomes to unruptured aneurysms. Due to the great heterogeneity in the studies (as indicated in **Table 1.1**), we were unable to make a direct comparison in this study.

There seems to be a lack of consensus about the necessity of antithrombotic medication. Even the WEBCAST and French Observatory Trial did not have specific protocols for anticoagulation, instead deferring this decision to the medical centers involved.[21,24] The authors of the WEBCAST trial suggested that no anticoagulation is necessary, as the WEB device is intrasaccular as opposed to intravascular devices such as stents. Furthermore, the authors found no significant relationship between the absence of anti-platelet prophylaxis and thromboembolic events when compared to patients on antiplatelet prophylaxis (p=0.6663).[21] In the other studies, there was also no consensus. While one study reported the use of antiplatelet prophylaxis for six months in ruptured aneurysm cases, another used no anticoagulation at all for all patients.[12,25] Similarly, a recent meta-analysis identified great variation in use of antiplatelet therapy in stent-assisted coiling.[36] The variation observed in this study might thus reflect variability in antiplatelet use for endovascular treatment of aneurysms in general.

Only one study examined the learning curve for WEB device deployment, showing that treatment was initially successful in approximately 40% of cases, which increased to approximately 80% in later cases.[9] In our opinion, this indicates a considerable learning curve and makes a practice model a necessity. Furthermore, outcomes could continue to improve with better deployment of the WEB device, but also through better case selection. Especially since every aneurysm is unique, and with the WEB device targeted at wide-neck and bifurcation aneurysms, outcomes could be improved with more specific guidelines.[6] For instance, thrombosed aneurysms seem to be associated with poor outcomes.[15] In terms of current clinical application, one center even reports that WEB device use has become the standard of care for all types of aneurysms despite the fact that follow up of reported prospective studies is short and only for specific aneurysms.[21,24,25]

Currently, two other trials are being conducted for the use of WEB devices for intracranial aneurysm treatment: the CLARYS (CLinical Assessment of WEB® Device in Ruptured aneurYSms, NCT02687607) trial, an observational, non-randomized, multi-center trial investigating outcomes of the WEB device in ruptured aneurysms, and the WEB-IT clinical study (NCT02191618), a multi-center single arm cohort including patients with wide-neck aneurysms. However, as the highest level of evidence of the (currently active) studies assessing WEB devices is 4 (Oxford Centre for Evidence-based Medicine- Levels of Evidence), due to a lack of a comparison group, this leaves much room for improvement. Improving the quality of these studies would contribute to better decision-making for treatment of a specific aneurysm.

We suggest that future research for aneurysm treatment should be conducted in accordance with a framework like the IDEAL (Idea, Development, Exploration, Assessment, Long-term Follow-up) framework for surgical innovation.[37] The IDEAL framework describes consecutive phases for innovative surgical research and procedures and requires that a new procedure is studied prospectively and randomized in comparison with the current practice (here, coiling or clipping) before implementation of a new procedure.[4,5,37-39] Also, involvement of the producer of the device, which was reported in 17 out 19 clinical studies, should be kept to a minimum to make sure results are reported without conflicts of interest.[6,9-12,14-25,28] Furthermore, we deem it essential that patients give informed consent for being treated with an unproven innovative device, which was only identified in six studies.[6,8,17,19,21,24] Overall, the WEB device has a potential role in the treatment of complex aneurysms, however, well-designed prospective trials should be performed before these devices should be routinely used in patients.

Conclusion

The WEB device is a promising innovative endovascular treatment for wide-neck and bifurcation aneurysms. For these aneurysms, which were previously not ideal for endovascular treatment, the WEB device has shown promising results in two multi-center prospective trials.[21,24] Complete aneurysm closure was found in 85% and 79% of cases, defined as complete closure or a small neck remnant. Multidisciplinary teams treating these aneurysms with a WEB device, however, should be cautious, as the WEB device is potentially associated with a considerable learning curve. Also, the WEB device currently has been investigated mainly in unruptured aneurysms with a wide neck, which make results difficult to extrapolate to other aneurysms. Furthermore, long-term results remain unknown, and no comparison has been made with currently available treatment options such as stent-assisted coiling or clipping. In the future, well-designed studies are necessary to determine the true added value of treating intracranial aneurysms with a WEB device.

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Table 1.3: Search syntax

Pubmed (29-05-2016)
(((((WEB[Title/Abstract]) OR Woven Endobridge[Title/Abstract])) OR ((((("Endovascular Procedures"[Majr:NoExp]) OR "Embolization, Therapeutic"[Majr:NoExp])) OR ((((endovascular[Title/Abstract]) OR intravascular[Title/Abstract])) AND (((((((technique*[Title/Abstract]) OR procedur*[Title/Abstract]) OR treatment[Title/Abstract]) OR surgery[Title/Abstract]) OR therapy[Title/Abstract]) OR flow disrupt*[Title/Abstract]) OR Embolization[Title/Abstract])))))) AND ((((((aneurism*[Title/Abstract]) OR aneurysm*[Title/Abstract])) AND (((((cerebral[Title/Abstract]) OR ruptured[Title/Abstract]) OR unruptured[Title/Abstract]) OR brain[Title/Abstract]) OR intracranial[Title/Abstract]))) OR intracranial aneurysm[MeSH Terms])
Embase (29-05-2016)
(('web':ab,ti OR 'woven endobridge':ab,ti) OR ((endovascular:ab,ti OR intravascular:ab,ti) AND (technique*:ab,ti OR procedur*:ab,ti OR treatment:ab,ti OR surgery:ab,ti OR therapy:ab,ti)) OR ('endovascular aneurysm repair'/exp OR 'neurovascular embolaization device'/exp OR 'device embolization'/exp OR 'artificial embolism'/exp)) ->8 AND (((aneurism*:ab,ti OR aneurysm*:ab,ti) AND (cerebral:ab,ti OR ruptured:ab,ti OR unruptured:ab,ti OR brain:ab,ti OR intracranial:ab,ti)) OR 'brain artery aneurysm'/exp OR 'intracranial aneurysm'/exp) AND [embase]/lim AND [2011-2016]/py

2

Outcomes of retreatment for intracranial aneurysms - a meta-analysis

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***Introduction**: Long term results from the International Subarachnoid Hemorrhage Trial (ISAT) and Barrow Ruptured Aneurysm Trial (BRAT) indicate considerably higher retreatment rates for aneurysms treated with coiling compared to clipping, but do not report the outcome of retreatment. **Objective**: The aim of this meta-analysis was to evaluate retreatment related outcomes. **Methods**: A meta-analysis in accordance with PRISMA guidelines was conducted using Medline search engines PubMed and EMBASE to identify articles describing outcomes after retreatment for intracranial aneurysms. Pooled prevalence rates for complete occlusion rate and mortality were calculated. Outcomes of different treatment and retreatment combinations were not compared because of indication bias. **Results**: Twenty-five articles that met the inclusion criteria were included in the meta-analysis. Surgery after coiling had a pooled complete occlusion rate of 91.2% (95%-CI: 87.0-94.1) and a pooled mortality rate of 5.6% (95%-CI: 3.7-8.3). Coiling after coiling had a pooled complete occlusion rate of 51.3% (95%-CI: 22.1-78.0) and a pooled mortality rate of 0.8% (95%-CI: 0.15-3.7). Surgery after surgery did not provide a pooled estimate for complete occlusion as only one study was identified but had a pooled mortality rate of 5.9% (95%-CI: 3.1-11.2). Coiling after surgery had a pooled complete occlusion rate of 56.1% (95%-CI: 11.4- 92.7)*

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and a pooled mortality rate of 9.3% (95%-CI: 4.1-19.9). All pooled incidence rates were produced using random-effect models. ***Conclusions****: Surgical retreatment was associated with a high complete occlusion rate but considerable mortality. Conversely, endovascular retreatment was associated with low mortality but also a low complete occlusion rate.*

Introduction

The current mainstay treatment modalities for both ruptured and unruptured intracranial aneurysms are microsurgical clipping and endovascular treatment such as coiling .[30,37] There is a growing preference to treat intracranial aneurysms with an endovascular treatment modality, as short-term and medium-long term outcomes seem to show a superiority over clipping with regard to morbidity, mortality, and functional outcomes.[30,37,24,38] Endovascular treatment is also considered to be less invasive and is suggested to be preferred by most patients.[30,37,24,38] However, regrowth and subsequent retreatment rate are considerably higher in patients treated with coiling compared to clipping in the long term (BRAT 6 year follow-up data: retreatment: 16.4% for coiling vs 4.6% for clipping, respectively).[37] Furthermore, the results from the ISAT indicate significantly higher rates of re-bleeding and retreatment rates for endovascular treated aneurysms compared to surgically treated aneurysms at ten-year follow-up (retreatment: 17.4% for coiling vs. 3.9% for clipping, respectively).[30,3] However, there was no significant difference in mortality and functional outcome, which may indicate that regrowth does not result in worse outcomes.[30,3] Therefore, questions remain regarding possibility, efficacy, and safety of retreatment after regrowth as a result of the often-occurring regrowth of aneurysms. For instance, aneurysms may be difficult to surgically retreat because of increased mass, scar tissue, and may even require a bypass.[7] One meta-analysis indicated that microsurgical retreatment may be considered safe. [33] However, this meta-analysis was limited by the studies included. Furthermore, other treatment and retreatment combinations were subjected to a meta-analysis.[33] In addition, different treatment and retreatment combinations have not been compared. There is a great variety of initial treatment options which include: clipping, coiling, Pipeline Embolization Device (PED, ®Chestnut Medical, Menlo Park, California), surgical (high flow) bypass, wrapping, and trapping, Woven Endobridge (WEB, ©Sequent Medical Inc., Aliso Viejo, California, USA) device, all of which can be used for retreatment.[7,1,16,11,5,9] The aim of this meta-analysis was to evaluate the efficacy and safety of retreatment of intracranial aneurysms for all available treatment-retreatment combinations.

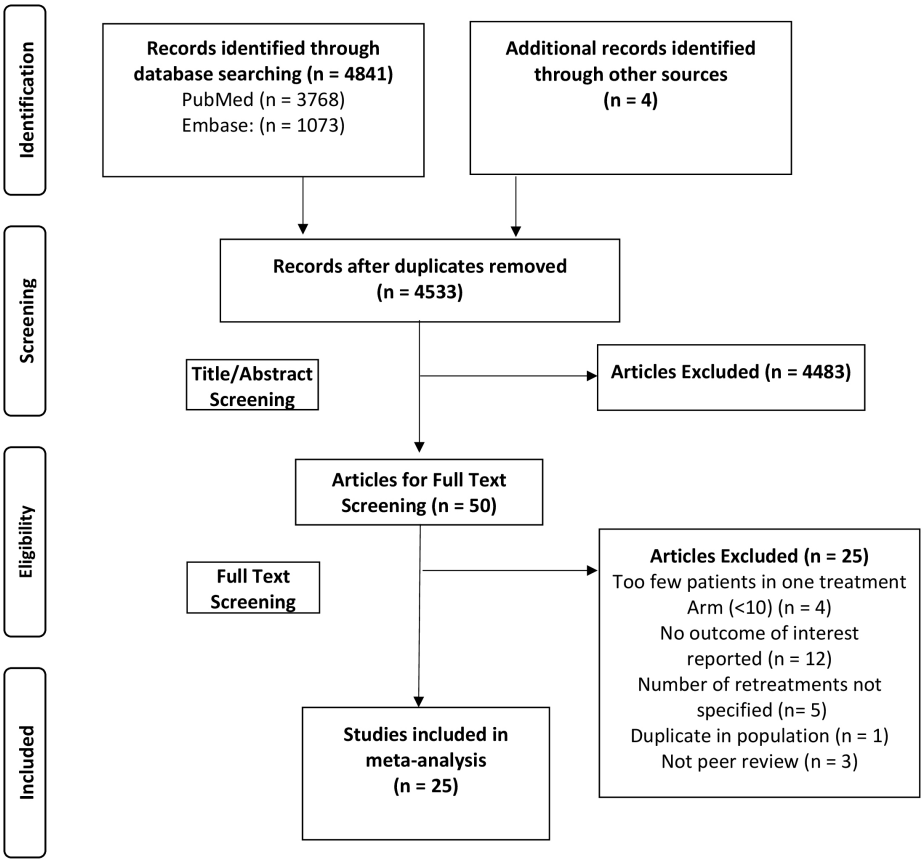
Methods

Study selection

A systematic review and meta-analysis of available literature was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[29] PubMed and Embase databases were searched through October 2017 for studies reporting outcomes of re-intervention for intracranial aneurysms (Figure 1). The search syntax was drafted with Appropriate Medical Subject Headings (MeSH) and Emtree terms for PubMed and Embase, respectively

(**Supplementary Table 2.3**). The search was not limited by date of publication. Duplicates in identified articles were removed using Endnote X7.5 (Clarivate Analytics). All abstracts were screened in duplicate and discrepancies between reviewers were resolved by a senior author. Articles that were selected for full-text review were evaluated by two authors. Reference lists were checked for possible additional articles.

Figure 2.1: Flowchart of the study selection process



Inclusion criteria

All studies that were screened full-text were included if the following inclusion criteria were met: (1) The study was original and written in English or Dutch (2) The study included a treatment retreatment combination arm that consisted of a minimum of ten patients (3) The study was conducted in an adult population (4) The study had been subjected to peer-review (5) The study reported outcomes of retreatment for intracranial aneurysms. Only the most recent study was included if results from a

series of patients had been reported in multiple articles.

Data extraction and study quality assessment

All included studies were evaluated for the following study characteristics: continent, year of publication, sample size, study design, and follow-up (months). The following population characteristics were extracted for the initial treatment and retreatment combinations: mean age (years), number of females and males, initial presentation (subarachnoid hemorrhage or incidental), initial treatment modality, retreatment modality, indication for initial treatment, indication for retreatment, aneurysm location, percentage of initial successful occlusion, mean total aneurysm size at retreatment, number of large aneurysms (1.0 – 2.5 cm), number of giant aneurysms (>2.5 cm), and mean time to retreatment (months). The following outcomes were extracted: percentage of complete occlusion on imaging (angiogram or CTA), number of patients that died within 30 days after surgery (regardless of reason), and clinical outcome (modified Rankin Scale (mRS) or Glasgow Outcome Scale (GOS)).[17,45] Clinical outcomes were only extracted if the patients' status before and after the retreatment procedure was documented and had less than 10% missing values. A good clinical outcomes score was defined as less than 3 and greater than 4 on the modified Rankin Scale (mRS) and Glasgow Outcome Scale (GOS), respectively.[17,45] The extraction of the study characteristics and outcomes was performed by two independent investigators and discrepancies were solved by discussion or consultation of senior authors. All included studies were also evaluated for study quality using the Newcastle Ottawa Scale (NOS).[44] Comparability was not scored for studies that did not have a comparison group. Again, discrepancies were solved by consultation of senior authors.

Meta-analysis

The meta-analysis was conducted using R 3.4.2 (R Core Team, Auckland, New Zealand) with use of the "meta" package, which is partially built on the "Metafor" package.[42,36] Pooled prevalence ratios of complete occlusion rate and mortality rate were calculated using both fixed- and random-effect models for the following treatment and re-treatment combinations: surgery after coiling, coiling after coiling, coiling after surgery, surgery after surgery, PED after coiling, and PED after PED. Forest plots were created for the outcomes complete occlusion rate and mortality rate. The different initial treatment and retreatment combinations were not directly compared because of indication bias. The Cochran's Q test ($p<0.10$) and I^2 statistic (I^2 value >50% was considered significant) were used to evaluate possible heterogeneity among the included studies.[15] Meta-regression was applied to identify sources of heterogeneity for the following study characteristics: continent, year of publication, NOS-score, percentage of females, mean age (years), percentage of patients that initially presented with a subarachnoid hemorrhage, percentage of initial successful treatment, mean total aneurysm size at retreatment, percentage of patients with an aneurysm located in the posterior circulation, percentage of patients with large or giant aneurysms, mean time to re-intervention (months). Meta-regression separately was applied to all study characteristics and was only possible if a minimal of 3

studies were included in a specific treatment retreatment analysis and if no missing values were among the study characteristics and Bonferroni correction was applied to correct for multiple testing (critical p-value: 0.004 based on 13 degrees of freedom). Publication bias was evaluated by constructing Funnel plots, Eggers's linear regression test, and the Begg's and Mazumdar rank correlation test (p-value < 0.05 was considered significant).[2,10]

Results

The search strategy yielded 4529 studies after removal of duplicates (**Figure 2.1**). Twenty-five unique studies were included in the meta-analysis to evaluate outcomes of first retreatment for intracerebral aneurysms.[3-7,9,11-13,16,18,20-23,25,26,31,32,34,35,39,41,43,46]

Baseline characteristics

The 25 studies reported the outcomes in 1064 patients (**Table 2.1**). The median of mean age of the populations was 50.6 years at time of retreatment and the median of mean female percentage of the populations was 65.0. The studies had a mean follow-up of 22.9 months. Regarding aneurysm characteristics, the median of mean percentage of patients that initially presented with a subarachnoid hemorrhage was 75.9%. The median of mean percentage of posterior location was 10.3%. The median of mean size at retreatment was 7.0 mm, median of mean percentage of large aneurysms was 18.3%, and the median of mean percentage of giant aneurysms was 4.4%. Regarding the retreatment, the median of mean number of months to retreatment was 20.8. Early retreatment (within the first month) occurred in 6.0% of cases (median of mean percentage). The NOS score did not vary greatly among the studies as most were retrospective case series and cohort studies that did not make comparison between the different treatment retreatment combinations, except for the ISAT.[3]

Thirteen studies evaluated outcomes of surgery after coiling[4,5,7,12,21,22,25,31,32,35,41,43,46], 3 studies evaluated outcomes of coiling after coiling[7,18,39], 4 studies evaluated coiling after surgery[16,20,26,34], 3 studies evaluated surgery after surgery[9,16,32], 2 studied evaluated PED after coiling[6,23], and 2 studies evaluated PED after PED.[11,13]

In studies that described outcomes of surgery after coiling, extrusion of coils and coil compaction were observed in 18.8% and 30.5% of cases, respectively. Coils were extracted in 22.7% of cases and intraoperative rupture occurred in 5.6% of cases. Clipping was performed in 89.2% of cases, a bypass procedure was performed in 4.6% of cases, wrapping in 4.3% of cases, trapping in 3.6% of cases, and parent artery occlusion in 1.4% of cases.

Table 2.1: Base line characteristics of the studies.

Intervention retreatment combination	*Study (year of publication)*	*Location*	*Study design*	*Number of patients with outcomes available*	*Mean age of population (years)*	*Percentage of females*	*Percentage posterior circulation aneurysms*	*Successful initial treatment (percentage)*	*Mean total aneurysm size at retreatment (mm)*	*Percentage of initial SAH presentation*	*Mean time to intervention (months)*	*NOS-score*
Surgery after coiling	Campi et al. (2007)	International	RCT	22	NA	NA	NA	NA	NA	NA	NA	9
	Chung et al. (2010)	South-Korea	Retrospective Case Series	29	48.1	44.8	3.5	NA	7	96.6	11.4	6
	Daou et al. (2016)	USA	Retrospective Case Series	111	50.5	73.9	2.7	NA	7	79.3	23	6
	Dorfer et al. (2012)	Austria	Retrospective Cohort Study	52	49.8	63.5	17.3	23.1	11.6	NA	9.4	6
	Gurian et al. (1995)	USA	Retrospective Case Series	21	55.8	90.5	19.1	0.0	18.1	57.1	NA	5
	Klein et al. (2008)	France	Retrospective Case Series	13	43.3	53.9	0.0	0.0	5.1	100.0	48.6	6
	Konig et al. (2007)	Germany	Retrospective Case Series	10	46	80.0	0.0	42.9	NA	60.0	14.3	5
	Lejeune et al. (2008)	France	Retrospective CS	21	NA	42.9	5.0	57.1	4.2	95.2	8.5	6
	Nakamura et al. (2013)	Germany	Retrospective Case Series	15	50.6	46.7	0.0	40.0	6.9	93.3	76.5	6
	Owen et al. (2015)	USA	Retrospective Cohort Study	73	49.0	79.4	23.3	58.9	NA	87.7	NA	6
	Romani et al. (2011)	Finland	Retrospective Case Series	82	47	65.4	31.2	NA	NA	74.4	NA	5
	Veznedaroglu et al. (2004)	USA	Retrospective Case Series	18	NA	NA	NA	NA	NA	NA	NA	5
	Wang et al. (2017)	China	Retrospective Case Series	19	51.3	47.4	10.5	73.7	6.5	84.2	25	6
	Zhang et al (2003)	USA	Retrospective Case Series	38	50.6	71.8	30.6	NA	14.2	60.5	NA	5
Coiling after coiling	Campi et al. (2007)	International	RCT	65	NA	NA	NA	NA	NA	NA	NA	9
	Dorfer et al. (2012)	Austria	Retrospective Cohort Study	75	50.8	36.0	42.6	46.6	11.9	NA	12.8	6
	Kang et al. (2006)	Korea	Retrospective Case Series	32	NA	NA	31.3	34.4	NA	NA	NA	6
	Teleb et al. (2014)	USA	Retrospective Case Series	111	53	58.6	23.4	NA	7	60.4	8	6
Coiling after surgery	Campi et al. (2007)	International	RCT	6	NA	NA	NA	NA	NA	NA	NA	9
	Hokari et al. (2016)	Japan	Retrospective Cohort Study	10	66.5	90.0	10.0	NA	7.1	90.0	15.3	5
	Li et al. (2013)	South-Korea	Retrospective Case Series	31	58.2	64.5	6.5	NA	NA	77.4	19	6
	Owen et al. (2015)	USA	Retrospective Cohort Study	4	45.5	NA	25.0	NA	NA	NA	NA	6
	Rabinstein et al. (2003)	USA	Retrospective Case Series	21	50.6	61.9	35.0	62.0	NA	61.9	90	6
	Kim et al. (2010)	Korea	Retrospective Case Series	24	51.8	54.2	0.0	58.3	NA	91.7	30.4	6
Surgery after surgery	Hokari et al. (2016)	Japan	Retrospective Cohort Study	13	62.9	23.1	0.0	NA	9.4	30.1	15.5	5
	Owen et al. (2015)	USA	Retrospective Cohort Study	20	53.7	NA	20.0	NA	NA	100.0	NA	6
	Drake et al. (1984)	Canada	Retrospective Case Series	88	NA	NA	63.1	39.1	NA	NA	NA	5
PED after surgery	Kuhn et al. (2017)	USA	Retrospective Case Series	6	NA	NA	33.3	66.6	NA	50.0	11.0	5
	Daou et al. (2015)	USA	Retrospective Case Series	32	53	75.0	10.0	NA	NA	51.5	27	6
PED after PED	Heiferman et al. (2017)	USA	Retrospective Case Series	25	51	72.0	NA	NA	NA	36.0	NA	5
	Fischer et al. (2011)	Germany	Retrospective Case Series	30	NA	66.0	NA	NA	NA	NA	NA	5
PED after coiling	Kuhn et al. (2017)	USA	Retrospective Case Series	18	NA	NA	50.0	NA	NA	38.8	26.0	5

Legend: Abbreviations: NOS: New-Castle Ottawa Scale for quality reporting of observational studies, reported on a scale of 0-9; NA: not available; USA: United States of America; PED: Pipeline embolization device.

Table 2.2: Outcomes by study

Intervention retreatment combination	Study	Complete occlusion (n/N (%))	Mortality occlusion (n/N (%))	Clinical outcome*			
				Before treatment		After treatment	
				Good	Bad	Good	Bad
Surgery after coiling	Campi et al. (2007)	NA	NA	19/22	3/21	17/22	5/22
	Chung et al. (2010)	NA	0/29 (0.0)	18/22	4/22	21/22	1/22
	Daou et al. (2016)	108/111 (97.3)	3/111 (2.7)	NA	NA	NA	NA
	Dorfer et al. (2012)	45/52 (86.5)	1/52 (1.9)	NA	NA	NA	NA
	Gurian et al. (1995)	NA	3/21 (14.3)	NA	NA	NA	NA
	Klein et al. (2008)	13/13 (100.0)	0/13 (0.0)	NA	NA	NA	NA
	Konig et al. (2007)	10/10 (100.0)	0/10 (0.0)	NA	NA	NA	NA
	Lejeune et al. (2008)	19/21 (90.5)	0/21 (0.0)	21/21	0/21	19/21	2/21
	Nakamura et al. (2013)	15/15 (100.0)	1/15 (6.7)	NA	NA	NA	NA
	Owen et al. (2015)	65/73 (89.0)	3/73 (4.1)	NA	NA	NA	NA
	Romani et al. (2011)	77/81 (95.1)	6/81 (7.4)	NA	NA	NA	NA
	Veznedaroglu et al. (2004)	15/18 (83.3)	NA	NA	NA	NA	NA
	Wang et al. (2017)	16/19 (84.2)	1/19 (5.3)	NA	NA	NA	NA
	Zhang et al (2003)	NA	3/38 (7.9)	NA	NA	NA	NA
Coiling after coiling	Campi et al. (2007)	NA	NA	53/65	12/65	52/65	13/65
	Dorfer et al. (2012)	50/75 (66.7)	0/75 (0.0)	NA	NA	NA	NA
	Kang et al. (2006)	11/32 (34.4)	0/32 (0.0)	NA	NA	NA	NA
	Teleb et al. (2014)	NA	0/111 (0.0)	NA	NA	NA	NA
Coiling after surgery	Campi et al. (2007)	NA	NA	6/6	0/6	4/6	1/6
	Hokari et al. (2016)	NA	0/10 (0.0)	9/10	1/10	8/10	2/10
	Li et al. (2013)	9/31 (29.0)	2/31 (6.5)	NA	NA	NA	NA
	Owen et al. (2015)	NA	0/4 (0.0)	NA	NA	NA	NA
	Rabinstein et al. (2003)	17/21 (81.0)	3/21 (14.3)	NA	NA	NA	NA
	Kim et al. (2010)	NA	NA	19/19	0/19	16/19	3/19
Surgery after surgery	Hokari et al. (2016)	NA	0/13 (0.0)	12/13	1/13	10/13	3/13
	Owen et al. (2015)	NA	2/20 (10.0)	NA	NA	NA	NA
	Drake et al. (1984)	102/115 (88.7)	6/115 (5.2)	NA	NA	NA	NA
PED after surgery	Kuhn et al. (2017)	3/6 (50.0)	0/6 (0.0)	5/6	1/6	5/6	1/6
	Daou et al. (2015)	23/32 (71.9)	0/32 (0.0)	NA	NA	NA	NA
PED after PED	Heiferman et al. (2017)	9/19 (47.4)	0/19 (0.0)	NA	NA	NA	NA
	Fischer et al. (2011)	20/30 (66.7)	0/30 (0.0)	86/88	2/88	81/88	7/88
PED after coiling	Kuhn et al. (2017)	8/11 (72.7)	0/14 (0.0)	17/18	1/18	17/18	1/18

Legend: *Good outcome was defined as a modified Rankin Scale (mRS) <3 or a Glasgow Outcome Scale (GOS)>4. Abbreviations: PED: Pipeline embolization device; NA: Not Available.

Complete occlusion

Complete occlusion rates varied considerably among the treatment retreatment combinations (**Table 2.2**).). Pooled prevalence rates for complete occlusion were 91.2% (95-% CI: 87.0-94.2) for surgery after coiling, 51.3% (95-% CI: 22.1-78.0) for coiling after coiling, 72.1% (95-% CI: 57.0- 83.3) for PED after coiling, 56.1% (95-% CI: 11.4 – 92.7) for coiling after surgery, and 58.2% (95-% CI: 39.0 – 75.2) for PED after PED, respectively (Random-effect model, **Figure 2.2**, **Table 2.4**). Fixed-effect models yielded similar results. It was not possible to calculate a prevalence rate for surgery after surgery as only one study was available for analysis, which reported a complete occlusion rate of 89%.[9]

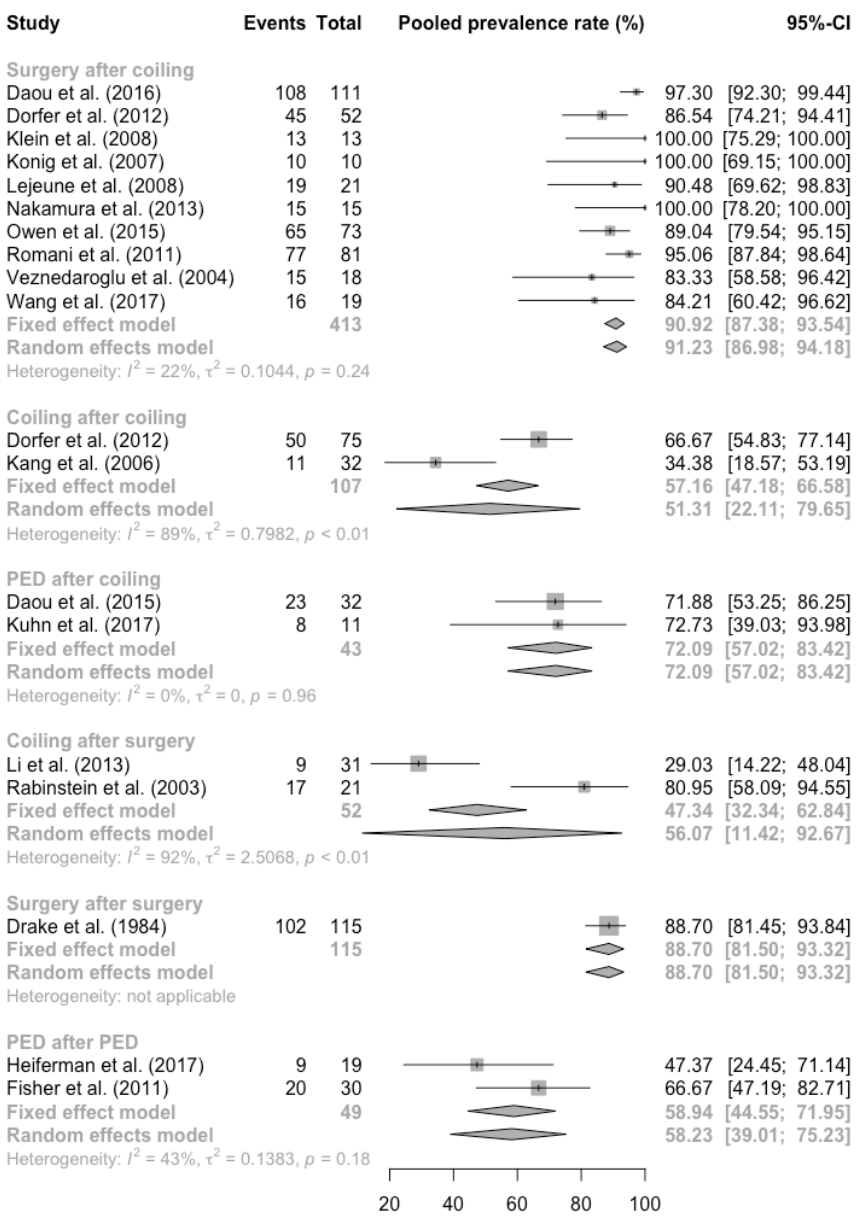
The treatment retreatment combinations coiling after coiling and coiling after surgery came with considerable heterogeneity (88.9% and 91.5%, respectively). No significant sources of heterogeneity were identified for surgery after coiling using meta-regression after correction for multiple testing. Meta-regression for other treatment and retreatment combination was not possible due to the low number of studies included in the analysis. It was only possible to evaluate publication bias in the surgery after coiling treatment retreatment combination, which was insignificant, as the other analysis had too few studies to evaluate publication bias.

Mortality

Similar to complete occlusion rates, the pooled prevalence rates of mortality varied considerably among the treatment retreatment combinations (**Table 2.2**). Pooled mortality rates for mortality were 5.6% (95-% CI: 3.7 - 8.3) for surgery after coiling, 0.8% (95-% CI: 0.15 - 3.7) for coiling after coiling, 2.2% (95-% CI: 0.3 - 14.3) for PED after coiling, 5.9% (95-% CI: 3.1 - 11.2) for surgery after surgery, 9.3 % (95-% CI: 4.1 - 19.9) for coiling after surgery, and 2.0% (95-% CI: 0.3 - 12.9) for PED after PED, respectively (Fixed-effect model, **Figure 2.3**, **Table 2.4**) SUPPP table 2. Fixed-effect models showed similar results. All the intervention retreatment combinations came with low heterogeneity (I^2 = 0.0% for all studies). With regard to publication bias, the pooled prevalence rate of mortality for surgery after coiling may be subject to publication bias (Egger's test p-value: 0.08). However, the Funnel plot indicated no publication bias (not shown), the trim and fill method yielded a similar pooled prevalence rate (pooled prevalence rate: 0.8%, 95%-CI: 0.2 – 3.7), and the Begg's test indicated no significant publication bias (p=0.12). It was not possible to evaluate publication bias for the surgery after surgery, PED after coiling, and PED after PED treatment retreatment combinations due to a low number of studies included in the analysis.

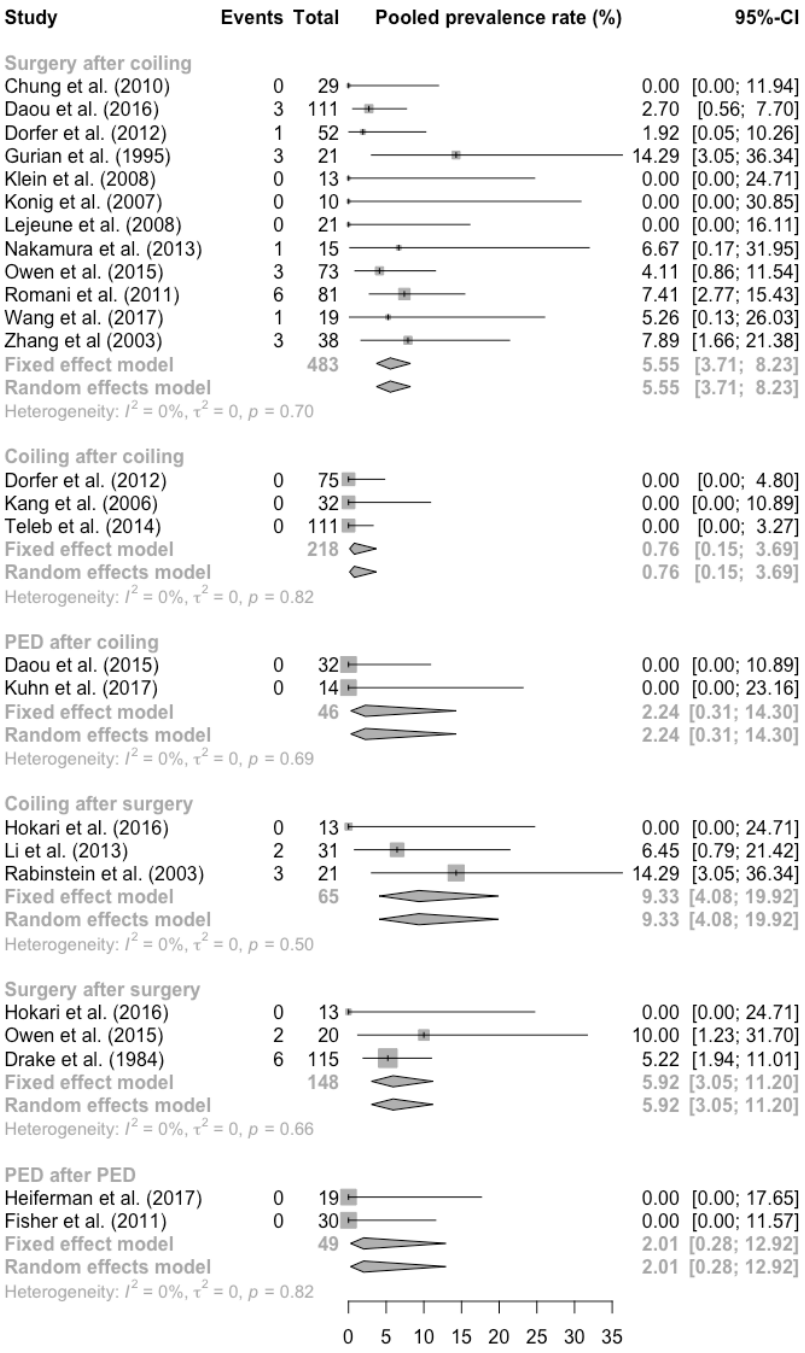
For surgery after coiling, only publication year was identified as a potential source of heterogeneity (estimate: -0.06, p-value: 0.04), but this association did not remain significant after correction for multiple testing. Meta-regression for other treatment retreatment combinations was not possible due to the low number of studies included in the analysis.

Figure 2.2: Forest plot of pooled prevalence rate of complete occlusion by treatment retreatment population.



Legend: Forest plot of pooled prevalence rate of complete occlusion by treatment retreatment group. Forest plot for prevalence rate of complete occlusion are shown by treatment and retreatment combination. Solid squares represent the point estimate of each study and the diamond represents the pooled estimate of the prevalence rate. The I^2 value for heterogeneity is shown.

Figure 2.3: Forest plot of pooled prevalence rate of mortality by treatment retreatment population.



Legend: Forest plot of pooled prevalence rate of mortality by treatment retreatment group. Forest plot for prevalence rate for mortality are shown by treatment and retreatment combination. Solid squares represent the point estimate of each study and the diamond represents the pooled estimate of the prevalence rate. The I^2 value for heterogeneity is shown.

Functional outcomes

Contrary to the occlusion rates or mortality rates, the functional outcomes were not reported consistently (**Table 2.2**).[3,4,11,16,20,23,25] The clinical improvement or deterioration after the second intervention varied considerably among the treatment retreatment combinations. In general, no large differences were seen in functional outcome before and after intervention between the different treatment and retreatment combinations.

Discussion

This meta-analysis aimed to evaluate outcomes of retreatment of intracranial aneurysms. Overall, aneurysms retreated with surgery showed a high rate of complete occlusion. However, this came with a relatively high pooled prevalence rate of mortality. Contrarily, intracranial aneurysms retreated with coiling or a PED have a relative low complete occlusion rate, but also a low pooled prevalence rate of mortality. Functional outcomes were reported very infrequently and did not show a great variation between the different treatment retreatment combinations. The overall quality of the studies was low, as no prospective studies were available, except for the ISAT, which only reported functional outcomes.[3]

The occlusion rate for surgically retreated patients appears to be high based on the results of our meta-analysis. One other meta-analysis suggested an occlusion rate of 98.3%.[33] One systematic review evaluating outcomes of surgically treated aneurysms concluded an occlusion rate of 93%.[1] These outcomes are broadly similar to the findings in this meta-analysis. One series that evaluated outcomes of 2360 intracranial aneurysm patients, initially treated with endovascular approaches, found that 350 (12.3%) patients required endovascular retreatment and reported a complete occlusion rate of only 46.9% after the second session of coiling.[14] Furthermore, 94 patients required three or more coiling sessions with a complete occlusion rate of 35.6% (maximum of 9 sessions, n =1).[14] The potential necessity of multiple subsequent recoiling sessions may emphasize the need from complete initial occlusion of aneurysms. The latter study was not included in this meta-analysis as the initial endovascular treatment was preceded by various microsurgical procedures in some patients.[14] However, incomplete coiling is not the only factor associated with regrowth as increased total aneurysm size, packing density, older age, male sex, hypertension, and ruptured aneurysm have also been associated with aneurysm regrowth after coiling in retrospective analyses.[27,8,28]

The mortality rate seems to be high in patients that received surgical retreatment based on our meta-analysis. Another meta-analysis suggested that mortality may actually be 0 % (95%CI=0.0–2.5 %).[33] One other review reported a mortality prevalence of 3.6% for aneurysms that were surgically retreated after initial endovascular occlusion, which is similar to the findings in this meta-analysis.[1] One explanation for the mortality in surgically retreated patients rate may be the necessity of trapping, wrapping, ligation, or a bypass, which was necessary in 1.9%, 2.7%, 1.8%, and 2.1% of cases, respectively, which is largely similar to the findings of this study.[1] Another explanation may also be mortality due to non-procedural complications or presentation with a rebleed, as was seen in the cohort described by Romani et al.[35]One large series inves-

tigating multiple recoiling sessions in 350 patients reported a morbidity rate of 2.2% and only had one mortality.[14] Coiling after surgery was associated with a relatively high mortality, but this was probably the result of rebleed related complications in the two studies that had mortalities.[34,26]

The high mortality and poor occlusion rates for surgical retreatment and endovascular retreatment respectively show the importance of treatment modality selection when patients initially present with intracranial aneurysms. Initial coiling may be preferable because of lower morbidity and less invasive nature if no additional retreatment is to be expected.[3] The necessity for retreatment after coiling is approximately three to four times higher than after microsurgical clipping based on two RCTs.[37,3] Therefore, patients that require surgery after coiling would probably not have needed a secondary procedure if surgery had been the primary treatment modality. Furthermore, recoiling may increase the size of the aneurysm with every additional placement of coils due to its low success rate. The difficulty of surgical treatment of previously coiled aneurysms probably increases after every recoiling session as the aneurysm increases in size. Similarly, the complete occlusion rate appears to go down with every subsequent recoiling procedure.[14] Although this does not seem to result in mortality for patients, rebleeding rates could be higher and patients may develop symptoms as the result of mass-effect from the aneurysm.[14,19,40] Currently, no prospective and comparative outcomes are known for retreated intracranial aneurysm and little is known on factors that contribute to regrowth.

This is the first meta-analysis that evaluated the outcomes of retreatment for intracranial aneurysms and was conducted in accordance with PRISMA guidelines.[29] This meta-analysis also evaluated all available intervention and retreatment combinations. However, this meta-analysis is limited by several factors. The available studies from the literature were of poor quality, based on the NOS-scale. All studies were retrospective in nature and generally had a small sample size and limited follow-up. There was little consistency with regard to reported outcomes as most studies only consistently reported mortality and complete occlusion rate which was why no meta-analysis was conducted for functional outcomes. The limited reporting on baseline characteristics and outcomes of specific subgroups such as patients that initially presented with a subarachnoid hemorrhage did not allow for further subgroup analyses. Authors were not contacted to provide the necessary information due to the great many studies that did not present this information. This especially holds serious implications for mortality as other unevaluated factors such as the number of patients presenting with a rebleed and non-procedure related complications may influence mortality. The number of studies could also be considered low for the respective treatment retreatment combinations (e.g. only two studies reporting on outcomes of coiling after coiling were included). This is partially the result of the inclusion criteria of a minimum of 10 patients per arm and that only outcomes of first retreatment were evaluated. There was also considerable heterogeneity among various outcomes for which it was often not possible to identify contributing factors due to a low number of studies and variation in reporting of base-line characteristics by meta-regression. No comparison was made between the different treatment and retreatment combinations with regard to outcomes because of indication bias. It was also not possible

to study the effect of timing of retreatment in relation to outcomes as timing was rarely reported. Meta-regression was also only applied for individual study characteristics and was often not possible due to the low number of studies and variation in reporting. Furthermore, none of the identified associations remained significant after correction for multiple testing. Findings of this meta-analysis were not validated in an existing prospective cohort.

Knowledge of the outcomes of retreatment could be expanded by prospective evaluation of outcomes. A potential trial design could be a prospective registry that evaluates outcomes of intracranial aneurysms irrespective of initial treatment. This could both provide insight into which aneurysms require retreatment on the long term, how the necessity of retreatment can be avoided, and what retreatment strategy results in superior outcomes. The outcomes of such a registry could also prediction model to aid clinical decision-making and improve outcomes of intracranial aneurysm patients.

Conclusion

Surgical retreatment of intracranial aneurysms may be associated with relatively high occlusion rates but also a relatively high mortality. Contrarily, secondary coiling may be associated with relatively lower mortality but also with low rates of complete occlusion. Outcomes of this meta-analysis should be interpreted with caution due to various limitations. Nevertheless, the outcomes from this meta-analysis could potentially stress the need for complete initial treatment of intracranial aneurysms to prevent the retreatment. The findings of this meta-analysis could also potentially strengthen the argument for opting to clip an intracranial aneurysm when initial coiling may not result in complete occlusion. Further knowledge on what contributes to regrowth of coiled aneurysm is needed to optimize initial treatment selection for individual patients.

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Table 2.3: Search syntax

PubMed:
("Intracranial Aneurysm"[Mesh] OR aneurysm[Title/Abstract] OR aneurysms[Title/Abstract]) **AND** ("Recurrence"[Mesh] OR recurrent[Title/Abstract] OR recurrence[Title/Abstract] OR recurring[Title/Abstract] OR retreatment*[Title/Abstract] OR "Treatment Failure"[Mesh] OR treatment failure*[Title/Abstract] OR residual[Title/Abstract] OR additional therap*[Title/Abstract] OR recanaliz*[Title/Abstract] OR recanalis*[Title/Abstract] OR regrow*[Title/Abstract]) **AND** (clip*[Title/Abstract] OR coil*[Title/Abstract] OR flow disrupt*[Title/Abstract] OR divert*[Title/Abstract] OR stent*[Title/Abstract] OR pipeline[Title/Abstract] OR embolization[Title/Abstract] OR "Embolization, Therapeutic"[MAJR] OR "Endovascular Procedures"[MAJR])
Embase
'intracranial aneurysm'/exp OR 'intracranial aneurysm' OR aneurysm:ab,ti OR aneurysms:ab,ti **AND** ('recurrent disease'/exp OR 'recurrent disease' OR recurrent:ab,ti OR recurrence:ab,ti OR recurring:ab,ti OR retreatment*:ab,ti OR 'retreatment'/exp OR 'retreatment' OR 'treatment failure'/exp OR 'treatment failure' OR 'treatment failure*':ab,ti OR residual:ab,ti OR 'additional therap*':ab,ti OR recanaliz*:ab,ti OR 'recanalization'/exp OR 'recanalization' OR recanalis*:ab,ti OR regrow*:ab,ti) **AND** (clip*:ab,ti OR coil*:ab,ti OR 'coil embolization'/exp OR 'coil embolization' OR 'artificial embolization'/exp OR 'artificial embolization' OR 'flow disrupt*':ab,ti OR 'arterial stent'/exp OR 'arterial stent' OR 'divert*':ab,ti OR 'stent*':ab,ti OR pipeline:ab,ti OR embolization:ab,ti OR 'endovascular surgery'/mj/exp OR 'endovascular surgery') **AND** [embase]/lim NOT [medline]/lim AND ([article]/lim OR [article in press]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim)

Table 2.4: Outcomes of meta-analysis by outcome.

Outcome	*Intervention retreatment combination*	*Model*	*Prevalence rate (%)*	*95%-CI*	*I-squared (%)*	*Q-Test for heterogeneity (p-value)*	*Egger's-test (p-value)*	*Begg's-test (p-value)*
Complete occlusion	***Surgery after coiling***	FE	90.1	87.4-93.5	21.6	0.24	0.27	0.53
		RE	91.2	87.0-94.2				
	Coiling after coiling	FE	57.2	47.2-66.6	88.9	0.0026	NA	NA
		RE	51.3	22.1-78.0				
	PED after coiling	FE	72.1	57.0- 83.3	0.00	0.96	NA	NA
		RE	72.1	57.0- 83.3				
	Surgery after surgery*	FE	NA	NA	NA	NA	NA	NA
		RE	NA	NA				
	Coiling after surgery	FE	47.3	32.3-62.8	91.5	0.0006	NA	NA
		RE	56.1	11.4- 92.7				
	PED after PED	FE	58.9	44.6-72.0	43.4	0.18	NA	NA
		RE	58.2	39.0-75.2				
Mortality	***Surgery after coiling***	FE	5.6	3.7-8.3	0.00	0.61	0.16	0.70
		RE	5.6	3.7-8.3				
	Coiling after coiling	FE	0.8	0.15-3.7	0.00	0.82	0.08	0.12
		RE	0.8	0.15-3.7				
	PED after coiling	FE	2.2	0.3-14.3	0.00	0.69	NA	NA
		RE	2.2	0.3-14.3				
	Surgery after surgery	FE	5.9	3.1-11.2	0.00	0.66	0.93	0.62
		RE	5.9	3.1-11.2				
	Coiling after surgery	FE	9.3	4.1-19.9	0.00	0.50	0.43	0.12
		RE	9.3	4.1-19.9				
	PED after PED	FE	2.0	0.3-12.9	0.00	0.82	NA	NA
		RE	2.0	0.3-12.9				

3

The endoscopic endonasal approach is not superior to the microscopic transcranial approach for anterior skull base meningiomas

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Introduction*: In the past decade, the endonasal transsphenoidal approach (eTSA) has become an alternative to the microsurgical transcranial approach (mTCA) for tuberculum sellae meningiomas (TSMs) and olfactory groove meningiomas (OGMs). The aim of this meta-analysis was to evaluate which approach offered the best surgical outcomes.* ***Methods****: A systematic review of the literature from 2004 and meta-analysis were conducted in accordance with the PRISMA guidelines. Pooled incidence was calculated for gross total resection (GTR), visual improvement, cerebrospinal fluid (CSF) leak, intraoperative arterial injury, and mortality, comparing eTSA and mTCA, with p-interaction values.* ***Results****: Out of 1684 studies, 64 case series were included in the meta-analysis. Using the fixed-effects model, GTR rate was significantly higher among mTCA patients for OGM (eTSA:*

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70.9% vs. mTCA: 88.5%, p-interaction< 0.01), but not significantly higher for TSM (eTSA: 83.0% vs. mTCA: 85.8%, p-interaction=0.34). Despite considerable heterogeneity, visual improvement was higher for eTSA than mTCA for TSM (p-interaction<0.01), but not for OGM (p-interaction=0.33). CSF leak was significantly higher among eTSA patients for both OGM (eTSA: 25.1% vs. mTCA: 10.5%, p-interaction<0.01) and TSM (eTSA: 19.3%, vs. mTCA: 5.81%, p-interaction<0.01). Intraoperative arterial injury was higher among eTSA (4.89%) than mTCA patients (1.86%) for TSM (p-interaction=0.03), but not for OGM resection (p-interaction=0.10). Mortality was not significantly different between eTSA and mTCA patients for both TSM (p-interaction=0.14) and OGM resection (p-interaction=0.88). Random-effect models yielded similar results. ***Conclusions****: In this meta-analysis, eTSA was not shown to be superior to mTCA for resection of both OGMs and TSMs.*

Introduction

The mainstay of treatment for tuberculum sellae meningiomas (TSMs) and olfactory groove meningiomas (OGMs) is surgery. Goals of surgery include obtaining tissue for histopathological diagnosis and relieving pressure caused by the tumor on neighboring structures such as the olfactory nerves, anterior cerebral arteries, optic nerves, and the pituitary gland. At the same time, these structures are very susceptible to manipulation and damage to these structures can lead to great morbidity[51]

Traditionally, TSMs and OGMs are resected using a microscopic transcranial approach (mTCA). Various approaches have been described, including interhemispheric, pterional, bifrontal, and subfrontal mTCA[1, 2, 5-7, 9, 47, 51, 56, 64, 70] In the last decade, however, as a result of the evolution of endoscopic surgery for pituitary adenomas, these meningiomas have been increasingly resected using an endonasal endoscopic transsphenoidal approach (eTSA), as first described by Jho et al. in 2004[38] Although the endoscopic approach is generally viewed as less invasive, with some studies suggesting that eTSA caused fewer post-operative changes on magnetic resonance imaging (MRI) compared to mTCA possibly indicating less manipulation,[22] it has been suggested that eTSA results in higher rates of CSF leaks, and potentially different outcomes (e.g. less GTR)[18, 42] However, a direct comparison between eTSA and mTCA is currently lacking. Therefore, the aim of this systematic review and meta-analysis was to evaluate which approach (eTSA vs. mTCA) offers the best surgical outcomes.

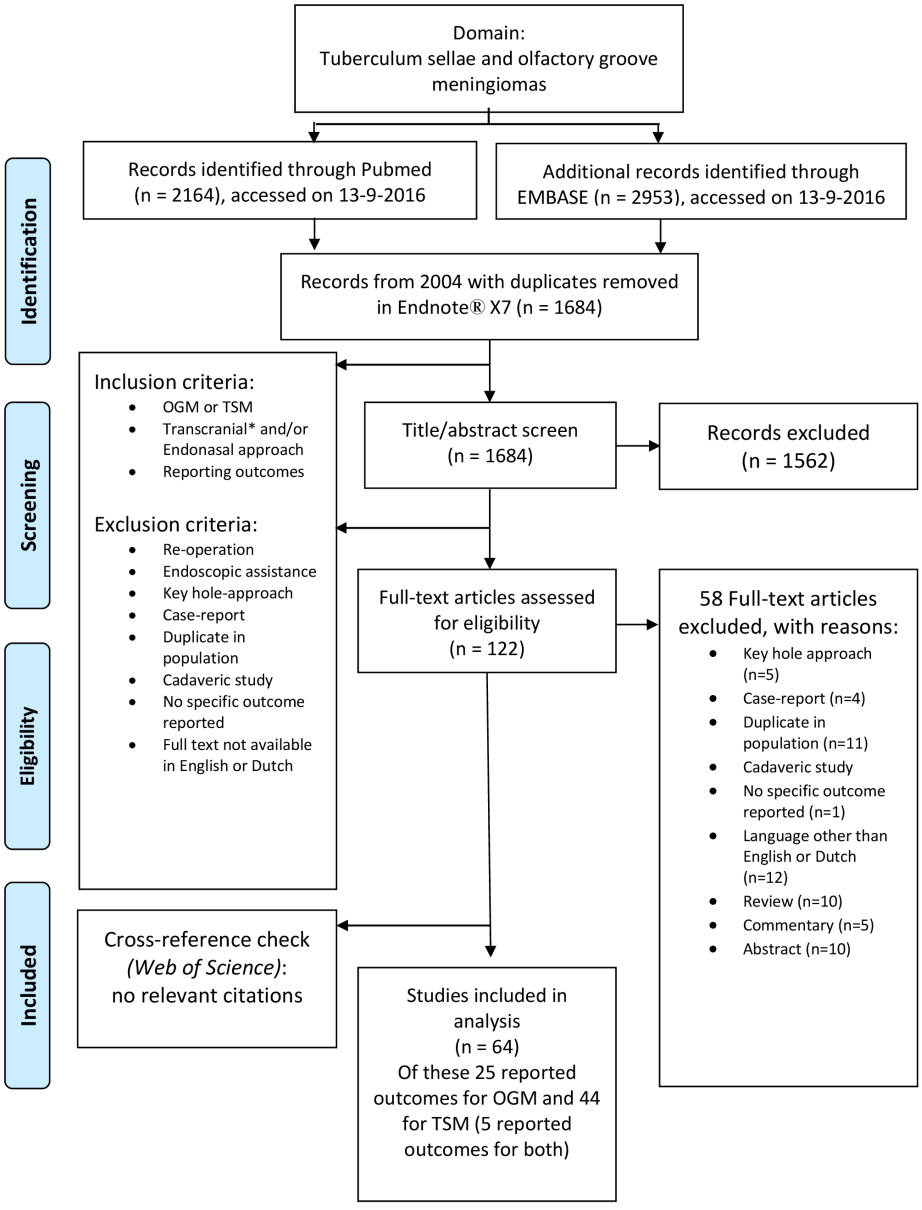
Methods

Search strategy and paper selection

In order to identify studies reporting on outcomes of surgically-treated TSMs and OGMs, a systematic review of the literature was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement[54] Both PubMed and Embase databases were searched on September 12, 2016. Because the outcomes of endoscopic surgery were first described in 2004 and microscopic resection has seen a continuous improvement, only articles published in 2004 or later were included[26, 38] The search strategy was drawn up using the keywords "Meningioma", "Tuberculum Sellae", "Olfactory Groove" and synonyms

(**Supplementary Table 3.5**). Duplicates were removed using Endnote X7.5.

Figure 3.1: Flowchart



Legend: Abbreviations: OGM: olfactory groove meningioma, TSM: tuberculum sellae meningioma

Table 3.1: Study characteristics of tuberculum sellae menigoma (TSM) studies

Authors	*TSM (N)*	*Mean age (range)*	*Meningioma Grade: WHOII and WHOIII (N)*	*% Male*	*Meningioma size*	*Approach*	*Mean Follow-up (years)*	*Modified NOS**
Ali et al.[3]	30	48 (34-63)	0 & 0	43	NR	mTCA	2.5 (range: 0.5 – 4)	3
Bassiouni et al.[5]	62	53 (29-81)	NS	26	NR	mTCA	6 (range: 1.5 – 14)	3
Bohman et al.[9]	5	53 (24-77)	NS	40	Mean DM: 4.74 cm	eTSA	0.65 (range: 0.18 – 1.42)	4
Bowers et al.[11]	27	54 (23-77)	NS	18.5	NR	mTCA + eTSA	NR	3
Ceylan et al.[12]	23	52.9 (23-77)	NS	18.5	Mean DM 2.55 cm	eTSA	1.82 (range: 0.17 – 2.42)	3
Chen et al.[13]	6	49.8 (4-78)	NS	33	NR	mTCA	2.44 (range: 0.5 – 4.04)	4
Chokyu et al.[15]	34	55.7 (23-78)	0 & 0	15	Mean DM: 2.43 cm	mTCA	7.98 (range: 1.25 – 16.2)	3
Chowdhury et al.[16]	6	39.5 (29-52)	NS	33	Mean DM: 3.5 cm	eTSA	0.58 (range: 0.16 – 1)	4
cook et al.[20]	3	40.3 (32-55)	NS	0	NR	eTSA	NR	3
Curey et al.[21]	20	59.1 (SD: 11.1)	0 & 0	15	Mean DM: 3.25 (SD: 1.38 cm)	mTCA	4.69 (SD: 2.83)	4
De Divitiis et al.[23]	51	NS	NS	20	DM: 6: < 2cm, 33: 2-4cm, 5: >4 cm	mTCA + eTSA	Range: 0.75 - 21	4
Della puppa et al.[25]	23	NS	NS	0	NR	mTCA	3.42 (range: 0.25 – 6.42)	3
Fatemi et al.[29]	23	40 (SD: 22)	NS	30	Mean DM:3.08 cm	mTCA + eTSA	eTSA: 1.67 (range: 0.25 – 5), mTCA: 1.17 (range: 0.92 – 1.5)	4
Gadgil et al.[30]	5	51 (31-66)	0 & 0	40	Mean volume: 6.3 cm^3	eTSA	1.25 (range: 0.25 – 2.25)	4
Ganna et al.[32]	24	53.8 (33-80)	0 & 0	17	Mean DM: 2.63 cm	mTCA	4.33 (range: 1.5 – 7.67)	3
Goel et al.[34]	85	NS	NS	NS	NR	mTCA	4 (range 0.5 – 9)	4
Haylurst et al.[35]	9	48.7 (29-65)	0 & 0	42	NR	eTSA	Median follow-up 38.6 (range 12 – 60 months)	4
Jang et al.[35]	24	49.5 (25-70)	NS	21	Mean DM: 2.06 cm	mTCA	1.73 (range: 0.25 – 4.5)	3
Khan et al.[40]	20	56.5 (31-81)	0 & 0	30	Mean volume: 11.98 cm^3	eTSA	NS	3
Kitano et al.[41]	28	Median: 55 (range:42-76)	NS	14%	Mean volume: 8.1 mm^3 (range 0.7–31.4 mm^3)	mTCA + eTSA	NS	3
Koutourousiou et al.[43]	70	57.3 (36-88)	0 & 0	16	Mean DM: 2.3 cm	eTSA	2.42 (range: 0.083 – 8.17	3
Landeiro et al.[45]	23	56.2 (38-77)	NS	35	NR	mTCA	2.6 (range: 0.5 – 10.3)	3
Leveque et al.[47]	18	63.8 (31-88)	NS		DM <4.0 cm: 11, >4.0 cm: 7	mTCA	4.74 (SD: 2.74)	4
Li et al.[48]	43	53.8 (24-68)	NS	28	DM: <2 cm: 8, 2-4 cm: 22, >4 cm: 13	mTCA	5.4 (range: 2 – 10)	3
Li-Hua et al.[49]	67	48.7 (28-76)	NS	42	DM: <3 cm: 29, >3cm: 38	mTCA	2.44 (range: 0.5 – 4.04)	4
Liu et al.[50]	19	NS	NS		NR	mTCA	1.24 (range: 0.33 – 3.83)	4
Mahmoud et al.[51]	58	56 (13-80)	NS	31	Mean DM: 2.9	mTCA	1.92 (up to 12 years)	4
Margalit et al.[52]	51	57.1 (28 -83)	NS	32	Mean max DM 2.94 cm (SD: 1.07)	mTCA	3.51 (range 0.17 – 7)	3
Mathiesen et al.[53]	29	58.3 (30 -84)	0 & 0	21	Mean max DM: 23.9 cm	mTCA	6 (1.5 - 10)	4
Nakamura et al.[56]	72	54.3 (30 -86)	1 & 0	24	Mean max 2.5 cm	mTCA	3.8 (range: 0.33 – 19.8)	3
Nanda et al.[58]	24	NS	NS	NS	DM: <3 cm: 3, 3-5 cm: 6, >5 cm: 21	mTCA	Median: 1.5	4
Ogawa et al.[61]	29	58.9 (43 -79)	2 & 0	26	NR	eTSA	2.98 (range: 0.5 – 4.92)	3
Padhye et al.[62]	3	66 (65 - 66)	0 & 0	0	Mean volume 25.7 cm^3	eTSA	1.83 (range: 0.25 – 6)	4

Abbreviations: WHO: World Health Organization, SD: Standard deviation, NR: Not Reported, DM: diameter, NS: not specified, mTCA: microscopic transsphenoidal approach, eTSA: endoscopic transsphenoidal approach, NOS: New-Castle Ottawa Scale.*The modified NOS score varied between 3 and 4; the difference was mainly caused by variation in specifying completeness of follow-up.

Table 3.1: Study characteristics of tuberculum sellae menigoma (TSM) studies (continued)

Palani et al.[63]	41	NR	NR	37	NR	mTCA	Range: 0.5 – 4	4
Pamir et al.[65]	42	53 (24-79)	3 & 1	33	Range 7.5-210 mm^3	mTCA	3.13 (range: 0.25 0 16)	3
Park et al.[66]	21	51	NS	14	Mean volume: 12.4 cm^3	mTCA	6.33 (range: 1 – 12.6)	4
Refaat et al.[68]	16	NS	NS	19	Mean DM: 2.5cm	mTCA	1.17 (range: 0.67 – 1.5)	3
Romani et al.[69]	52	Median: 59 (14-87)	1 & 0	19	Mean DM: 3.1 cm	mTCA	Median: 4.91 (range: 0.08 – 11.1)	3
Schick et al.[72]	53	52.6 (27-78)	NS	25	Mean DM 2.6 cm	mTCA	2.49 (range: 0.5 – 9)	4
Seol et al.[73]	86	49 (24-75)	NS	23	Mean Dm: 2.41	mTCA	3.25 (range: 0.6 – 12.2)	3
Terasaka et al.[77]	9	64 (57-83)	0 & 0	11	NR	mTCA	2.1 (0.5 - 5.92)	4
Wang et al.[79]	12	56.7 (40 -67)	0 & 0	33	Mean DM: 3.03 cm	eTSA	2.1 (range: 0.5 – 5)	3
Wilk et al.[81]	18	50.5 (30 - 73)	0 & 0	17	Mean volume 6.915 mm^3	mTCA	1.96 (range: 0.5 – 3.25)	4
Zhou et al.[82]	56	42.5 (21-69)	NS	46	DM: <3 cm: 24, 3-5 cm: 26 > 5m: 6	mTCA	2.29 (range: 0.08 – 3)	4

Data extraction

Two authors (IM and TO) independently screened the titles and abstracts of the articles for papers reporting surgical outcomes of resected OGMs and TSMs. After full-text screening, articles that reported outcomes of surgically-treated OGMs and TSMs were included. Case reports, commentaries, congress abstracts, reviews, animal studies, studies describing an endoscopically-assisted approach, studies reporting on the use of a keyhole-approach, studies in pediatric patients (<18 years old), re-operations, and cadaveric studies were excluded. Only literature in English and Dutch was reviewed. Discrepancies in selection were sorted out by discussion, and a senior author (MB) was consulted if the discrepancy could not be solved by discussion.

The following study characteristics were extracted from the full text of the selected studies: study design, number of patients, follow-up duration, study geographic location, percentage of WHO II and III meningiomas, percentage of males in the study population, mean age of the study population, and surgery type (transcranial or endoscopic endonasal). The following outcomes were extracted: number of patients with GTR (defined as Simpson grade I or II), number of patients with pre-operative visual problems, number of patients with improved vision post-surgery, post-operative cerebrospinal fluid (CSF) leakage, number of intraoperative arterial injury, and all-cause mortality (within 30 days after resection). Furthermore, perioperative blood loss, hospital length of stay, and operation length were extracted. Study quality was assessed with the adjusted New-Castle Ottawa Scale (NOS)[80] If the study in question was a case series, comparability was ignored.

Table 3.2: Study characteristics of olfactory groove meningioma (OGM) studies

Authors	*TSM (N)*	*Mean age (range)*	*Meningioma Grade: WHOII and WHOIII (N)*	*% Male*	*Meningioma size*	*Approach*	*Mean Follow-up (years)*	*Modified NOS**
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Bohman et al.[9]	5	53 (24-77)	NS	40	Mean DM: 4.74 cm	eTSA	0.65 (range: 0.18 – 1.42)	4
Bowers et al.[11]	27	54 (23-77)	NS	18.5	NR	mTCA + eTSA	NR	3
Ceylan et al.[12]	23	52.9 (23-77)	NS	18.5	Mean DM 2.55 cm	eTSA	1.82 (range: 0.17 – 2.42)	3
Chen et al.[13]	6	49.8 (4-78)	NS	33	NR	mTCA	2.44 (range: 0.5 – 4.04)	4
Chokyu et al.[15]	34	55.7 (23-78)	0 & 0	15	Mean DM: 2.43 cm	mTCA	7.98 (range: 1.25 – 16.2)	3
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Curey et al.[21]	20	59.1 (SD: 11.1)	0 & 0	15	Mean DM: 3.25 (SD: 1.38 cm)	mTCA	4.69 (SD: 2.83)	4
De Divitiis et al.[23]	51	NS	NS	20	DM: 6: < 2cm, 33: 2-4cm, 5: >4 cm	mTCA + eTSA	Range: 0.75 - 21	4
Della puppa et al.[25]	23	NS	NS	0	NR	mTCA	3.42 (range: 0.25 – 6.42)	3
Fatemi et al.[29]	23	40 (SD: 22)	NS	30	Mean DM:3.08 cm	mTCA + eTSA	eTSA: 1.67 (range: 0.25 – 5), mTCA: 1.17 (range: 0.92 – 1.5)	4
Gadgil et al.[30]	5	51 (31-66)	0 & 0	40	Mean volume: 6.3 cm^3	eTSA	1.25 (range: 0.25 – 2.25)	4
Ganna et al.[32]	24	53.8 (33-80)	0 & 0	17	Mean DM: 2.63 cm	mTCA	4.33 (range: 1.5 – 7.67)	3
Goel et al.[34]	85	NS	NS	NS	NR	mTCA	4 (range 0.5 – 9)	4
Haylurst et al.[35]	9	48.7 (29-65)	0 & 0	42	NR	eTSA	Median follow-up 38.6 (range 12 – 60 months)	4
Jang et al.[35]	24	49.5 (25-70)	NS	21	Mean DM: 2.06 cm	mTCA	1.73 (range: 0.25 – 4.5)	3
Khan et al.[40]	20	56.5 (31-81)	0 & 0	30	Mean volume: 11.98 cm^3	eTSA	NS	3
Kitano et al.[41]	28	Median: 55 (range:42-76)	NS	14%	Mean volume: 8.1 mm^3 (range 0.7–31.4 mm^3)	mTCA + eTSA	NS	3
Koutourousiou et al.[43]	70	57.3 (36-88)	0 & 0	16	Mean DM: 2.3 cm	eTSA	2.42 (range: 0.083 – 8.17	3
Landeiro et al.[45]	23	56.2 (38-77)	NS	35	NR	mTCA	2.6 (range: 0.5 – 10.3)	3
Leveque et al.[47]	18	63.8 (31-88)	NS		DM <4.0 cm: 11, >4.0 cm: 7	mTCA	4.74 (SD: 2.74)	4
Li et al.[48]	43	53.8 (24-68)	NS	28	DM: <2 cm: 8, 2-4 cm: 22, >4 cm: 13	mTCA	5.4 (range: 2 – 10)	3
Li-Hua et al.[49]	67	48.7 (28-76)	NS	42	DM: <3 cm: 29, >3cm: 38	mTCA	2.44 (range: 0.5 – 4.04)	4
Liu et al.[50]	19	NS	NS		NR	mTCA	1.24 (range: 0.33 – 3.83)	4
Mahmoud et al.[51]	58	56 (13-80)	NS	31	Mean DM: 2.9	mTCA	1.92 (up to 12 years)	4
Margalit et al.[52]	51	57.1 (28 -83)	NS	32	Mean max DM 2.94 cm (SD: 1.07)	mTCA	3.51 (range 0.17 – 7)	3
Mathiesen et al.[53]	29	58.3 (30 -84)	0 & 0	21	Mean max DM: 23.9 cm	mTCA	6 (1.5 - 10)	4
Nakamura et al.[56]	72	54.3 (30 -86)	1 & 0	24	Mean max 2.5 cm	mTCA	3.8 (range: 0.33 – 19.8)	3
Nanda et al.[58]	24	NS	NS	NS	DM: <3 cm: 3, 3-5 cm: 6, >5 cm: 21	mTCA	Median: 1.5	4
Ogawa et al.[61]	29	58.9 (43 -79)	2 & 0	26	NR	eTSA	2.98 (range: 0.5 – 4.92)	3
Padhye et al.[62]	3	66 (65 - 66)	0 & 0	0	Mean volume 25.7 cm^3	eTSA	1.83 (range: 0.25 – 6)	4

Legend: Abbreviations; NS: Not specified, NR: not reported, DM: diameter, eTSA: endoscopic transsphenoidal approach, mTCA: microscopic transcranial approach, SD: Standard deviation, NOS: New-Castle Ottawa Scale.*The modified NOS score varied between 3 and 4; the difference was mainly caused by not specifying the completeness of follow-up.† One OGM study (ref 13) compared eTSA to mTCA and was given 5 stars

Meta-analysis

Comprehensive meta-analysis (CMA) version 3 was used to calculate separate overall incidence using the fixed-effect model with the inverse variance method and the random-effect model according to the method of DerSimonian and Laird,[27] in the endonasal endoscopic and transcranial approach for the following variables: GTR, arterial injury, visual improvement, CSF leakage, and mortality. A resulting p-interaction value from the subgroup analysis comparing eTSA and mTCA was considered significant if < 0.05. Study heterogeneity was assessed by calculating I-squared values and P-values from the Cochrane Q test. Publication bias was assessed with Begg's tests and was corrected for by a trim-and-fill method. Finally, a meta-regression was conducted on each of age, gender (dichotomized by male percentage below/above the median category), and continent (North America as the reference) for eTSA and mTCA separately. For visual outcomes, only continent could be assessed as a source of heterogeneity as not all patients presented with visual problems and baseline characteristics from this subgroup were not available. A subgroup analysis for tumor size and grade was not possible due to great variance in reporting.

Results

After removing duplicates, 1684 articles were identified. After screening for titles and abstracts, 1426 articles were excluded and 216 full texts were reviewed (Figure 3.1). For TSM, 44 case series (of which 11 in eTSA, 29 in mTCA, and 4 in both) were included in the meta-analysis for the different outcomes, including a total of 1444 patients[3, 5, 8, 11-13, 15, 16, 20, 21, 23, 25, 29, 30, 32, 34-36, 40, 41, 43, 45, 47-53, 56, 58, 61-63, 65, 66 68, 69, 72, 73, 77, 79, 81, 82] As for OGM, 25 case series (of which 6 in eTSA, 18 in mTCA, and 1 in both) were included describing outcomes in 891 patients[2, 4, 6, 7, 17, 19, 22, 24, 25, 35, 37, 40, 44, 47, 55, 57, 60, 62, 64, 67, 68, 70, 75, 76, 78]

The median number of patients per study was 24 for TSM (**Table 3.1**) and 29 for OGM (**Table 3.2**). The average percentage of male patients was 27% for TSM and 32% for OGM. The median age was 51.0 for TSM and 52.0 for OGM. The median follow-up time was 6.0 years based on 35 studies for TSM[3, 5, 8, 12, 13, 15, 16, 21, 25, 29, 30, 32, 34, 36, 43, 45, 47-53, 56, 61, 62, 65, 66, 68, 72, 73, 77, 79, 81 82] and 7.0 years based on 20 studies for OGM[2, 4, 6, 7, 17, 19, 22, 24, 25, 37, 44, 47, 55, 57, 60 62, 67, 68, 76, 78] The modified NOS score varied between 3 and 4 out of 7 among the TSM and OGM case series[3, 5, 8, 11-13, 15, 16, 20, 21, 23, 25, 29, 30, 32, 34-36, 40, 41, 43, 45, 47-53, 56, 58, 61-63, 65, 66 68, 69, 72, 73, 77, 79, 81, 82] Outcomes of the meta-analysis for TSM (**Table 3.3**) and OGM (**Table 3.4**) are shown.

Gross Total Resection

For TSM, GTR after eTSA was reported in 14 studies[8, 11-13, 16, 20, 23, 29, 30, 40, 43, 61, 62, 79] and after mTCA was reported in 31 studies3, [5, 11, 13, 15, 21, 23, 25, 29, 32, 34, 36, 45, 47-49, 51-53, 56, 58, 63, 65, 66, 68, 69, 72, 77, 79, 81, 82] In a fixed effect model, the overall incidence for GTR was not significantly different comparing eTSA (incidence=83.0%; 95%-CI=76.7-88.0%, p-heterogeneity=0.74, I^2=0%, 221 patients) to mTCA (incidence=85.8% (95%-CI=83.6-87.9%, p-heterogeneity=0.07, I^2:

Table 3.3: Outcomes of the tuberculum sellae meningioma (TSM) meta-analysis

Outcomes in TSM	*# of studies*	*prevalence % (95% CI) Fixed & random*	*P-interaction Fixed & Random effects*	*I² (%)*	*Cochrance Q test (p-value)*	*Begg's test (p-value) for publication bias*	*Meta-regression on age,*	*Meta-regression on Gender, (<27% vs. ≥27% males)*	*Meta-regression on continent (north america as reference)*
GTR							**COEFFICIENT (P-VALUE); RANDOM EFFECT**		**OVERALL P-VALUE; RANDOM EFFECT**
eTSA; FIXED	14	83.0 (76.7-88.0)	0.34						
RANDOm		83.1 (76.2-88.3)	0.33	0.00	0.74		0.05 (0.26)	0.28 (0.50)	0.62
MTCA; FIXED	31	85.8 (83.6-87.9)				0.31			
RANDOm		86.1 (83.5-88.4)		28.4	0.07		0.01 (0.78)	**0.49 (0.03)**	**0.02**
Visual improvement									
eTSA; FIXED	12	77.7 (70.3-83.7)	**<0.01**						
RANDOm		77.0 (64.8-85.9)	**0.04**	7.90	0.37		*	*	0.42
MTCA; FIXED	28	60.7 (57.3-64.0)				0.14			
RANDOm		62.6 (55.2-69.3)		77.4	**<0.01**		*	*	0.30
CSF Leak									
eTSA; FIXED	15	19.3 (14.1-25.8)	**<0.01**						
RANDOm		19.3 (14.1-25.8)	**<0.01**	0.00	0.50		0.01 (0.77)	0.27 (0.51)	0.16
MTCA; FIXED	24	5.81 (4.33-7.75)				0.98			
RANDOm		5.81 (4.33-7.75)		0.00	0.93		0.03 (0.52)	0.02 (0.96)	0.94
Arterial Injury									
eTSA; FIXED	12	4.89 (2.33-9.94)	**0.03**						
RANDOm		4.89 (2.33-9.94)	**0.03**	0.00	0.97		-0.04 (0.54)	-0.51 (0.52)	0.69
MTCA; FIXED	27	1.86 (1.13-3.05)				**<0.01**†			
RANDOm		1.86 (1.13-3.05)		0.00	0.99		-0.01 (0.96)	-0.14 (0.79)	0.78
Mortality									
eTSA; FIXED	10	5.15 (2.39-10.8)	0.14						
RANDOm		5.15 (2.39-10.8)	0.14	0.00	0.85		-0.02 (0.81)	0.00 (0.99)	0.91
MTCA; FIXED	30	2.67 (1.77-4.02)				**<0.01**‡			
RANDOm		2.67 (1.77-4.02)		0.00	0.99		-0.02 (0.76)	-0.34 (0.43)	0.99

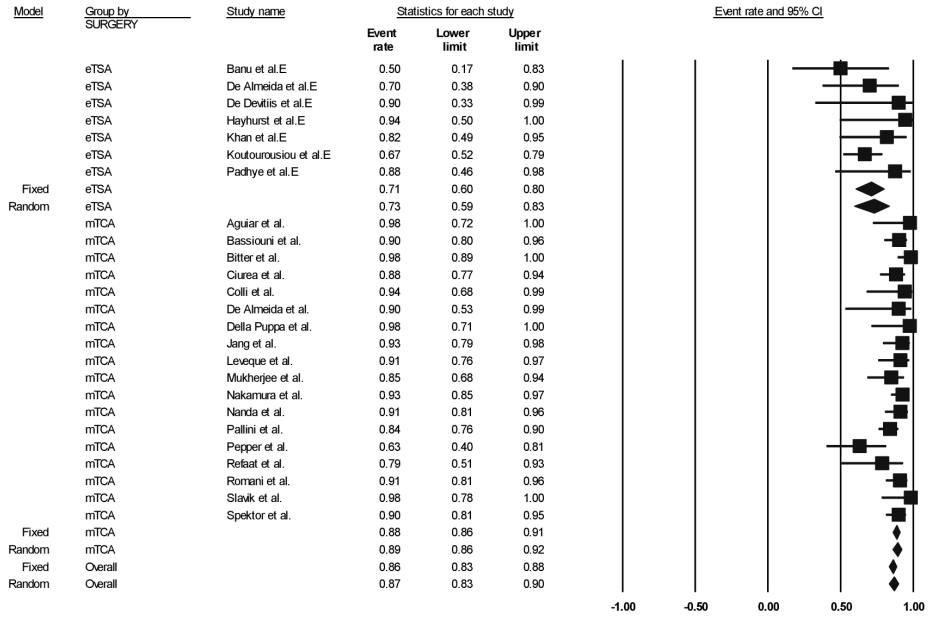
Legend: Abbreviations: GTR, gross total resection; mTCA: microscopic transcranial approach, eTSA: endoscopic transsphenoidal approach; CSF, cerebrospinal fluid; *meta-regression for age and gender was not possible for visual outcomes because the numbers were given for all subjects in the study and not all patients presented with visual problems †The Egger's p-value for publication bias was 0.35, non-significant. ‡The Egger's p-value for publication bias was 0.45, non-significant.

Table 3.4: Outcomes of the olfactory groove meningioma (OGM) meta-analysis

Outcomes in OGM	*# of studies*	*Fixed & random prevalence % (95% CI)*	*P-interaction Fixed & Random effectS*	*I² (%)*	*Cochrance Q test (p-value)*	*Begg's test (p-value) for publication bias*	*Meta-regression on age,*	*Meta-regression on Gender, (<29% vs. ≥29% males)*	*Meta-regression on continent (north america as reference)*
							COEFFICIENT (P-VALUE); RANDOM EFFECT		**OVERALL P-VALUE; RANDOM EFFECT**
GTR									
eTSA; FIXED	7	70.9 (60.3-79.7)	**<0.01**						
RANDOm		72.9 (59.4-83.2)	**<0.01**	0.00	0.45		**-0.18 (0.05)**	0.52 (0.44)	0.15
						0.48			
MTCA; FIXED	18	88.5 (85.9-90.7)							
RANDOm		89.1 (85.8-91.8)		36.5	0.06		0.05 (0.17)	0.11 (0.82)	0.30
Visual improvement									
eTSA; FIXED	4	64.5 (37.9-84.4)	0.33						
RANDOm		63.3 (30.9-87.0)	0.40	65.5	0.03		*	*	0.34
						0.25			
MTCA; FIXED	9	50.6 (42.9-58.4)							
RANDOm		47.4 (31.9-63.5)		68.6	**<0.01**		*	*	0.57
CSF Leak									
eTSA; FIXED	7	25.1 (17.5-34.8)	**<0.01**						
RANDOm		20.1 (10.4-35.1)	**0.04**	25.8	0.22		0.01 (0.94)	-0.30 (0.60)	0.54
						0.30			
MTCA; FIXED	17	10.5 (8.22-13.4)							
RANDOm		9.11 (6.01-13.6)		60.2	**<0.01**		**-0.12 (<0.01)**	0.07 (0.91)	0.22
Arterial Injury									
eTSA; FIXED	7	3.88 (1.55-9.43)	0.12						
RANDOm		3.89 (1.55-9.43)	0.12	0.00	0.98		-0.06 (0.67)	0.97 (0.38)	0.79
						<0.01†			
MTCA; FIXED	17	1.62 (0.87-2.98)							
RANDOm		1.62 (0.87-2.98)		0.00	0.99		-0.10 (0.22)	0.22 (0.81)	0.87
Mortality									
eTSA; FIXED	7	4.27 (1.50-11.6)	0.88						
RANDOm		4.27 (1.50-11.6)	0.88	0.00	0.94		-0.06 (0.68)	1.20 (0.34)	0.78
						0.21			
MTCA; FIXED	19	3.92 (2.66-5.75)							
RANDOm		3.92 (2.66-5.75)		0.00	0.74		-0.04 (0.44)	**1.02 (0.02)**	0.08

Legend: Abbreviations: GTR, gross total resection; mTCA: microscopic transcranial approach, eTSA: endoscopic transsphenoidal approach; CSF, cerebrospinal fluid; *meta-regression for age and gender was not possible for visual outcomes because the numbers were given for all subjects in the study and not all patients presented with visual problems †The Egger's p-value for publication bias was 0.50, non-significant.

Figure 3.2: Pooled prevalence of gross total resection by approach for olfactory groove meningioma resection: endoscopic transsphenoidal approach vs. microscopic transcranial approach.



P-interaction value < 0.01. Abbreviations: eTSA: endoscopic transsphenoidal approach, mTCA: microscopic transcranial approach.

28.4%, 1223 patients); (p-interaction value=0.34). In meta-regression, TSM studies with lower percentage of males had a higher rate of GTR (p=0.03). Studies conducted in Europe and Africa had significantly higher rates of GTR than North America (p=0.02). Begg's test for publication bias was non-significant (p=0.31, **Table 3.3**).[4, 22, 24, 35, 40, 44, 62] studies and 18 mTCA studies[2, 6, 7, 17, 19, 22, 25, 37, 47, 55, 57, 60, 64 67, 68, 70, 75, 76] Unlike TSM, the overall fixed incidence of GTR was significantly lower in eTSA (incidence=70.9%; 95%-CI=60.3-79.9%, p-heterogeneity=0.45, I^2=0%, 86 patients) compared to mTCA (88.5%; 95%-CI=85.9-90.7%, p-heterogeneity=0.06, I^2:36.5%, 786 patients); (p-interaction<0.01; Figure 3.2). In meta-regression, only higher age was associated with lower GTR in resected OGM with the eTSA approach with borderline significance (p=0.05). Begg's test for publication bias was non-significant (p=0.48) (**Table 3.4**).

Visual improvement

Visual outcomes were reported in 12 studies for eTSA[8, 12, 16, 23, 29, 30, 35, 40, 43, 61, 62, 79] and 28 studies for mTCA[3, 5, 13, 15, 21, 23, 25, 29, 32, 34, 36, 47-51, 56, 63, 65, 66, 68, 69, 72, 73, 77, 81, 82] with a total of 1139 patients presenting with visual

problems.[3, 5, 8, 12, 13, 15, 16, 21, 23, 25, 29, 30, 32, 34-36, 40, 43, 47-51, 53, 56, 61-63, 65, 66, 68, 69, 72, 73, 77, 79, 81, 82] Post-operative visual improvement was significantly higher for eTSA (incidence= 77.7%; 95%-CI=70.3-83.7%, p-heterogeneity=0.37, I^2=7.90%, 167 patients) than mTCA (incidence=60.7% (95%-CI=57.3-64.0, p-heterogeneity< 0.01, I^2=77.4%, 1139 patients) in fixed-effect models (p-interaction < 0.01). Because age and male percentage were not provided for this subgroup of patients who presented with visual problems, only continent could be assessed as a source of heterogeneity, which was not a significant source of heterogeneity for TSM resection using eTSA or MTCA. Begg's test for publication bias was non-significant (p=0.14, **Table 3.3**). One study specifically addressed visual improvement per approach in TSM resection, finding that eTSA was associated with more visual acuity improvement (≥5%; p-value: 0.01), but not with improvement of visual field deficits (p-value=0.61)[41]

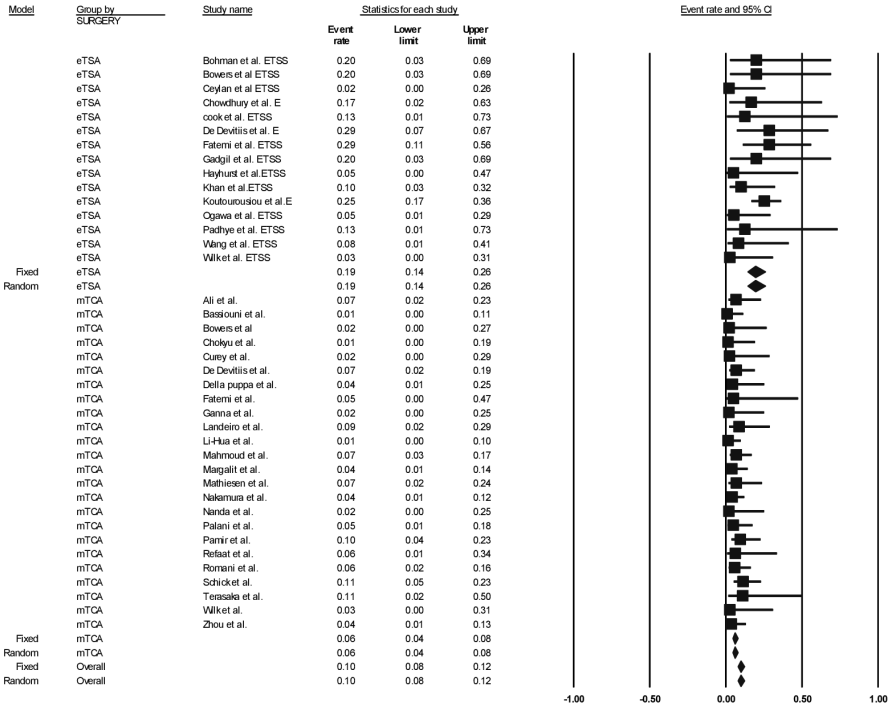
Visual improvement in OGM patients was described 4 eTSA studies[4, 40, 44, 62] and 9 mTCA studies[6, 7, 47, 57, 60, 68, 70, 75, 78] with 224 patients presenting with visual symptoms. The resulting fixed overall improvement rate was 64.5% (95%-CI: 37.9-84.4%, p-heterogeneity=0.03; I^2=65.5%) for eTSA compared to 50.6% (95%-CI=42.9-58.4%, p-heterogeneity <0.01, I^2=68.6%) for mTCA; however, this difference was not significant (p-interaction value: 0.33). Continent was not identified as a significant source of heterogeneity for eTSA (p=0.34) and mTCA (p=0.57). Begg's test for publication bias was non-significant (p=0.25, **Table 3.4**).

Cerebrospinal fluid leakage

CSF leak occurrence after TSM resection was extracted from 15 eTSA studies[8, 11, 16, 20, 23, 29, 30, 35, 40, 43, 61, 62, 79, 81] and 24 mTCA studies. The overall incidence of post-operative CSF leakage was significantly higher in patients treated with the eTSA approach (incidence=19.3%; 95%-CI=14.1-25.8%, p-heterogeneity=0.50, I^2=0%, 225 patients) than with mTSA (incidence= 5.81%; 95%-CI=4.33-7.75%, p-heterogeneity=0.93, I^2=0%, 879 patients) in fixed models (p-interaction value <0.01, Figure **??**). Age, gender and continent were not identified as sources of heterogeneity using meta-regression (all p-value > 0.05). Begg's test revealed no significant publication bias (p=0.98) (**Table 3.3**).

In OGM, 7 eTSA studies[4, 22, 24, 35, 40, 44, 62] and 17 mTCA studies[2, 6, 7, 17, 19, 22, 25, 37, 55, 57, 60, 64, 67, 68, 70, 75, 76, 78] including 889 patients described whether patients postoperatively developed a CSF leak. The overall incidence in fixed models was statistically significantly higher (p-interaction<0.01) for eTSA (incidence=25.1%; 95%-CI=17.5-34.8%, p-heterogeneity=0.22, I^2=25.8%) than mTCA (incidence=10.5%; 95%-CI=8.22-13.4%, p-heterogeneity <0.01, I^2=60.2%) (Figure 3.3). In meta-regression, only older age was significantly associated with lower CSF leakage rate for mTCA (p<0.01). For eTSA, age, gender, and continent were not identified as potential effect modifiers (p-interaction for all > 0.05). Begg's test indicated no significant publication bias (p=0.30, **Table 3.4**).

Figure 3.3: Pooled prevalence of cerebrospinal fluid leak by approach for tuberculum sellae meningioma resection: endoscopic transsphenoidal approach vs. microscopic transcranial approach

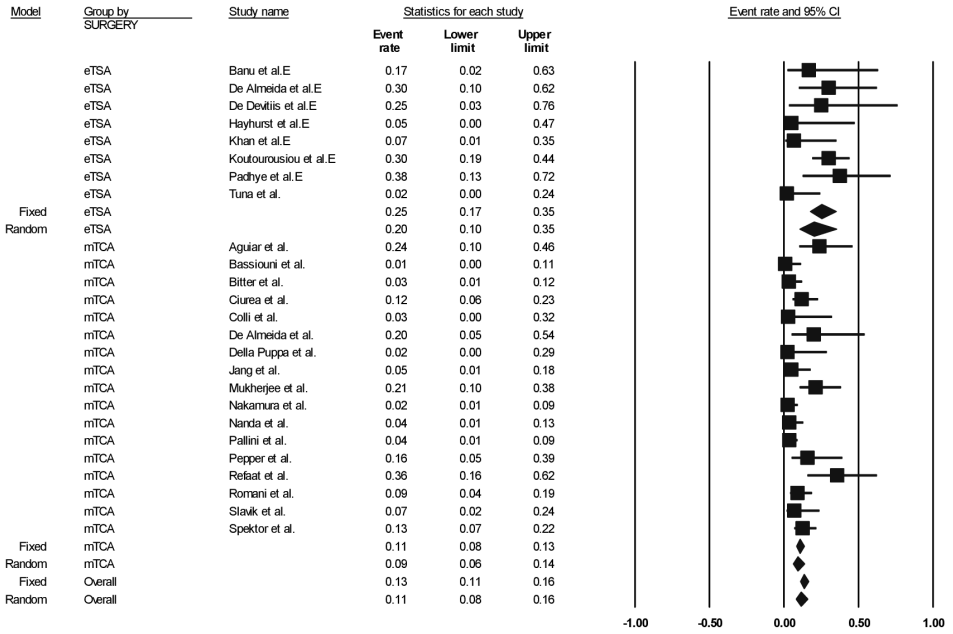


P-interaction value < 0.01. Abbreviations: CSF: cerebrospinal fluid eTSA: endoscopic transsphenoidal approach, mTCA: microscopic transcranial approach.

Intraoperative arterial injury

For intraoperative arterial injury, outcomes were extracted from 12 eTSA studies[8, 11, 16, 23, 29, 30, 35, 40, 43, 61, 62, 79] and 27 mTCA studies for TSM[3, 5, 11, 12, 15, 21, 23, 25, 29, 32, 36, 45, 48, 49, 51, 52, 56, 58, 63, 65, 68, 69, 72, 77, 81, 82] The overall incidence of intraoperative arterial injury was significantly higher for eTSA (incidence=4.89%; 95%-CI=2.33-9.94%, p-heterogeneity=0.97, I^2=0%, 225 patients) than for MTCA (incidence=1.86%; 95%-CI=1.13-3.05%, p-heterogeneity=0.99, I^2 =0%, 225 patients) in fixed effect models (p-interaction value=0.03; Figure 3.4). Trial-level covariates such as age, continent, and gender did not significantly contribute to any heterogeneity in the models, both for eTSA and mTCA (all p-interaction values>0.05). There was a significant publication bias, indicating that study results with higher arterial injury incidence tended not to be published (Begg's test p-value<0.01 **Table 3.3**). However, the imputed overall incidence estimate for TSM was not materially different from the original incidence rate (not shown).

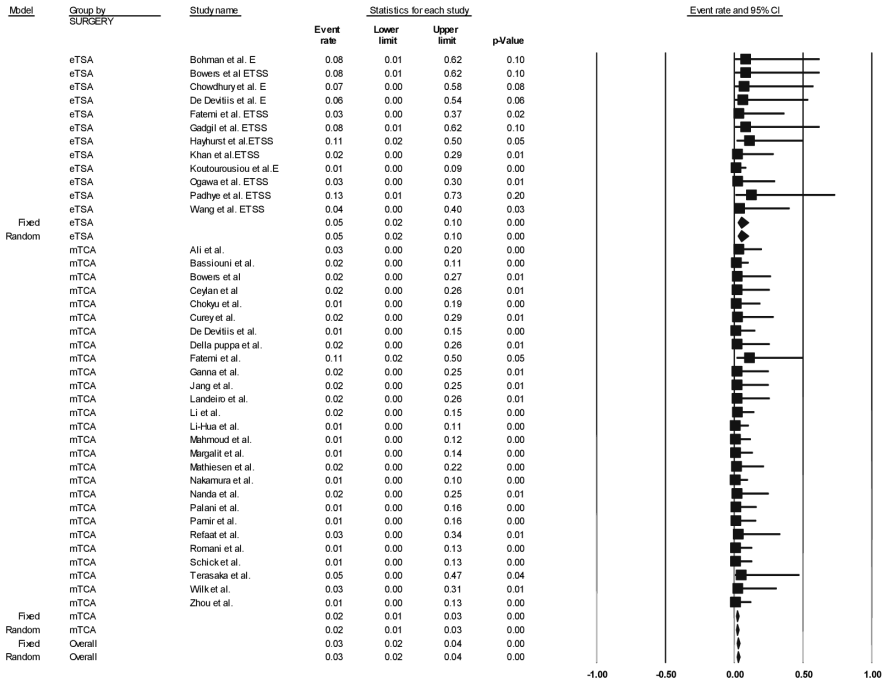
Figure 3.3: Pooled prevalence rates of cerebrospinal fluid leak by approach for olfactory groove meningioma resection: endoscopic transsphenoidal approach vs. microscopic transcranial approach



P-interaction value < 0.01; Abbreviations: CSF: cerebrospinal fluid eTSA: endoscopic transsphenoidal approach, mTCA: microscopic transcranial approach.

For OGM, the incidence of intraoperative arterial injury was extracted from 858 patients in 7 eTSA studies[4, 22, 24, 35, 44, 62] and 17 mTCA studies[2, 6, 7, 17, 19, 22, 25, 37, 55, 57, 60, 64, 67, 68, 70, 75, 76, 78] For eTSA, the fixed overall incidence of intraoperative arterial injury was 3.88% (95%-CI=1.55-9.43%, p-heterogeneity=0.98, I^2=0%). Although lower, the incidence for mTCA was 1.62% (95%-CI=0.87 - 2.98%, p-heterogeneity=0.99, I^2=0%) but not significantly different (p-interaction = 0.12). Covariates such as age, gender, and continent were not identified as sources of heterogeneity for both eTSa and mTCA procedures (all p-interaction> 0.05). Although Begg's Test for publication bias indicated the presence of publication bias (p-value < 0.01), Egger's test did not (p-value=0.50,**Table 3.4**). Moreover, the imputed overall incidence estimates for OGM were not materially different from the original incidence values (not shown).

Figure 3.4: Pooled prevalence rates of intra operative arterial injury by approach for tuberculum sellae meningioma resection: endoscopic transsphenoidal approach vs. microscopic transcranial approach.



Legend: P-interaction value: 0.03. Abbreviations: eTSA: endoscopic transsphenoidal approach, mTCA: microscopic transcranial approach.

Mortality

Mortality after TSM surgery was described in a total of 10 eTSA studies[8, 11, 23, 29, 40, 43, 61, 62, 79] and 30 mTCA studies[3, 5, 11-13, 15, 21, 23, 25, 29, 30, 35, 36, 45, 48, 49, 51-53, 56, 58, 63, 65, 68, 69, 72, 77, 81, 82] eTSA resulted in a 30-day mortality incidence of 5.15% (95%-CI=2.39-10.8, p-heterogeneity=0.85, I^2=0%, 194 patients), which was not significantly different from mTCA (incidence=2.67%; 95%-CI=1.77-4.02, p-heterogeneity=0.99, I^2=0%, 962 patients) in fixed models (p-interaction=0.14). Age, gender, and continent did not appear to have different incidence values based on the meta-regression results for both eTSA and mTCA (all p>0.05). Begg's test p-value for publication bias was significant indicating that articles with higher mortality rates tend not to be published (p < 0.01, **Table 3.3**); however, the trim-and-fill method suggested that the imputed overall incidence estimates for TSM were not materially different from the original incidence values (not shown).

For OGM, 7 eTSA studies[4, 22, 24, 35, 40, 44, 62] and 19 mTCA studies[2, 6, 7, 17, 19, 22, 25, 37, 47, 55, 57, 60, 64, 67, 68, 70, 75, 76, 78] including described mortality incidence. For eTSA, the overall 30-day mortality incidence was 4.27%

(95%-CI=1.50-11.6%, p-heterogeneity=0.94; I^2=0%; 82 patients), which was not significantly different from the mortality incidence in the mTCA group (incidence = 3.92%, 95%-CI=2.66-5.75, p-heterogeneity=0.74, I^2=0%; 779 patients) in fixed models (p-interaction=0.88). In a meta-regression for gender, it was identified that studies with a lower male percentage were significantly associated with a higher mortality incidence for mTCA (p=0.02) but not for eTSA (p=0.34), while age and continent were not. Begg's test for publication bias was non-significant (p=0.21) (**Table 3.4**).

Random-effect models

For all the above-mentioned results, the random-effect models yielded similar results (**Table 3.3 and 3.4**).

Blood loss, operating time, and length of stay in hospital

For blood loss, operating time and length of hospital stay, a quantitative meta-analysis was not feasible because of the paucity of studies reporting them; hence, these few studies were systematically reviewed. In TSM, mean blood loss ranged from 448 to 970 mL in three studies describing mTCA, compared to 200 to 617 mL for eTSA[21, 30, 41, 47] The mean operating time ranged from 375 to 444 minutes for eTSA in two studies, and from 116 to 426 minutes for mTCA in four studies[21, 23, 41, 47, 69] Hospital length of stay ranged from 6 to 21 days in one study in patients treated by an eTSA[23]

For OGM, blood loss was only reported in one case series in patients operated with an interhemispheric approach (mean: 570.9 ml, SD: 442)[47] The mean hospital length of stay for eTSA ranged from 11 to 13.5 days in 2 studies 9, 13, compared to 8.5 to 18 days for mTCA[7, 22, 24, 78] Of these studies, one described the mean length of stay in both approaches, with a mean length of stay of 11 days for eTSA compared to 8.5 days in mTCA (p=0.54)[22] Operating time ranged from six to ten hours in one study reporting outcomes from eTSA[24] In a study examining patients with an interhemispheric approach, the mean operating time was 209 minutes (standard deviation: 103)[47]

Discussion

In this meta-analysis, eTSA was not shown to be superior to mTCA for resection of both OGMs and TSMs. Only in patients with preoperative visual deficits due to TSM, eTSA seems superior to mTCA, but with great hetereogeneity. In patients with TSM, eTSA resulted in higher rates of visual improvement, similar rates of GTR and more CSF leaks and intraoperative arterial injury. While in patients with OGM, results of both techniques were similar for visual improvement and intraoperative arterial injury, but worse in patients operated with eTSA for GTR and CSF leaks. There seems to be no substantial difference in peri-operative blood loss, operating time, or length of hospital stay between the two approaches. There was no substantial difference between in incidence rates between in fixed- and random-effect models. This could be explained by a relative lack of difference between the study populations in the studies, which could have been implicated in the case of a difference between the models. However, mTCA was associated with considerable heterogeneity for out-

comes visual improvement in TSMs and CSF leak for OGMs which could reflect a relatively greater inter-study variability for these outcomes.

Although no significant difference was identified in GTR rate for TSM, mTCA resulted in higher GTR rates in OGM. As OGMs are located more anterior than TSM an extended eTSA approach is needed for OGM which requires more extensive drilling of the anterior skull base and a potential suboptimal view because of the angle of the scope. However, it should also be noted that GTR was not always the primary the goal of surgery (e.g. the goal could be preserving vision)[43, 72] Furthermore, many other factors seem to influence GTR rate. One factor may be the learning curve associated with eTSA, as seen with pituitary adenoma resection[10, 14, 46] Also, tumor factors such as large size and vascular enhancement can significantly lower GTR rate for eTSA, as seen in one study in TSM[43] Furthermore, presence of a "cortical cuff" (a layer of brain between the tumor capsule and cerebral vessels) on MRI was associated with more GTR in OGM[40]

For visual improvement, it remains to be determined whether eTSA is truly associated with more visual improvement than mTCA in TSM, as the heterogeneity among mTCA studies could not be corrected for. Therefore, the difference witnessed may very well be insignificant as seen with OGM. Furthermore, as the variance in reporting of tumor size did not allow for it to be incorporated in a meta-regression, the TSMs in the eTSA group may very well be smaller compared to the mTCA group. However, regarding visual outcomes, one study looking at the mTCA approach suggests that visual outcomes are associated with age and duration of visual symptoms but not with actual tumor size[28]

Both for OGM and TSM, eTSA was significantly associated with more CSF leakage. However, prophylactic lumbar drain placement varied greatly; in some studies almost all patients were given a prophylactic pre-operative lumbar drain, while in other studies none of the included patients were drained[8, 24, 30, 35, 40, 44] Also, the different studies used different reconstruction techniques (e.g. introduction of a vascularized flap and use of certain glues), although this caused no considerable heterogeneity among the studies[40, 44, 62]Another factor in the post-operative CSF leakage rate may be the level of neurosurgeon's experience. Although the difference was not significant and in a small number of patients, one group had two leaks in their first group of patients (n=8), compared to none in the latter group (n=12)[40] Also, the use of a vascularized flap for reconstruction of the skull base seems to bring CSF leakage rate down considerably[40, 43, 62] Still, this rate is considerably higher than overall incidence calculated for mTCA. Further improvement with more sophisticated reconstruction techniques following eTSA may bring the rate of CSF leakage down to those reported for mTCA.

MTCA for TSM resulted in a significantly lower rate of intraoperative arterial injury compared to eTSA. However, this seems not to have caused a significant difference in mortality. Nevertheless, a relative low number of patients treated with an eTSA may have caused a relatively low power, as the p-interaction value for mortality for TSM approaches significance (p=0.14). A significant association between intraoperative arterial injury and eTSA was not seen in OGM, again this may be explained by low power and a low number of studies, but also because of the anterior location

of the tumor. Previously, two reviews have described a comparison between eTSA and mTCA for both TSM and OGM. The first review identified higher GTR rate and less CSF leak associated with mTCA for both OGM and TSM (p<0.01 for both, using chi-squared test and Fisher's exact test respectively), which is similar to our findings except for the GTR rate for TSM[42] A second review found significantly more visual improvement (p<0.01) and CSF leakage (p<0.01) for eTSA and no difference in mortality (p=0.15) for TSM and OGM together, which is similar to our findings. eTSA was also found to be associated with a lower GTR rate (p<0.01) compared to mTCA, which was only the case in OGM in this meta-analysis[71] Finally, the authors of a meta-analysis for TSM found that eTSA was significantly associated with CSF leakage (OR: 3.9; 95%-CI: 1.15-15.75, p<0.05) and visual improvement (OR 1.5; 95%-CI 1.18, 1.82, p<0.05), which again is similar to our results[18]

Strengths of this study include an extensive review of the literature and evaluation of outcomes such as arterial injury, length of hospital stay, and blood loss. The use of both fixed- and random-effect models, evaluation of heterogeneity between the included studies, and assessment of publication bias ensures a rigorous evaluation of outcomes with appropriate valuation of the results. All outcomes were also subjected to meta-regression for various study characteristics where possible to try to identify sources of heterogeneity between the studies.

There are several limitations of this meta-analysis. First, the decision of discarding studies published before 2004 produces limitation. The decision to do so was based on the assumption that also mTCA outcomes improve over time with continual innovation and that meningiomas were not reported to be resected with an eTSA before that time[26, 38] Regarding the included studies, only case series were identified, resulting in the inability of calculation overall odds ratios. There is probably also a great difference between the population of patients that were deemed eligible for a eTSA resection, compared to those resected with mTCA, due to size, extension and invasion of the tumors (confounding by indication). Furthermore, one could argue that only looking at perioperative outcomes may not be conclusive, as especially recurrence happens during follow-up. However, as GTR and World Health Organization (WHO) grade remain the main prognostic factors for predicting recurrence, opting for eTSA should be done with great caution, as high grade meningiomas may be harder to resect completely[59, 74] However, it was not possible to correct for meningioma size, which is unfortunate as very small meningiomas may show very different results. Furthermore, it was no possible to correct for WHO grade, which could theoretically alter the results[31] Also, the choice of approach varied greatly among mTCA approach studies[1, 2, 5-7, 9, 47, 51, 56, 64, 70]

Indications for eTSA vary between groups. One group reported to operate all midline meningiomas regardless of size, extension, or configuration except for those tumors that extend from the anterior clinoid process[43] It has also been suggested that if the tumor extends laterally over the internal carotid artery, chances of GTR are limited[61] Others have suggested that larger tumors, tumors that extend laterally, involve vasculature or are calcified are also lesser candidates[23, 44] Therefore, confounding by indication cannot be ruled out, especially since the patients in these studies were not randomized to either treatment. As a result, the exact indications and

contra-indications for eTSA remain to be determined.

Future studies should, therefore, focus on identifying clear indications for eTSA for OGM and TSM and its safety by direct comparison in a randomized study. Such a study should ideally be conducted in a research setting by experienced surgeons, as its safety has not been prospectively compared to mTCA and as both approaches seem to come with a considerable learning curve which results in different outcomes[43] Given the observation that younger patients seem to benefit more from eTSA compared to older patients (p=0.02, n=34), it is not unlikely that specific groups might benefit more from one of the approaches[39] Probably, patients with relatively small (<3 cm), midline TSMs would probably be the best early candidates. These patients may benefit from a potential higher incidence of visual improvement postoperatively and the relative invasiveness of the eTSA approach. Further evaluation could be focused at characteristics such as size, a cortical cuff, and WHO grading to identify the best potential candidates for either approach[40] However, due to the low incidence of TSMs and OGMs in general and the great variety in anatomical characteristics among them this may very well be challenging. Therefore, other trial designs - e.g. a registry - should be considered when answering this question. Also, future improvement of the instruments used (e.g. 3D-endoscopes or glues) may improve results obtained by eTSA over time[33]

Conclusion

This meta-analysis indicates that the endoscopic transsphenoidal approach (eTSA) has not been shown to be superior to the microscopic transsphenoidal approach (mTCA) for both olfactory groove meningiomas (OGMs) and tuberculum sellae menigniomas (TSMs). More specifically, eTSA was associated with lower GTR rate for OGMs compared to eTSA and higher rate of arterial injury in TSMs. Furthermore, eTSA was associated with more CSF leaks in in both OGMs and TSMs compared to mTCA. On the other hand, eTSA was associated with a higher rate of visual improvement postoperatively compared to mTCA, which was not observed for OGMs. All conclusions should, however, be interpreted with caution due to limitations of this study.

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Table 3.5: Search syntax

Pubmed (09-12-2016) from 2004
(Tuberculum[Title/Abstract] OR Suprasellar[Title/Abstract] OR sellar[Title/Abstract] OR sella[Title/Abstract] OR sellae[Title/Abstract] OR cribriform[Title/Abstract] OR Planum[Title/abstract] OR Sphenoid*[Title/abstract] OR olfactory[Title/abstract] OR sphenoid bone[MeSH Terms] OR anterior skull base[Title/Abstract] OR "Cranial Fossa, Anterior"[Mesh]) AND (Meningioma*[Title/Abstract] OR meningioma[MeSH Terms] OR meningeoma*[Title/abstract] OR meningeal neoplasms[MeSH Terms] OR TSM[Title/abstract] OR OGM[Title/abstract] OR PSM[Title/abstract])
Embase (09-12-2016) from 2004
(Olfactory:ab,ti OR tuberculum:ab,ti OR suprasellar:ab,ti OR sellar:ab,ti OR sella:ab,ti OR Sellae:ab,ti OR planum:ab,ti OR cribriform:ab,ti OR sphenoid*:ab,ti OR 'sphenoid'/exp OR 'anterior skull base':ab,ti) AND (meningioma*:ab,ti OR 'meningioma'/exp OR meningeoma*ab,ti OR TSM:ab,ti OR OGM:ab,ti OR PSM:ab,ti)

4

Randomized controlled trials comparing surgery to conservative management in neurosurgery: a systematic review

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***Introduction**: A randomized controlled trial (RCT) remains the pinnacle of trial design. However, RCTs in neurosurgery are rare, especially those that compare surgery to conservative treatment, and their relevance and applicability has been questioned. The aim of this study is to evaluate the clinical impact and final results of RCTs in neurosurgery, using trials that compare surgery to conservative management. **Methods**: From 2000, PubMed and Embase databases and four trial registries (ClinicalTrials.gov, EudraCT, ISRCTN, and ICTRP) were searched for RCTs comparing a surgical procedure with conservative management. RCTs were evaluated for study design, funding, adjustments to reported outcome measures, accrual of patients, and clinical impact. **Results**: 82 individual RCTs were identified in the literature (40 spinal, 19 vascular, 11 functional, 10 peripheral nerve, and 2 oncological). 84 RCTs were found to be registered of which some are ongoing. Trial registration rate*

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differed per subspecialty. Funding was mostly from non-industry institutions (58.5%), but 25.6% of RCTs did not report funding sources. 63.4% of RCTs reported a favourable outcome for surgery, compared to 3.7% for conservative treatment. Primary and secondary outcome measures were changed in 13.2% and 34.2% of RCTs respectively and varied by subspecialty. 41.9% of RCTs subtracted ≥10% of the anticipated accrual of patients and 12.9% of RCTs added ≥10%. 7.3% of registered RCTs were terminated, most commonly due to slow recruitment. Subspecialty, registration, funding, masking, population size, changing outcome measures, and Jadad score were not significantly associated with a reported benefit of surgery. ***Conclusions****: RCTs comparing surgical to conservative treatment remain rare in neurosurgery and often find a benefit for surgical treatment. Changes to outcome measurements and anticipated accrual are not uncommon. Half of the trials are registered, and funding sources are not always reported. Successfulness of future neurosurgical RCTs could be improved by trial registration prior to patient inclusion and pilot studies.*

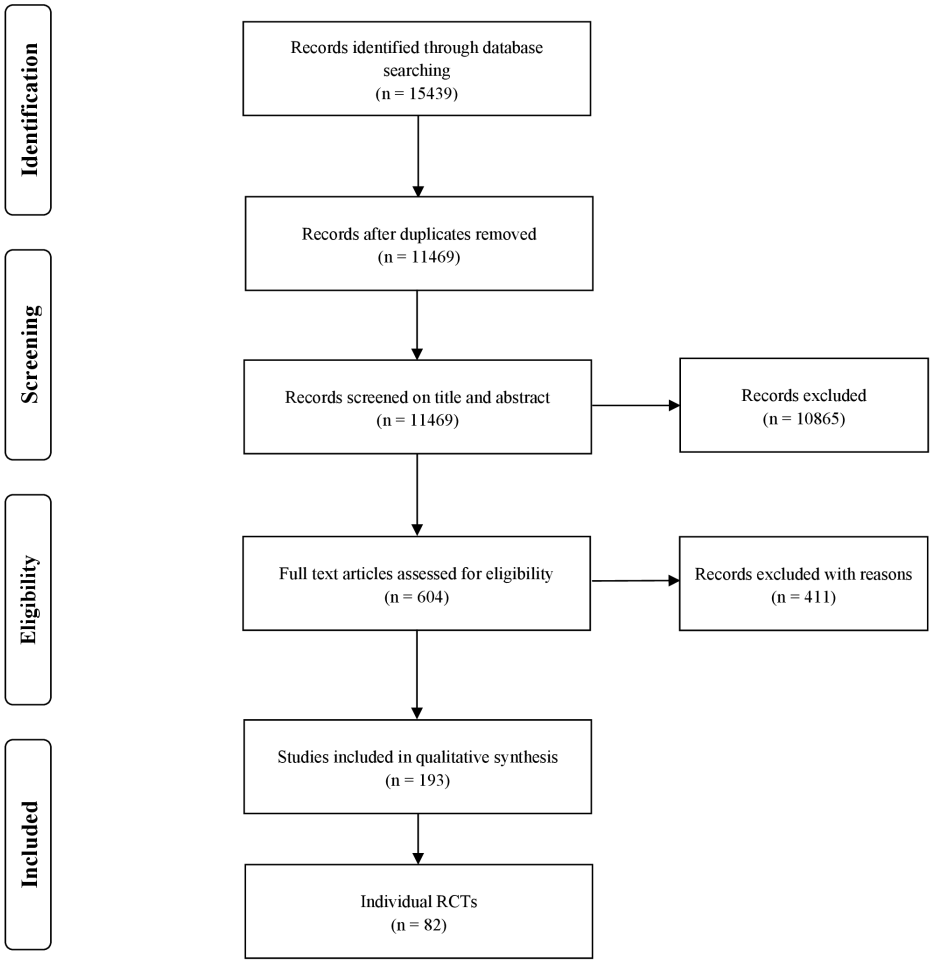
Introduction

Most neurosurgical procedures are the result of continuous improvement and evolvement of existing procedures and are rarely compared with conservative management in a methodologically sound manner to prove true undisputed benefit. The randomized controlled trial (RCT) is commonly regarded as the pinnacle of trial design and is thought to produce the highest quality evidence.[16] Conducting a randomized controlled trial in neurosurgery could be regarded as problematic due to problems with e.g. patient inclusion, defining relevant outcomes, lack of equipoise, and providing a conclusive answer.[17, 23] Perhaps partially as a result, RCTs in neurosurgery are relatively infrequently conducted and their quality has been suggested to be poor.[2, 9, 13] This may even be more the case when a neurosurgical procedure is compared to conservative management, rather than a different neurosurgical procedure or use of a medical device.[4, 8, 17]

Evaluations of RCT quality in other surgical fields have also identified a relatively low quality, as seen in ophthalmologic surgery and vascular surgery.[3, 22] However, others have suggested that the quality of surgical RCTs has improved over the years.[1] Questions remain regarding trial quality, reporting, and if trial design affects the outcome of a surgical benefit in neurosurgical RCTs.

In this systematic review, the literature is evaluated for neurosurgical RCTs that compare a neurosurgical procedure with conservative management. The aim of this review is to evaluate neurosurgical RCT design, quality, conduction, and reported outcomes. An additional aim is to identify which trial characteristics are associated with a reported surgical benefit. Moreover, this review will evaluate how often predefined outcome measures and accrual of patients are changed, and how the latter may influence trial findings.

Figure 4.1: Flowchart Depicting Study Selection



Methods

A systematic search was performed in both Pubmed and Embase databases according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, [20] in order to identify all potentially relevant trials as of January 2017. The search string was drafted with the help of a professional librarian using search terms related to 'neurosurgery' together with specific neurosurgical procedures and synonyms of 'randomized trial'. The databases were only searched for RCTs published after 2000. The exact search syntaxes for Pubmed and Embase are shown in **Supplementary Table 4.6**. Studies were included if they described data from a randomized controlled trial that compared any form of surgery to a non-surgical group.

Papers were excluded that 1) were not randomized 2) did not have a conservative treatment arm 3) were not part of a trial of which the results were already published 4) had no full text was available 5) were not written in English, Dutch, German, or French. The initial review was carried out by four independent authors (EM, IM, JS, AD). Disagreements were solved through discussion, in which one additional author was involved (MB). The amount of published papers per trial was recorded, including design or protocol and reported pilot studies or early results. Data were extracted from the first published paper on main results. These included a) trial start and end date b) neurosurgical subspecialty c) countries involved d) number of countries involved e) number of participating centers f) funding source (non-industry, industry, or not reported) g) total amount of anticipated and included patients h) patients per study arm i) masking j) and if the outcome favored surgery or conservative treatment. Scopus was consulted for the number of times the first results of the study were cited. The impact factor of the journal was determined as the journal's indicated impact factor of 2016. Jadad scales were calculated for each trial to measure study quality.[5]

Table 4.1: RCT demographics per subspecialty

		Total	*Spinal*	*Vascular*	*Functional*	*PNS*	*Oncological*
No. Trials		82	40 (48.8%)	19 (23.2%)	11 (13.4%)	10 (12.2%)	2 (2.4%)
Registered		38 (46.3%)	15 (37.5%)	13 (68.4%)	5 (45.5%)	5 (50%)	0 (0%)
No. Publications	Median (IQR)	2 (1-3)	2 (1-4)	1 (1-2)	2 (1-2)	1 (1-2)	1 (1-1)
No. Centers	Multicenter	48 (58.5%)	22 (55%)	16 (84.2%)	7 (63.6%)	2 (20%)	1 (50%)
	Single-centered	30 (36.6%)	15 (37.5%)	2 (10.5%)	4 (36.4%)	8 (80%)	1 (50%)
	Unknown	4 (4.9%)	3 (7.5%)	1 (5.3%)	0 (0%)	0 (0%)	0 (0%)
	Median (IQR)	3.5 (1.0-13.0)	3.0 (1.0-9.0)	18.5 (6.0-47.3)	3.0 (1.0-8.5)	1.0 (1.0-1.0)	23.5 (12.3-34.8)
No. Countries	Median (IQR)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-7.8)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	4.0 (2.5-5.5)
Duration (months)	Median (IQR)	42 (27.8-68)	42 (35.5-60)	63 (21.8-90.8)	47 (39.8-58)	18 (12.5-36.5)	*NA*
No. Patients	Total (Median)	95 (50.0-174.5)	98 (62.8-177.5)	112 (35.0-300.0)	48 (35.0-118.0)	108 (51.8-119.0)	61.5 (41.8-81.3)
	Sx (Median)	47.5 (26.0-87.0)	50 (30.3-87.3)	61 (21.0-174.8)	26 (15.8-38.8)	53.5 (18.3-59.5)	30.5 (20.8-40.3)
	Non-Sx (Median)	47 (24.0-82.0)	49 (30.3-70.8)	72.5 (19.3-163.8)	21.0 (15.8-39.0)	54 (30.3-59.8)	31.0 (21.0-41.0)
Masking	Double Blind	7 (8.5%)	3 (7.5%)	0 (0%)	4 (36.4%)	0 (0%)	0 (0%)
	Single Blind	26 (31.7%)	8 (20%)	9 (47.4%)	5 (45.5%)	4 (40%)	0 (0%)
	Open Label	49 (59.8%)	29 (72.5%)	10 (52.6%)	2 (18.2%)	6 (60%)	2 (100%)
Outcome	Surgical	52 (63.4%)	23 (57.5%)	13 (68.4%)	8 (72.7%)	8 (80%)	0 (0%)
	Conservative	3 (3.7%)	2 (5%)	1 (5.3%)	0 (0%)	0 (0%)	0 (0%)
	No Difference	27 (32.9%)	15 (37.5%)	5 (26.3%)	3 (27.3%)	2 (20%)	2 (100%)
Funding	Non-Industry	48 (58.5%)	25 (62.5%)	11 (57.9%)	7 (63.6%)	5 (50%)	0 (0%)
	Industry	13 (15.9%)	7 (17.5%)	1 (5.3%)	4 (36.4%)	0 (0%)	1 (50%)
	Not reported	21 (25.6%)	8 (20%)	7 (36.8%)	0 (0%)	5 (50%)	1 (50%)
No. Citations	Median (IQR)	95 (21.8-296.0)	127.5 (22.8-286.0)	135 (30.5-331.0)	258 (64.5-1058.0)	48 (3.3-86.5)	40 (26.0-54.0)
Impact factor	Median (IQR)	6.1(2.4-39.3)	3.4 (2.1-32.1)	23.5 (3.6-44.0)	23.5 (8.9-48.6)	8.2 (3.0-15.0)	3.5 (3.5-3.5)
Jadad	Median (IQR)	3 (2-3)	2.5 (2-3)	3 (2-3)	3 (2-4)	3 (1.25-3)	1 (1-1)

Abbreviations:IQR: interquartile range, mo: months, No.: number of, PNS: peripheral nerve surgery, SD: standard deviation, Sx: surgical arm

Four trial registries (ClinicalTrials.gov, EudraCT, ISRCTN, and ICTRP) were searched as well with synonyms of 'neurosurgery'. All randomized trials investi-

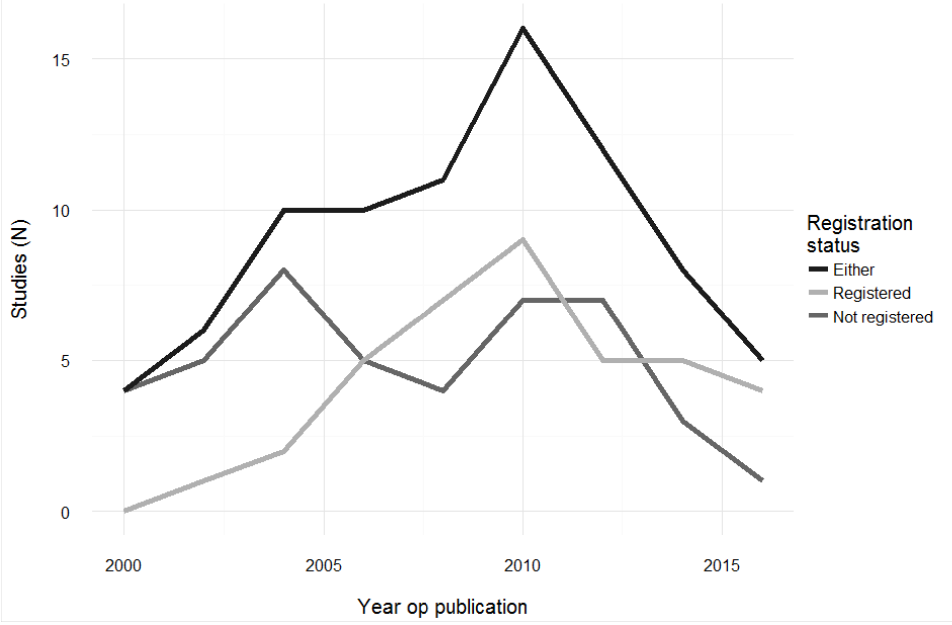
gating a neurosurgical treatment to a non-surgical treatment were included. Registry data and published protocols were used to determine if and what changes were made to primary and secondary outcome measurements in comparison to first published main results. Additionally, the anticipated accrual of patients was evaluated for whether it was met or surpassed. The current status of registered trials was also noted.

Methodological characteristics (as listed above) were evaluated for association with surgical or non-surgical reported benefit by univariate logistic regression. Statistical analyses and data visualization were conducted using R version 3.4.3 (R Core Team, 2017).

Results

After removal of duplicates, a total of 11469 citations were identified in Pubmed and Embase databases. 604 potentially relevant articles were selected through title/abstract screening, of which 193 articles were selected for qualitative synthesis after full-text screening (**Figure 4.1**). A total of 82 individual RCTs were identified (**Table 4.1**). A total of 84 RCTs were found registered in one of the registries searched.

Figure 4.2: Registration Status over Time.



Study characteristics

Of all randomized trials 40 (48.8%) were in spine, 19 (23.2%) vascular, 11 (13.4%) functional, 10 (12.2%) peripheral nerve, and 2 (2.4%) oncological subspecialty (**Table 4.1**).

The latter only included pituitary tumors. Overall, a median of 2 papers (IQR: 1-3) were published per trial, with spinal (2, IQR: 1-4) and functional (2, IQR: 1-2) subspecialties having most publications per RCT. Trial registration was highest in vascular neurosurgery (68.4%) and lowest in spine surgery (37.5%). Twenty RCTs were multicenter, but this was only the case in 20% of peripheral nerve surgery trials (n = 2). Median time to trial completion was 42 months (IQR: 27.8-68.0). RCTs in peripheral nerve surgery had the lowest median time to study completion (18 months, IQR: 12.5-36.5). Overall, median number of patients included in an RCT was 95 (IQR: 50.0-174.5), with relatively smaller populations in functional neurosurgery trials (48, IQR: 35-118). Study arms were generally evenly distributed (**Table 4.1**). Most trials were open label (59.8%) whereas double blind trials were relatively rare (8.5%). Double blind trials were most common in functional neurosurgery (36.4%). Funding was usually from non-industry parties (58.5%). However, the funding was not reported in 25.6% of RCTs. Median Jadad scores were 3 (IQR: 2-3). Trial registration rate seems to increase just a little over time (**Figure 4.2**).

Factors associated with trial outcome

The majority of trials reported a favorable outcome for surgical intervention (63.4%) (**Table 4.1**). Only 3.7% of all trials reported a beneficial effect of the non-surgical intervention, while the rest (32.9%) did not find any statistical differences. Only high Jadad scores (≥4) were associated with no surgical benefit (OR: 0.10, 95%-CI: 0.01-0.89). None of the other trial characteristics showed a significant relationship to an outcome favoring surgical treatment (all p-values > 0.05, **Table 4.2**).

Changes in primary and secondary outcome measures

Only registered trials (n = 38) were available for assessment of changes in primary and secondary outcome. 13.2% of these RCTs changed their primary outcome measurement between registration and publication (n = 5, **Table 4.3**). 60% of these changes were simple changes to the primary outcome measure (n = 3), 20% added a primary outcome measure (n = 1), and 20% removed one of the primary outcome measures (n = 1, **Table 4.3**). Secondary outcome measures were changed in 34.2% of all RCTs (n = 16). 50% were simply changed (n = 8), 37.5% had an additional secondary outcome measure (n = 6), and 12.5% removed one or more of their secondary outcome measures (n = 2).

Trial continuation and anticipated

accrual of patients 65.9% of registered RCTs were completed and 26.8% was still ongoing (**Table 4.4**). 7.3% of RCTs were indicated as terminated. This was most commonly due to slow recruitment or meeting a pre-specified futility boundary. The initial anticipated accrual was lowered by more than 10% in 41.9% of all RCTs. The accrual was diminished by 58.5% on average (SD: 25.1%). In 12.9% of trials, initial estimated accrual surpassed 110% of planned patient enrollment (mean added percentage: 41.2, SD: 36.0%).

Table 4.2: Univariate Analysis of Trial Outcome

		No Surgical benefit (N = 30)	*Surgical benefit (N = 52)*	*OR (95%-CI)*	*P-value*
Subspecialty (%)	Spinal	17 (56.7)	23 (44.2)	Ref.	
	Vascular	6 (20.0)	13 (25.0)	1.60 (0.52-5.35)	0.42
	Functional	3 (10.0)	8 (15.4)	1.97 (0.49-10.0)	0.36
	PNS	2 (6.7)	8 (15.4)	2.96 (0.64-21.3)	0.20
	Oncological	2 (6.7)	0 (0.0)	*NA*	
Registered (%)	Not registered	16 (53.3)	28 (53.8)	Ref.	
	Registered	14 (46.7)	24 (46.2)	0.98 (0.40-2.43)	0.96
Funding (%)	Non-industry	20 (66.7)	28 (53.8)	Ref.	
	Industry	5 (16.7)	8 (15.4)	1.14 (0.33-4.26)	0.84
	Unknown	5 (16.7)	16 (30.8)	2.29 (0.75-7.92)	0.16
Multicentered (%)	Singlecenter	9 (30.0)	21 (40.4)	Ref.	
	Multicenter	20 (66.7)	28 (53.8)	0.60 (0.23-1.58)	0.30
	NA	1 (3.3)	3 (5.8)	1.29 (0.12-14.09)	0.84
Masking (%)	Open label	16 (53.3)	33 (63.5)	Ref.	
	Single blind	9 (30.0)	17 (32.7)	0.92 (0.34-2.56)	0.86
	Double blind	5 (16.7)	2 (3.8)	0.19 (0.03-1.01)	0.07
Number of patients (%)	<100	13 (43.3)	29 (55.8)	Ref.	
	≥100	17 (56.7)	23 (44.2)	0.61 (0.24-1.49)	0.28
Change in primary outcome measure (%)	No change	14 (46.7)	19 (36.5)	Ref.	
	Change	1 (3.3)	4 (7.7)	2.95 (0.38-61.1)	0.36
	Unknown	15 (50.0)	29 (55.8)	1.42 (0.56-3.64)	0.46
Change in secondary outcome measure (%)	No change	8 (26.7)	14 (26.9)	Ref.	
	Change	5 (16.7)	9 (17.3)	1.03 (0.26-4.34)	0.97
	Unknown	17 (56.7)	29 (55.8)	0.97 (0.33-2.77)	0.96
Jadad (%)	Jadad <3	11 (36.7)	27 (51.9)	Ref.	
	Jadad ≥3	19 (63.3)	25 (48.1)	0.54 (0.21-1.33)	0.18
	Jadad <4	25 (83.3)	51 (98.1)	Ref.	
	Jadad ≥4	5 (16.7)	1 (1.9)	**0.10 (0.01-0.89)**	**0.01**

Legend: Abbreviations: OR: odds ratio

Table 4.3: Changes in Primary and Secondary Outcome Measures

		Percentage
Change Primary Outcome	Changed	60%
	Added	20%
	Removed	20%
Change Secondary Outcome	Changed	50%
	Added	37.5%
	Removed	12.5%

Academic impact

The median number of citations per study was 95 (IQR: 21.8-296.0). Peripheral nerve surgery and oncological trials had the lowest median number of citations (48, IQR: 3.3-86.5, and 40, IQR 26.0-54.0 respectively, **Table 4.5**). Median impact factor was 6.1 (IQR: 2.4-39.3). Functional neurosurgery trials had the highest median impact

factor at 23.5 (IQR: 8.9-48.6).The median number of citations and impact factor did not differ for trial outcome overall ($p > 0.05$). Post-hoc analyses also did not show any significant difference in number of citations or impact factor between two trial outcomes (all $p > 0.05$).

Figure 4.3: Changes Made in Primary and Secondary Outcome Measures

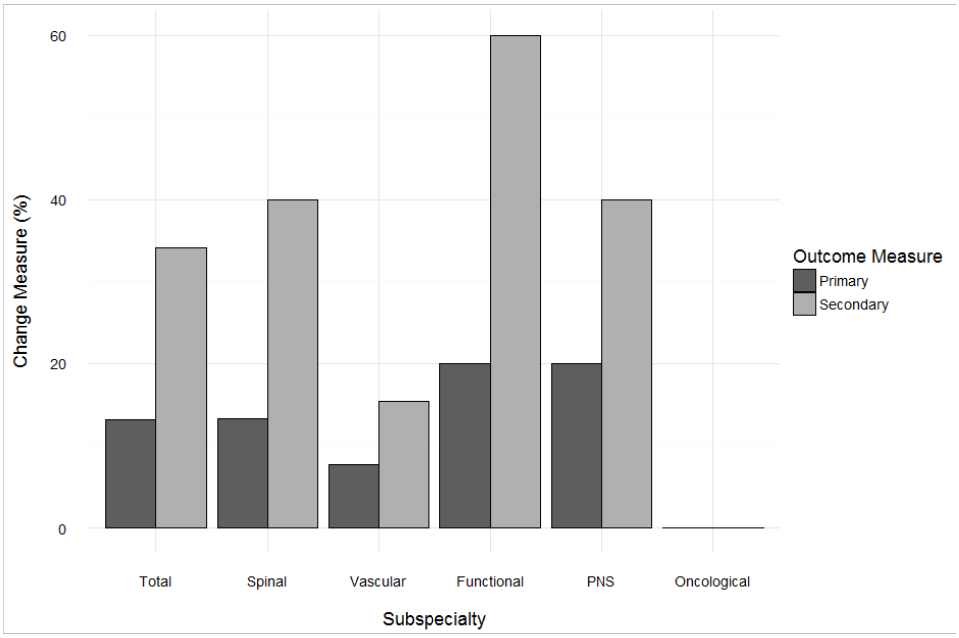


Table 4.4: Trial Registration Data

		Percentage
RCT Status	**Completed**	65.9%
	Active	26.8%
	Terminated	7.3%
Accrual Patients	**Subtracted >10%**	41.9%
	Mean (SD)	58.5% (25.1)
	Added >10%	12.9%
	Mean (SD)	41.2% (36.0)

Table 4.5: Average Academic Impact per Outcome

	Citations Median (IQR)	*P-value*	*Impact Factor Median (IQR)*	*P-value*
Surgical	103.0 (19.5-331.5)	0.33*	6.1 (2.3-44.0)	0.73*
Non-surgical	119.0 (0-NA)		2.1 (2.1-NA)	
No difference	72.0 (24.0-301.0)		5.8 (2.4-26.5)	

Discussion

The aim of this study was to evaluate trial outcomes in recent neurosurgical RCTs comparing surgery to conservative treatment. The authors of the identified RCTs are to be applauded as many trials reported a protocol, registered their trial, and published their protocol. However, this study identified several challenges common among neurosurgical RCTs. Trial outcomes favoring conservative treatment are rarely seen, with 63.4% of RCTs in favor of surgery, and hardly ever was surgery found to be inferior. Funding sources were not reported consistently among all studies identified and many trials were not registered. Changes to primary or secondary outcome measures occurred frequently, but were not shown to influence whether surgery was found to be superior to a surgical procedure. The overall quality of the identified studies based on the Jadad score could be considered poor. Nevertheless, most studies still had a considerable academic impact.

Trial registration and outcome measurement

Differences between registered and published outcomes are suggested to be common among RCTs and were not suggested to be the result of funding sources, which is similar to our study.[7] One study that evaluated outcome reporting among 51 surgical RCTs found that registration is often omitted and primary and secondary outcome measures are often changed, which is also similar to our findings in neurosurgery.[18] A second study among surgical trials showed that 91.7% of trials that changed outcome measures published significant results.[10] Trials in cardiology, rheumatology, and gastroenterology were also found to regularly change outcome measures, which had a significant association with finding a significant outcome.[15] Regardless of how the results of RCTs are produced, one study among RCTs in spine surgery indicated that statistical findings could be considered fragile as the addition of only few events or non-events would have changed the significance of the reported finding.[2]

Trial quality

One study evaluated trial quality among 61 neurosurgical RCTs.[13] They found that the median CONSORT score[19] was 36, what could be considered to be low. Median Jadad scores were less than 3, which is similar to the findings in this study. The study also identified that trials that evaluated surgical procedures met their targets less often than trials that evaluated drugs or medical devises, which was not evaluated in our study. This may implicate that conducting a trial for surgical procedures is

more difficult but may also be the result of bias. A second study that evaluated 27 neurosurgical RCTs found a mean CONSORT score of 41 and a mean Jadad score of 3.42, again similar to our findings.[9] This study also identified that studies published in high impact journals had higher mean CONSORT and Jadad scores, which could implicate that higher impact journals demand higher quality journals and reporting.[9] Findings of this study, however, indicate that the finding of a surgical benefit does not affect academic impact.

Strengths and limitations

This is the first study that sought to evaluate in neurosurgical RCTs comparing a surgical procedure to conservative management which trial characteristics were associated with the identification of a surgical benefit. Both MEDLINE search engines and trial registries were extensively evaluated. The findings provide a valuable insight into the frequency of trial cessation, adjustment of trial design, and quality of reporting, which may provide useful insights for future neurosurgical RCTs.

There are also several limitations to this study. The search engines and registries only provided a relatively small number of RCTs. There is a possibility that trials that were not registered or reported were not identified, which limits the true implications of the findings in the analysis. This may be why only a very low number of studies were identified that found a neurosurgical procedure to be associated with inferior outcomes. Only RCTs published after 2000 were included, which may further limit the number of trials included. Analysis to determine which trial characteristics may be associated with a surgical benefit was complicated because only a minority of the published trials had also been registered and had their protocol available. Therefore, it was not possible to evaluate whether protocols were changed for unregistered studies, which may have provided additional valuable insights. This study is also limited by the sole inclusion of RCTs that compared a surgical procedure with conservative management. This mainly has implications for oncologic RCTs, as often different radiation and medical regimens are compared instead of a surgical procedure.[14] Lastly, only trial characteristics were comparable, which may limit our findings.

Future studies on the conduction of neurosurgical RCTs could study subspecialty specific trial characteristics even more profoundly and their influence on trial quality and findings. Also, investigating trials comparing a novel neurosurgical procedure to current standard of practice in a similar fashion to this study may give insightful information on how to better interpret their results. Finally, evaluation of neurosurgical RCTs could be aided by the introduction of a trial registry that is specific to neurosurgery and takes into account the unique challenges of a neurosurgical RCT.

Implication for future neurosurgical RCTs

The findings of this study regarding trial registry, patient accrual, trial completion, publication, and alteration of outcome measures provide suggestions for improvement of future neurosurgical RCTs. Neurosurgical RCTs should seek to answer questions that live among the neurosurgical community and are answerable by an RCT. This requires true equipoise, the availability of patients, and sufficient funding among other things. Other trial designs, such as a prospective observational study,

should be considered if they are more suitable to answer unresolved controversies in neurosurgery.[12]

Most journals nowadays require an RCT to be registered, disclose their funding sources, and publish a protocol to increase transparency. The protocol should ideally be published in a neurosurgical journal to provide a neurosurgical readership the possibility to suggest alterations to the trial design to improve trial quality and make the potential findings as relevant as possible. Alterations to outcome measures should always be disclosed to readers together with a reason for this alteration. Investigators should be realistic about in- and exclusion criteria to meet the estimated of number of patients to be included and should optimize the inclusion process. Similar to our results another study found trial discontinuation to be common in neurosurgical trials in general, most commonly due to slow recruitment.[6] A pilot study to evaluate the patient inclusion process that also provides an estimate of the outcome measure may aid this.[11] One study also found that telephone reminders to non-responders, opt-out procedures, and financial incentives may help patient inclusion.[21]

Although conducting a neurosurgical RCT may be considered burdensome, they should in the end provide answers of the highest possible quality that are relevant to the neurosurgical community. A well designed and conducted trial could make sure that the effort and funding put in do not go to waste. Again, all of this may be aided by the introduction of a trial registry that is specific to neurosurgery.

Conclusion

RCTs comparing surgical to conservative treatment remain rare in neurosurgery. Most RCTs identify a benefit for surgical treatment. However, outcome measurements change frequently and anticipated accrual of patient often differs from the number of included patients. Trial registration is still only done in half of RCTs and funding sources are not always reported. Nonetheless, these are not factors that influence a surgical benefit over conservative treatment in neurosurgical RCTs. Lastly, trial termination is not uncommon, with the most common reason being slow recruitment. Successfulness of future neurosurgical RCTs could be improved by trial registration prior to patient inclusion and pilot studies.

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Table 4.6: Search syntax

PubMed search: 1-2017	*(((((((neurosurg*[tw] OR cranial surg*[tw] OR spine surg*[tw] OR spinal surg*[tw] OR Temporal Lobectom*[tw] OR cortectom*[tw] OR "Brain Tissue Transplantation"[tw] OR "Cerebral Decortication"[tw] OR Hemispherectom*[tw] OR Cerebrospinal Fluid Shunt*[tw] OR Ventriculoperitoneal Shunt*[tw] OR CSF Shunt*[tw] OR VP Shunt*[tw] OR "Trephining"[tw] OR "Parasympathectomy"[tw] OR "Sympathectomy"[tw] OR neurectom*[tw] OR spinal fusion[tw] OR disc fusion[tw] OR ACDF[tw] OR spinal decompression[tw] OR "Microvascular Decompression Surgery"[tw] OR "Nerve Transfer"[tw] OR "Split-Brain Procedure"[tw] OR "Neuronavigation"[tw] OR "Radiosurgery"[tw] OR (SRS[tw] NOT sexual[tw]) OR gamma knife[tw] OR cyber knife[tw] OR stereotactic radiotherapy[tw] OR deep brain stimulation[tw] OR (DBS[tw] NOT double bare metal stent[tw]) OR neurostimulation[tw] OR neurostimulator[tw] OR spinal cord stimulator*[tw] OR spinal cord stimulation[tw] OR "Diskectomy"[tw] OR disc replacement[tw] OR spinal decompression[tw] OR spinal cord decompression[tw] OR Ventriculostom*[tw] OR Craniotom*[tw] OR cranioplast*[tw] OR Decompressive Craniectom*[tw] OR Corpus callosotomy[tw] OR Vagotom*[tw] OR Ganglionectom*[tw] OR Axotom*[tw] OR Cordotom*[tw] OR Ganglionectom*[tw] OR Rhizotom*[tw] OR Vagotom*[tw] OR Foraminotom*[tw] OR Hypophysectom*[tw] OR Laminectom*[tw] OR laminotom*[tw] OR Laminoplast*[tw] OR Neuroendoscop*[tw] OR endonasal[tw] OR Pallidotom*[tw] OR thalamotom*[tw] OR cortical resection*[tw] OR Psychosurg*[tw] OR microvascular decompression surgery[tw] OR Radiosurg*[tw] OR Diskectom*[tw] OR Discectom*[tw] OR cranial vault resconstruction[tw] OR cranial vault remodeling[tw] OR craniosynostosis surgery[tw] OR auditory brainstem implant[tw] OR transphenoidal surger*[tw] OR cerebral stent[tw] OR cerebral stents[tw] OR cerebral stenting[tw] OR carotid stent[tw] OR carotid stents[tw] OR carotid stenting[tw] OR carotid endarterectom*[tw] OR (CEA[tw] NOT carcinoembryonic antigen[tw]) OR (angioplasty[tw] NOT (cardiac[tw] OR coronary[tw])) OR aneurysm coiling[tw] OR aneurysm clipping[tw] OR neurosurgical clipping[tw] OR endovascular coiling[tw] OR cerebral bypass[tw] OR cranial bypass[tw] OR middle cerebral artery bypass[tw] OR ((embolization[tw] OR resection[tw]) AND (AVM[tw] OR arteriovenous malformation[tw])) OR ((resection[tw] OR resect[tw] OR debulk*[tw]) AND (brain[tw] OR cranial[tw] OR intracranial[tw] OR cerebral[tw] OR spinal[tw] OR CNS[tw] OR glioma[tw] OR glioblastoma[tw] OR meningioma[tw] OR astrocytoma[tw] OR GBM[tw] OR neuroma[tw] OR pituitary tumor*[tw] OR lymphoma[tw] OR brain tumor[tw] OR brain metastasis[tw] OR brain metastases[tw])) OR "Neurosurgery"[Mesh] OR "Neurosurgical Procedures"[Mesh] OR "Spine/surgery"[mesh] OR "Spinal Diseases/surgery"[mesh] OR "Brain/surgery"[mesh] OR "Brain Diseases/surgery"[mesh] OR "Central Nervous System/surgery"[mesh] OR "Central Nervous System Diseases/surgery"[mesh] OR "Nervous System/surgery"[mesh] OR "Nervous System Diseases/surgery"[mesh])))) AND ((randomized controlled trial[tw] OR randomized controlled study[tw] OR randomly assigned[tw] OR randomized trial[tw] OR randomized, double-blind, placebo-controlled trial[tw] OR randomized, double blind, controlled trial[tw] OR randomized, double blind[tw] OR randomized trial[tw] OR prospective, double blind[tw] OR controlled clinical trial[tw] OR randomized clinical trial[tw] OR double blind[tw] OR prospective clinical trial[tw] OR randomised controlled trial[tw] OR randomised controlled study[tw] OR randomised trial[tw] OR randomised, double-blind, placebo-controlled trial[tw] OR randomised, double blind, controlled trial[tw] OR randomised, double blind[tw] OR randomised trial[tw] OR randomised clinical trial[tw] OR ("Randomized controlled trial"[publication type])))*
Embase search: 1-2017	(neurosurg* or cranial surg* or spine surg* or spinal surg* or Temporal Lobectom* or cortectom* or "Brain Tissue Transplantation" or "Cerebral Decortication" or Hemispherectom* or Cerebrospinal Fluid Shunt* or Ventriculoperitoneal Shunt* or CSF Shunt* or VP Shunt* or "Trephining" or "Parasympathectomy" or "Sympathectomy" or neurectom* or spinal fusion or disc fusion or ACDF or spinal decompression or "Microvascular Decompression Surgery." or "Nerve Transfer" or "Split-Brain Procedure" or "Neuronavigation" or "Radiosurgery" or (SRS not sexual) or gamma knife or cyber knife or stereotactic radiotherapy or deep brain stimulation or (DBS not double bare metal stent) or neurostimulation or neurostimulator or spinal cord stimulator* or spinal cord stimulation or "Diskectomy" or disc replacement or spinal decompression or spinal cord decompression or Ventriculostom* or Craniotom* or cranioplast* or Decompressive Craniectom* or Corpus callosotomy or Vagotom* or Ganglionectom* or Axotom* or Cordotom* or Ganglionectom* or Rhizotom* or Vagotom* or Foraminotom* or Hypophysectom* or Laminectom* or laminotom* or Laminoplast* or Neuroendoscop* or endonasal or Pallidotom* or thalamotom* or cortical resection* or Psychosurg* or microvascular decompression surgery or Radiosurg* or Diskectom* or Discectom* or cranial vault resconstruction or cranial vault remodeling or craniosynostosis surgery or auditory brainstem implant or transphenoidal surger* or cerebral stent or cerebral stents or cerebral stenting or carotid stent or carotid stents or carotid stenting or carotid endarterectom* or (CEA not carcinoembryonic antigen) or (angioplasty not (cardiac or coronary)) or aneurysm coiling or aneurysm clipping or neurosurgical clipping or endovascular coiling or cerebral bypass or cranial bypass or middle cerebral artery bypass or ((embolization or resection) and (AVM or arteriovenous malformation)) or ((resection or resect or debulk*) and (brain or cranial or intracranial or cerebral or spinal or CNS or glioma or glioblastoma or meningioma or astrocytoma or GBM or neuroma or pituitary tumor* or lymphoma or brain tumor or brain metastasis or brain metastases))).tw. or (neurosurgery/ or auditory brain stem implantation/ or neuroendoscopy/ or neuronavigation/ or exp skull surgery/ or exp spinal cord surgery/ or exp sympathectomy/ or exp vagotomy/ or exp ventriculostomy/ or exp spine/su or exp spine disease/su or exp brain/su or exp brain disease/su or exp central nervous system/su or exp central nervous system disease/su or neurologic disease/su) AND ((randomized controlled trial or randomized controlled study or randomized trial or randomized, double-blind, placebo-controlled trial or randomized, double blind, controlled trial or randomized, double blind or randomized trial or randomized clinical trial or double blind or randomly assigned or prospective, double blind or controlled clinical trial or prospective clinical trial or randomised controlled trial or randomised controlled study or randomised trial or randomised, double-blind, placebo-controlled trial or randomised, double blind, controlled trial or randomised, double blind or randomised trial or randomised clinical trial).tw)

II

Part 2: Ethics of neurosurgical innovation

5

Introduction of Novel Medical Devices in Surgery: Ethical Challenges of Current Oversight and Regulation

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***Summary**: Medical devices are an essential part of innovation in surgery and have tremendously improved patient outcomes. However, several medical devices have proven to be non-beneficial or even harmful to patients. Various forms of oversight and regulation are in place both in the United States (US) and in Europe to balance medical device safety and availability. Medical devices that are deemed safe receive FDA (Food and Drug Administration) approval or a CE-marking (Conformité Européenne), in the United States and Europe respectively. Although these approval processes vary, they share multiple ethical challenges with regard to risk-benefit ratio, informed consent, scientific validity, societal value, and justice towards patients. These include a possible lack of scientific validity as a result of exemption from formal evaluation. This also compromises informed consent as no data on efficacy and safety are available. Post-market surveillance is not mandatory which may put patients at increased risk. The differences in the approval processes also have ethical implications. High risk devices do not necessarily require a formal investigation in Europe. This*

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may unjustifiably put European patients at risks as most devices are approved in Europe first. Off-label use, which is allowed both in the US and EU, may increase risks for patients and compromises scientific validity as no form of oversight is in place. Potential change to current oversight mechanisms and legislation and the creation of awareness about the responsibilities of all involved parties to address current ethical challenges could aid device introduction. These changes should be aimed at minimizing risks for patients, adequate informed consent, methodologically sound evaluation of medical devices, and limiting disparities in current oversight and regulation.

Introduction

Innovation is at the heart of surgery, and innovative medical devices have contributed to advancements in surgery since its inception. Medical devices are instruments, implants, or mechanical agents intended to prevent, diagnose, or treat disease.[1] While device development has been critical in advancing surgery, not every novel device is an improvement over existing standards and unsafe medical devices can have deleterious consequences. Various devices, for example Poly Implant Prothèse (PIP) breast implants, vaginal meshes, metal-on-metal hip prosthesis, and interspinous devices (IDs) have been approved and applied to patients for years before safety studies uncovered major unforeseen side effects.[2–10]

Several forms of regulation and oversight have been created to ensure the safety of medical devices and the protection of patients in cases of investigational use. Regulation on a national level in United States (US) and an international level in the European Economic Area (EEA: the European Union (EU), Switzerland, Lichtenstein, Norway, and Iceland) ensure that medical devices gain approval before entering the market.

Current national and international regulations related to the innovation of medical devices in surgery pose several ethical challenges. In this perspective opinion piece, we review the current regulatory environment for medical device introduction both in the US and in the EEA and address the ethical challenges it creates.

Summary of current legislation

The Food and Drug Administration (FDA) and Conformité Européenne (CE) are government bodies that are responsible for medical device evaluation in the US and EEA, respectively. FDA approval and CE-marking are required for clinical application of medical devices in the US and EEA, respectively (**Table 5.1**).

Table 5.1: Overview of the approval process for CE-marking and FDA-approval

Approval process		*CE-Marking*	*FDA Approval*
Device classification	**Class I/II**	Approval by national competent authorities based on safety and efficacy studies	510(k)
	Class III	Approval by Notified Bodies based on safety and efficacy studies	PMA study
Exemptions from approval		Devices deemed by national competent authorities to have low risk	IDE, 510(k) exemption, humanitarian exception
Post-market evaluation		EUDAMED	MAUDE Database, MEDSUN device, "522 study"

Legend: Abbreviations: CE: Conformité Européenne; FDA: Food and Drug Administration; PMA: pre-market approval; MAUDE: Manufacturer and User Facility Device Experience; IDE: Investigational Device Exemption; EUDAMED: European Database on Medical Devices

FDA

The manufacturer of a medical device must register with the FDA to apply for approval and each device receives a classification.[11,12] According to the FDA: "Device classification depends on the intended use of the device and also upon indications for use." ... "In addition, classification is risk based, that is, the risk the device poses to the patient and/or the user is a major factor in the class it is assigned."[13]

However, the Product Code Classification Database provides classifications for specific devices, but does not create strict guidelines for the classification of novel devices.[14,15] Class I devices generally consist of relatively noninvasive products such as surgical gloves and instruments. Examples of class II devices are surgical meshes, absorbable sutures, and joint or vascular prostheses. Finally, class III devices are invasive devices that generate or modulate biological signals such as spinal stimulators and cochlear implants.[16]

The manufacturer must provide premarket notification (510(k)) of request for approval to the FDA for class I and II devices.[17] The 510(k) communication must contain evidence that compares the safety and efficacy of a novel device with a device regarded by the FDA to be "substantially equivalent" without further specification.[17] However, class I and II devices may be exempt from the 510(k) process by the FDA.[14,18] Conversely, the manufacturer must provide pre-market approval (PMA) studies to the FDA for class III medical devices.[11,19], Medical devices may be altered after approval through the PMA supplement pathway, which are rarely accompanied by a trial.[20-23]

The FDA may demand post-market surveillance known as "522 studies" after device approval to identify possible long-term complications and rare adverse events.[24-26] However, the FDA may only remove an approved device from the market because of concerns of safety, but not due to lack of efficacy.[23] The FDA's Manufacturer and User Facility Device Experience (MAUDE) is a registry that allows physicians, manufacturers, and patients to report complications from registered medical devices independently.[27] Also, 280 hospitals work together with the FDA and provide data to the online adverse event program "Medical Product Safety Network" (MedSun) to identify adverse events from medical devices.[28,29]

There are several circumstances in which FDA approval is not necessary to bring

a device to market. For instance, Investigational Device Exemption (IDE) allows the usage of a device for investigation in a clinical trial, in an emergent case, or in the compassionate use setting.[15,30-32] Furthermore, devices manufactured by surgeons for sole usage in their own practice do not require approval.[11] Finally, a medical device may receive a "humanitarian device exception" for treatment of rare disorders.[28]

CE-marking

Manufacturers must obtain CE-marking before a medical device is allowed onto market in the EEA and Turkey.[33-36] Furthermore, non-EEA based manufacturers require an authorized representative within the EEA to have their devices approved.[37] Three classes of medical devices based on associated risk related to invasiveness, reusability, potential use as an implant, use of a power source, and use near a critical anatomical location.[38,39]

The EU appoints national Competent Authorities, such as the Medicines and Healthcare Products Regulatory Agency (MHPRA) in the United Kingdom, to grant the CE-mark for low risk devices.[28] For higher risk devices, medical device companies are obligated to seek review for CE-marking by private, EU-authorized, third-party Notified Bodies, which review the efficacy and safety of the device.[28,40,41] CE-marking differs from FDA-approval as it does not require a trial to demonstrate safety and efficacy, even for class III devices.[28,33] Finally, the European Database on Medical Devices (EUDAMED) serves as a repository for (post-market surveillance) data of medical devices collected by national Competent Authorities.[42]

The CE-marking review process has been suggested to be inconsistent.[28,43] Notified Bodies operate independently of each other and only one Notified Body has to give approval for the device in question.[28,43] This can result in medical device companies approaching Notified Bodies known to have less stringent approval protocols. Indeed, a group of Dutch reporters received a reported likelihood of approval greater than 90% for a tangerine net that was to be used for prolapse repair.[44]

Off-label use

Both in the US and Europe, an approved medical device may be used for indications other than those it was initially approved for as long as the goal of its usage is to "practice medicine".[32,45] Studies have not compared off- and on-label use of medical devices, but the off-label usage of medical pharmaceuticals is independently associated with a higher rate of adverse events than on-label usage.[46] Risks may be even greater for medical devices due to different anatomical features and biophysical tissue properties in different pathologies. For instance, off-label use of rhBMP, which is also registered as a device, in anterior cervical spine surgery resulted in several adverse events such as heterotopic ossification, osteolysis, hematomas, and dysphagia.[47] This ultimately resulted in a formal FDA Public Health Notification Warning.[48,49]

Ethical considerations

The gaps in current legislation in the US and EEA risk undermining the ethical principles of risk-benefit ratio, informed consent, scientific validity, societal value,

and justice.

Risk-benefit ratio

Expected benefits should outweigh the estimated risks of introducing any innovation to be beneficial to patients. Medical devices used in the operating room are no exception. Benefits and risks have traditionally been defined in large comparative clinical trials and prospective follow-up studies, but preclinical studies and extrapolation from experience with other pathologies provide an estimate of benefit and risk with some inherent uncertainty. The knowledge of the risk-benefit ratio may be limited by a possible lack of standardization of clinical studies, varying quality of trials, and ineffective post-market surveillance.[19,26]

Several legislative loopholes allow the usage of medical devices with poorly defined risk-benefit ratios. Class I and II devices introduced in the US through the 510(k) exemption process do not have to undergo any clinical evaluation, preventing the rigorous definition of efficacy and risk.[14,18] For countries where devices receive a CE-marking, defining the risk-benefit ratio may be even more challenging as approval of all devices - including class III devices - do not necessarily require any clinical evidence of safety and efficacy.[28,33,38] Furthermore, the involvement of Notified Bodies in the approval process may introduce inconsistency and bias into the approval process, due to suggested variation in the approval process.[28,33,38] Also, off-label use with little or no previous experience may compromise patient outcomes as efficacy and safety are unknown. While surgeons may estimate benefit and risk through analysis of device usage for other indications, preclinical studies, and assessment of compatibility to a patient's anatomy, inter-provider variation may still cause the use of medical devices that are not beneficial for patients.

Informed consent

Patients must be adequately informed of the potential risks and benefits involved with a treatment to make autonomous decisions about their health care. Uncertain risk-benefit ratios obfuscate the informed consent process and do not respect patient's autonomy. For instance, low-quality clinical trials producing weak data limit patients' ability to evaluate treatment options adequately enough to provide informed consent.[19,26,28,33,38] The inaccessibility and incomprehensibility of many of the databases for registration of adverse events limit the ability of patients and surgeons to evaluate outcomes of a certain device for themselves.[29,42,50] Furthermore, there is currently no legislation in place that requires a patient to be informed that a device is being used off-label during surgery. The CE-marking of class III devices without proper investigation effectively eliminates the need to discuss the untested nature of the device during the informed consent procedure.[28]

Scientific validity

Scientific validity forms the basis of evidence-based practice and motivates the trust patients have in their surgeons. Clinical study of medical devices may range from pre-clinical study to randomized control trials (RCTs) comparing an innovative device to the standard of care. RCTs provide the highest quality clinical evidence from

a single trial, but are expensive and time-intensive to conduct. An RCT for every medical device is increasingly unfeasible and may stifle innovation altogether by increasing expense and decreasing speed of device introduction. Nevertheless, medical devices should have scientifically valid evidence justifying their introduction. The 510(k) exemption from FDA approval and the lack of requirement for trials in the CE-marking process do not guarantee evidence-based practice and may lead to patient harm.[14,18,28,33,38]

The Idea, Development, Exploration, Assessment, Long-term Follow-up (IDEAL) consortium of surgeons, statisticians, and epidemiologists has proposed the IDEAL-Device Framework (IDEAL-D) to introduce medical devices ethically.[51] It also suggests that after prospective investigational trials, a randomized comparison should be performed with the current standard of care as reference.[51] However, these requirements are rarely met, as seen with IDs that were compared with other devices instead of the gold standard lumbar decompression, as comparison with the gold standard is not required by the FDA.[2,23,52] In addition to problems during approval process, the quality of PMA studies varies greatly.[19] Off-label use of devices complicates the picture even more. The tempting logical leaps of using devices off-label for similar indications as those they have been approved for provide no evidence of the efficacy of the device.

Table 5.2: Responsibilities for all parties involved to improve regulation and oversight for the use of medical devices

Involved party	*Possible means of improvement*
Legislator and oversight bodies	- Create financial incentive for manufacturers to produce more safety and efficacy data. - Demand for clinical data showing efficacy and safety for devices that are currently approved through exemption. - Improve requirements for class III device evaluation in Europe. - Create alternative funding for device development (e.g. NIH). - Introduce oversight for off-label use of medical devices (e.g. a mandatory registry).
Medical device manufacturer	- Change business model to produce more safety and efficacy data. - Introduce medical devices simultaneously in the US and Europe. - Introduction of industry guidelines for ethical introduction of medical devices.
Surgeon	- Present conflicts of interest to the patient through a mandatory statement. - Participate in registries and Surgical Innovation Committees for off-label use of medical devices.
Patient	- Active participation in device development. - Allow sharing of their data to aid evaluation of medical devices.

Societal value

For an innovation to be ethical from a societal perspective, the net benefit derived from an innovation has to outweigh the costs for society. No rigorous peer-reviewed studies have estimated the benefit and costs of medical device introduction for society, although an industry report suggests $34 million for 510(k) approved devices and $94 million for PMA approved devices.[53] Moreover, current oversight mechanisms do not provide an infrastructure to assess societal value. FDA bylaws prohibit analysis of cost-effectiveness in the approval process altogether.[23] That 50% of side effects in drugs are discovered after FDA approval suggest that some adverse effects that reduce the societal value of devices would not be discovered until after approval.[23] Therefore, patients may continue to suffer increased health care costs associated with innovative technologies without any appreciable benefit.

Justice

Justice in innovation requires that the availability and associated risks are shared equally between all potential patients. The majority of medical devices is introduced in Europe first as a result of lower costs associated with the less strict regulation compared to the US.[54] This provides European patients with earlier access to medical devices compared to patients in the United States. In theory, this earlier access could lead to better outcomes for European patients due to improved standards of care. On the other hand, European patients may face increased risks due to the use of relatively untested medical devices compared to American patients.[54]

Recommendations for improvement of oversight and regulation

All involved parties - the device manufacturer, the regulation authority, the surgeon, and the patient - could improve current oversight environment for the introduction of medical devices and accept their respective responsibilities (**Table ??**). Shared goals could include patient safety, patient autonomy, surgeon support, and the facilitation of evidence-based practice in a climate of continuous innovation.

Legislator and oversight bodies

Legislators and oversight bodies could create legislation targeted towards removing the lapses in device introduction legislation. Incentives for manufacturers could be shifted from financial gain to patient safety and device efficacy by creating a financial incentive to conduct and publish pre-clinical and methodologically sound trials. For instance, FDA and CE-approval could require at least Level 2 evidence prior to approval and provide funding for manufacturers organizing Level 1 evidence studies, perhaps similar to the IDEAL-D framework.[51] This could also reduce the disparity in regulation between the US and Europe, ending the current practices of earlier introduction of devices in Europe, that may be associated with earlier access to potentially beneficial devices or increased harm for European patients.[54] These oversight bodies would also benefit from more organized structures to monitor the long-term outcomes and evaluation of rare adverse events to minimize risks faced by patients and

ensures scientific validity.

Alternatively, grants by government bodies could motivate financially-driven decisions by manufacturers away from the short-term aims encouraged by venture capital and towards long-term patient benefit.[51] Financial incentives may be limited by a cap on the funding by private parties, as this type of funding has been shown to influence outcomes in pharmaceutical trials.[55,56]

Legislative authorities could introduce oversight for off-label use of medical devices that treats medical devices as separate entities from pharmaceuticals. One solution could be to allow off label-use only if the procedure is registered with an oversight body and outcomes are reported. This offers the possibility to study outcomes in a systematic fashion, while at the same time respecting the judgment of the surgeon.

Stronger centralized systems that automatically store all data relevant to adverse outcomes, such as the "National Evaluation System for Health Technology," could greatly aid identification of unwanted and long-term outcomes as an adjunct to existing databases.[57,58] For example, a centralized registry recently showed that a cardiac medical device offered inferior outcomes after identification of adverse events.[59] An increase of post-market surveillance studies and implementation of registries could limit the duration a medical device is allowed onto the market.

Medical device manufacturer

The manufacturer has the primary responsibility to provide a product proven to be reliable and effective. Financial incentives do not align with this responsibility: most incentive structures encourage companies to acquire reimbursement for their medical devices to pay back investors and make profits.[60] The Medical Device Manufacturers Association could introduce guidelines and standards for the ethical introduction of devices together with an associated trademark as a form of self-regulation to achieve safer medical device introduction, as is seen in the food industry.[61] The medical device industry could also collaborate with oversight bodies, surgeons, and patients to work more transparently by generating and providing extensive safety and performance data, comparable to the aviation industry.[62]

Surgeon

Surgeons are the most direct participants in medical device innovation. They make conscious and creative decisions to innovate, and in the process, they weigh the balance between the benefits and risks of innovation. Financial and professional conflicts of interest (COIs) may influence the risk-benefit calculations surgeons make. Especially in Europe, more uniform legislation on an international level could limit financial gains from COI as regulation varies among EU countries.[51,63,64] A publicly accessible registry that includes all financial contributions could improve transparency towards patients.[51,63,64] In the US, the Sunshine Act mandates that all payments from the industry to physicians are registered in a transparent database. This database showed that, on average, neurosurgeons received $30,718.02 from companies in 2014.[65, 66] A cap on the amount a surgeon receives from the industry could limit COI. Another solution could be a requirement for surgeons to register the use and outcomes of a device for which potential COIs exist.

Surgeons may alter their informed consent process as well. A statement that includes the manufacturer, the amount of compensation, and alternative treatment options within the informed consent process could increase transparency towards the patient. Furthermore, an informed consent procedure that includes description of all available scientific evidence could ensure that the patient is truly informed.[28,33]

Registries created by surgeons to track outcomes from off-label use of devices could help to ensure patient safety and scientific validity on a hospital level. Within this registry, surgeons could be responsible for the evaluation of factors that government administrators and manufacturers cannot intuit, including surgical learning curve, long-term functional outcomes, and device-specific adverse events. Professional societies could create Surgical Innovation Committees (SIC) to provide a forum for surgeons to discuss and evaluate device-related innovation.[67] The SIC could be made responsible for appropriate oversight of innovation and a discussion panel on an institutional level as an adjunct to national oversight by the FDA.

Patients

Finally, patients have an essential role in the ethically sound introduction of medical devices. Patients who benefit from innovations carry some responsibility towards future patients, as the quality of their care is partially the result of risks taken by patients that preceded them.[68,69] Patients could participate in patient organizations that collaborate with manufacturers and legislators in setting priorities for medical devices. Patients could help define the limits of acceptable risk to safety as they will be the actual participants for the required trial. In addition, patients should be open to sharing their (electronic health record) data for safety monitoring.[68] At the same time, we recognize that patients can have an optimism-bias, resulting in over-optimistic expectations of devices, which could make them inclined to accept more risks. Therefore, we believe that patients should not be made responsible for the clinical evaluation of the devices for approval or for post-approval surveillance.

Conclusion

The oversight and regulation for the introduction of medical devices in surgery carries many unique ethical challenges. The need to strike a balance between patient safety and innovation and circumstances in which oversight or regulation may be lacking form the basis of many of these challenges, that relate to risk-benefit ratio, informed consent, scientific validity, societal value, and justice. We outline the current legislation oversight and its ethical challenges for the surgeon to consider. Potential changes of current oversight mechanisms and legislation and creating awareness about the responsibilities of all involved parties to address current challenges to the introduction of medical devices, could aid ethically sound introduction of medical devices in surgery. In the end, improving quality of patient care should be ultimate shared goal.

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6

Oversight and Ethical Regulation of Conflicts of Interest in Neurosurgery In the United States

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***Introduction**: Developmental incentives are fundamental to surgical progress, yet financial and professional incentives inherently create conflicts of interest (COI). Understanding how to manage COI held by neurosurgeons, industry, hospitals, and journal editors, without thwarting progress and innovation is critical. **Methods**: This article aims to present an overview of COI associated with innovation in neurosurgery, and review ways to manage these in an ethically sound manner. A review of the literature was performed to assess conflicts of interest that affect neurosurgical innovation, and review ways to manage COI of various parties while adhering to ethical standards. **Results**: COI are inherent to collaboration and innovation and are therefore an unavoidable component of neurosurgery. The lack of a clear distinction between clinical practice and innovation, ability to use devices off-label, and unstandardized disclosure requirements create inconsistencies in the way that conflicts of interest are handled. Additionally, lack of requirements to compare innovation to the standard of care and inherent bias that affects study design and interpretation can have profound effects on the medical literature. Conflicts of interest can have both direct*

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and downstream effects on neurosurgical practice, and it is possible to manage them while improving the quality of research and innovation. ***Conclusions****: Conflicts of interest are inherent to surgical innovation and can be handled in an ethically sound manner. Neurosurgeons, device companies, hospitals and medical journals can take steps to proactively confront bias and ensure patient autonomy and safety. These steps can preserve public trust and ultimately improve evidence-based neurosurgical practice.*

Introduction

A conflict of interest (COI) is a competing goal or motivation held by an individual or organization. They may stem from the potential for profit but may also arise from responsibility for multiple people or groups. Among the two, the latter is perhaps the more ubiquitous and difficult to discern. While COI is unavoidable and may go without impact, they also create to the possibility that decisions will adversely affect one group in the interest of another. In neurosurgery, COI is problematic if it adversely affects decision making and causes real or potential harm to patients or compromises the trust a patient places in neurosurgeons. Thus, it is important that COI is appropriately and ethically managed in order to respect patient autonomy, ensure beneficence of treatment, and avoid maleficence.

In neurosurgery, the medical device industry plays an important role in promoting innovation by helping to fund and facilitate research. The field's strong dependence on technology, however, creates many such COI for neurosurgeons involved with industry and in the development of new devices. In 2014 alone, payments to U.S. neurosurgeons tracked by the Open Payments Database - which was instated by the Affordable Care Act to publicize payments to physicians from medical device and pharmaceutical companies - surpassed $100,000,000. Notably, 1% of neurosurgeons received 54% of the payments tracked by this database.[4] While the contributions of neurosurgeons provide critical insight for new technology and financial compensation may reward risk and help to stimulate neurosurgeons to innovate, problems may arise if the business interests of a particular company impact clinical decision making and patient care through neurosurgeons with COI. Even among the many neurosurgeons without a financial stake in the medical device industry, there are numerous other nonfinancial COI and incentives for innovation. The desire to advance a career in academia, improve financial outcomes, publish papers, and gain status all create biases that can affect clinical decision making and patient care. While these are important to the success and advancement of neurosurgery, it is critical that care is taken to address the COI that naturally develop during these innovative pursuits so that patient safety is always protected. Furthermore, it is critical to remember that these supposed relationships can benefit patients by giving them access to cutting edge treatments that bring hope, and providing physicians with new knowledge and understanding of the field. Many forces are at play in the lives of all surgeon-innovators, and the neurosurgical literature could benefit from a robust discussion of the ethical principles and difficulties associated with COI in innovation. Here, we evaluate various COI that affect the neurosurgeon, industry, healthcare systems, and neurosurgical literature from an ethical perspective.

Neurosurgeon

Neurosurgical outcomes are increasingly being measured by various factors including quality of life, invasiveness of a procedure, and recovery time, all of which contribute to the complexity of surgical decision-making.[2] This is further complicated in the setting of novel procedures where complication rates and outcomes may be unknown or come with considerable uncertainty.[33] Without evidence that overwhelmingly supports a particular clinical decision, it is unavoidable that decisions are, at times, made based on personal experience. Personal experience and knowledge is undeniably an important source of guidance in surgical decision making, yet this flexibility leaves room for COI to inevitably influence decisions regarding procedures and use of devices in particular. Patients nonetheless expect that neurosurgeons make ethically sound decisions and avoid the influence of COI.[36] Introduction of medical devices to improve outcomes in neurosurgery is not inherently unethical in itself, is essential to move neurosurgery forward as a field, and can be carried out in an ethical fashion.

Furthermore, it is often hard to distinguish clinical care from innovation and research in neurosurgery. Whereas institutional oversight is required in the setting of formalized clinical research and novel devices, there is little oversight in place for innovative procedures.[35] Many of these procedures typically involve a gradual deviation from typical practice with the goal of improving the care for the patient.[8] An example of this is endoscopic endonasal meningioma surgery. Some argue that because of the nature of surgery overall and neurosurgery specifically, performing a new procedure or using a novel device should not be subjected to oversight at all.[31] This leaves many decisions related to innovation in neurosurgery up to the discretion of the individual surgeon, opening the possibility that financial or nonfinancial COI can inadvertently sway the surgeon.

All physicians may be influenced by both direct and indirect incentives. Direct incentives include financial ties to industry, which can create monetary incentives to use particular devices for financial gain and incentives to publish on novel techniques to improve academic standing. Indirectly, relationships with beneficiaries, including colleagues and industry representatives, may provide undue influence on decisions regarding medical devices. Similarly, using novel approaches can also give the physician an opportunity to improve their financial compensation, expand their referral volume, increase operative productivity, and improve their reputation.

While the neurosurgeon is the best equipped and should be able to discuss the risks and benefits of a procedure, the process of obtaining informed consent and how a procedure is portrayed to the patient may be affected by a physician's biases, experience, and financial COI, all of which affect physician estimates of risk.[11] These concerns highlight the importance of being aware of financial and nonfinancial COI, and how they may influence consent and subsequently a patient's autonomy. Surgeons are more likely to inform patients of complications they have personally encountered, for example.[7] In surgical practice there is a robust culture of innovation outside the formalized structure of randomized controlled trials (RCTs) and a lack of a clear distinction between clinical decision-making and innovative practice. Thus, there is variation in the evaluation of whether something is considered innovative

practice or a novel application, and there is a possibility that COI could affect how a procedure is portrayed, often unbeknownst to the physician. Furthermore, there is no formal oversight of patient consent, and no requirement that COI be disclosed in a clinical setting.

In addition, even if a patient is made aware of the innovative nature of a procedure and physician COI, they can sometimes fall victim to the assumption that novel is necessarily better.[2] Therapeutic misconception is the idea that patients do not fully understand the difference between treatment and research, and may believe that their providers will always act in their best interests. This has been shown in trials in which 100% of patients expect positive results.[3, 18] This is in addition to biases of the patient, which can affect their ability to adequately consent. Often, the severity of a diagnosis can influence a patient's acceptance of their prognosis and risks associated with procedures once they are informed. This is true even in the case in which a patient is determined to be fully competent of giving informed consent.[49] This is further complicated by the nature of surgery, in which there is not always a distinct boundary between innovation and clinical practice. Furthermore, there is often very limited available information about the long-term risks of innovative procedures, which can render an informed discussion about risks and benefits of a procedure impossible by no fault of the physician. Therefore, it may be hard for patients to assess the severity of the COI, even if a neurosurgeon discloses all relevant information. Neurosurgeons have the ethical responsibility to ensure that a decision is made which the patient understands, agrees with, and is in the best interest of the patient, even if COIs are present.

Industry

The close ties between the field of neurosurgery and the medical device industry is critical to the advancement of clinical care. Payments made to physician-innovators for their expertise and time can help drive innovation forward, incentivize progress, and compensate for personal risk. This process also allows physicians to become well versed in the utilization of new devices and learn about the devices directly from the company.[29, 48] The goals of the medical device industry, however, are naturally focused on a return on investment, which may be hard to align with the goals of academic research. This opens the possibility that industry involvements may lead to poor trial design, inadequate enrollment decisions, biased data interpretation, or inadequate reporting of adverse events if not handled appropriately.[37] While financial COI is an inevitable component of progress in neurosurgery, it is important that these COI are managed in a way that is ethically sound and clinically practical.

Physicians are listed as an inventor in about 20% of medical device patents.[16] The constant input and feedback provided by physicians to device manufacturers is crucial in the development of medical devices, and care can be taken to ensure that it does not interfere with clinical decisions. Richard Thaler, who received of the Nobel Prize for his work in behavioral economics, explained the irrational nature of human thought and decisions. For example, the "endowment effect" is the idea that we disproportionally ascribe more value to something we already own that to an equivalent product that we would like to own.[27] Similarly, the "IKEA effect" is the idea that

we value products that we created over equivalent products made by others.[38] Thus, the surgeon is at risk for unknowingly overvaluing devices or procedures that he/she helped create/optimize due to bias. In this realm, it is important to note that the bias and any related actions are unintentional.

In addition to their role as a device innovator, surgeons are often integrally involved in the early implementation of novel medical devices, consult with industry, sit on advisory boards, and receive industry funding for research - all of which drive innovation but can create a source of COI.[19, 26] In the state of Massachusetts alone, payments made to orthopedic surgeons totaled to almost 8 million dollars from July 2009 - December 2011. In this study, at least 40% of surgeons reported as receiving payments in four of the included surgical specialties (Neurosurgery, Orthopedic Surgery, Ophthalmology, Plastic Surgery).[28] These payments are thought to affect a surgeon's ability to be impartial if evaluating treatment options for patient, and may provide undue pressure on a physician to opt for a particular device due to previously favorable personal interactions or financial incentives.[19]

In a clinical setting, unintentional favorability towards a particular company is strong in surgical fields and it is common for industry representatives to be present in the operating room, where they often develop close personal relationships with surgeons.[26] Vendors are frequently present during operations to provide on-the-spot input in the use of novel hardware and surgical instruments. Input from surgeons can provide device manufacturers the valuable clinical insight needed to determine what areas to improve on, identify what limitations exist in the current technology, and ensure that the products are patient-focused.[2, 10, 26, 41] There is also the risk that the relationship with industry could compromise patient care.[20, 45] Unintentionally and indirectly, favorability between physicians and industry may also result from gifts and other material benefits that are perceived as normal by the physician and representative, but may be regarded as bribery from the perspective of the patient.[13, 30] Thus, the lack of agreement over what is deemed appropriate among surgeons and the public further complicates this issue of how COI can affect care.

Hospital

Hospitals may also have COI that affect the ability to provide care in the best interest of their patients. Hospitals often invest in new technologies in order to improve the status of the institution, patient volume, and quality of care.[33] When choosing a new technology from a vendor, hospital systems are often faced with choices that include certain "benefits," such as discounts or additional provided equipment. These further increase the costs incurred by the system, which in turn are passed onto payers. An investment in a novel surgical or imaging technology gives healthcare institutions an inherent incentive to use the technology to offset the costs associated with implementation and provide the service directly to patients who may benefit. While the potential for revenue gained from adopting new technology is important to improve the field over time, many patients may have no need for a technology that may only provide them with marginal benefit at an increased cost but may view the innovation as superior regardless.

Similar to our knowledge of new procedures, the data available on new technolo-

gies is often incomplete, biased, or conflicting. For example, the use of intraoperative MRI significantly increases the expense of treatment for the patient because the high cost of implementation and prolonged operative time, yet many feel that the improved imaging brings substantial benefit. The data on whether this improves outcomes remains a subject of debate.[52] Regardless, the belief that new, expensive, innovative approaches will improve outcomes affects the patient and may influence their decisions. This may be especially true in patients with particularly devastating diseases as is seen in neurosurgery. Therefore, hospitals have an added incentive to implement these innovative, expensive technologies in order to help patients before conclusive supporting evidence is available.

Disclosure

The medical device industry provides an unavoidable and invaluable source of funding for clinical research that drives essential progress. Industry involvement can also have a permeating effect on the influence of research. Research funded by industry has been independently shown to report positive outcomes at a higher rate in the medical literature than research without industry funding.[5] With this in mind, a clear disclosure policy is critical to enable the reader to interpret the results. The New England Journal of Medicine was the first journal to formally require disclosure of author conflicts of interest in 1984, citing both the inevitability of industry-academia relationships and the importance of maintaining public trust.[42] Since that time, disclosure of author COI has become commonplace, and now 70% and 90% of biomedical journals requiring reporting of nonfinancial and financial COI of authors, respectively.[9] Although the increased reporting over the past few decades is commendable, it is common for journals not to define COI to the authors or to publish disclosures selectively, thus creating inconsistencies in reporting and making the lack of a disclosure difficult to understand.[14, 40] Responsible reporting of COI is important to allow the readership to understand the research presented.

Additionally, even if there is a "gold standard" device available, innovative devices do not have to be compared to it in order to be published or to be approved by the FDA, which has caused harm to patients undergoing spine surgery in the past. For example, in the case of the interspinous process devices, single arm retrospective studies were the primary research evaluating the devices for 30 years until prospective studies and two randomized controlled trials eventually found the treatment to be inferior.[34] Additionally, another study that 24% of devices approved for use for neurologic, orthopedic, and cardiovascular indications between 2005-2010 had to be recalled for safety concerns as of 2016.[23] Thus, it is important to balance the importance of pushing innovation and new discoveries forward with the necessity of upholding the rigor of the literature and evaluating devices accurately.

Disclosure of COI is far less common for journal editors than it is for authors, with less than 40% of biomedical journals require reporting of COI for the journal editors.[9] Additionally, disclosures are not commonly available on journal websites for the reader to evaluate. Given the assumption of objectivity in the peer-review process, a process in which reviewers and editors have been described as the "gatekeepers" of science,[39] disclosure of COI among editors can help to maintain the legit-

imacy of peer-reviewed publications. Some ethical incidents -for instance, the trials of recombinant human bone morphogenic protein (rhBMP) spinal implant, - have resulted in stricter oversight in the editorial process. In this case, important COI were inadequately disclosed and a biased trial design was thought to have influenced the results. There were serious and life threatening events that were found later.[15] Despite examples like these, regulation of the COI held by reviewers and editors has not yet become the standard in medical journals.[25] This systematic flaw in how we evaluate research for publication[22] can be remedied to prevent future incidents. This will enable neurosurgeons to better evaluate the literature to make informed clinical decisions in the best interest of the patients, improve the quality of the research published, and help to maintain trust between journals and the medical community.

Some journals have started to acknowledge the potential role of editorial board COIs on the literature. An example is JAMA Ophthalmology, which has developed a transparent policy in which reviewers or editors with specific COI can recuse themselves from reviewing a particular manuscript. Specifically, this policy applies if the reviewer or editor has a financial interest in a company involved in the submission, and when the editor or reviewer is employed at the same institution as an author of the manuscript.[21] Consistent, transparent reporting of relevant COI is critical to allow the readers to understand the context of the research, and can be effectively accomplished without disrupting the editorial or review process.

For neurosurgical journals, disclosure policies regarding COI for reviewers and editors are not particularly strict. For example, The Journal of Neurosurgery and related journals, require that the editorial board members annually submit a disclosure statement. The editor-in-chief and editorial board members can then recuse themselves from reviewing any manuscript in which they have a COI that would affect their ability to be impartial.[1] One study of the spine journals found that at least 29% of editors of five leading spine journals had a financial conflict of interest reported at meetings, of whom 22% did not disclose. Of these editors with a financial COI, 76% of their financial relationships were with major medical device companies and 42% had more than $10,000 disclosed in a source other than the journal.[25]

At surgical meetings, device manufacturers frequently sponsor discussions about products and surgical dilemmas. These events may also unduly influence the clinical judgment of attendees, particularly if financial or other material incentives are present or if COI is not adequately disclosed to allow the reader to assess the content in context. It is particularly concerning that among physicians attending industry sponsored lectures, the sponsorship was shown to have a favorable effect on drug prescribing patterns.[47] This highlights the importance of mandating the reporting of COI and the role that the funder played in the work to allow the reader to judge the quality and independence of studies and form their own conclusions about the presented results, if desired.

Oversight and Ethical Regulation of Conflicts of Interest

The field of neurosurgery has traditionally given neurosurgeons the right to autonomy and self-governance, as well as the responsibility to act in the best interest of the patient despite COI. A physician has a moral obligation to act in the best interest

of the patient, and physicians take an oath to uphold ethical standards. Nevertheless, in the modern world, COI are particularly powerful forces that could be examined closely, and the effects of COI are not always overt to the beholder.

In particular, thought could be given to the oversight and management of neurosurgical COI by governments, institutions, the surgical community, institutions, and medical journals. Any attempt at ethical oversight and regulation should aim to encourage respect for patient autonomy in treatment decisions and preserve the rigor of the scientific literature without hindering innovation and progress. Declaration of COI is a simple yet tool that can help improve patient autonomy by giving patients, readers, and others knowledge of COI and thereby allowing them to inquire further, while also strengthening the integrity of physicians by reminding them of their duties to the patient. Solutions to COI can be achieved by bringing all parties together to develop a framework that ensures patient safety, optimal outcomes, and continuous innovation through a balanced, workable, and ethical collaboration.

Government Oversight

In the U.S., legal disclosure of financial COI was not required of physicians until more recently. In 2010, the Sunshine Act was enacted as part of the Patient Protection and Affordable Care Act (PPACA) to require physicians to report certain types of consulting fees, compensation, or company ownership in companies with at least one product covered by Medicare. This is intended to prevent inappropriate power of industry over clinical judgment.[46] Patients admittedly do not fully understand the extent of relationships between the device industry and physicians,[19] and find some of the gifts that physicians commonly accept to be immoral, yet patients are not necessarily in favor of stronger government regulations.[13] While the websites for the Sunshine Act are publicly searchable, the data available are difficult to interpret and not always accurate,[1] and there is a lack of public knowledge about the sites and what the COIs mean for patient care. Arguably, if the patient is unaware of the reporting, legal disclosure does little to reduce the influence of COI in practice.[26] While public disclosure is an important step in legal reporting of COI, it does not have a major effect on day-to-day patient care and may need to be supplemented with policies to address when additional consent, disclosure, and patient education is specifically needed. Examples could include standardized disclosure for innovative circumstances, such as off-label use of devices, and requiring disclosure of financial COI to patients when it involves an implant or device relevant to their care. It is important to note that disclosure to patients is not inherently negative, as it also shows a level of familiarity with the product and expertise in the field, as has been shown from the patient's perspective.[44] Furthermore, providing patients with the available information could preserve patient autonomy by ensuring that they have at least a minimal level of knowledge regarding their neurosurgeon's ties with industry and whether the device they are having implanted is innovative in nature.

Institutional Regulation

Though disclosure policies exist at the majority of medical schools, only 1% of institutions surveyed required disclosure to research subjects and many policies used vague

language and inadequately defined terminology, thus leaving the responsibility of reporting up to the physician.[32] If surgeons are to remain autonomous, patients expect accountability and sound decisions, regardless of COIs.[17] Awareness of the effects of bias and disclosure does little to change behavior,[12] further supporting the need for stricter institutional enforcement of COI policy.

Furthermore, patients have admitted to not necessarily being able to interpret disclosures,[13] and thus it is critical to give patients the opportunity to inquire about COI and assess the associated risks and benefits[50, 51] rather than bypassing patient involvement in their own care. While disclosure of COI is typically not required, disclosure of financial gain from a device to be implanted or any role in the device's development seems reasonable, and could improve public trust in the profession. From patients' perspectives, surgeon-initiated disclosure have been well received, and have instilled trust and given the patient the sense that the surgeon is in fact an expert.[44] Additionally, some have suggested that a physician who is unwilling to discuss COI is a reason to turn elsewhere for treatment.[43] Disclosure is certainly not the norm in clinical practice, and a more robust means of reporting may help maintain surgical patient autonomy. It is important, of course, to always discuss and evaluate policy within an institution to ensure that the policy meets ethical standards for practice.

Institutional policies need clear definitions within their policies and requirements for complete transparency with all financial relationships to ensure adequate disclosure. One example of a solution on the institutional level is to prohibit inventors from being involved in clinical testing for companies for which they invented devices for or have a consulting relationship with.[48] This has been criticized as being too strict as to stifle innovation[6] and has since been relaxed, yet it also prevents unintentional bias and increases the likelihood of obtaining results that are both reproducible and generalizable. Other suggestions to reach the same results have included giving some investigators read-only access to research data, and involving researchers without a financial COI to be involved in the study design and data interpretation.[24] It is also recommended that multiple neurosurgeons, especially those without ties to the innovation, are involved in implanting a device or performing a technique for the first time. This could ensure generalizability of results, increase adherence to evidence-based practice, and improve the overall quality of research and innovation.

Literature

Additional efforts by journals could help maintain the integrity of the scientific literature. Specifically, mandated disclosure and clear definitions on what constitutes a COI could be developed by the journals. By including author COI within each article, even if the authors have no disclosures, the reader is able to interpret the results in context. With regard to editor COI, this could also be publicly available on journal websites for readers to easily find and assess for themselves. Additionally, more effort can be made to improve the methodology of studies submitted. Requiring demonstration of methods to reduce the effects of bias to publish in neurosurgical journals could help improve trust with readership and prevent misrepresentation of research, especially for studies receiving industry funding.[15] Trials published in the neurosurgical literature could aim to compare, as much as possible, innovative devices and

procedures to the standard of care, and would ideally be designed by committed investigators without a financial stake in the results. Because of the small numbers of patients seen in neurosurgical practice and the autonomous nature of surgery, anonymous reporting of adverse events and long-term outcomes could add value so data can be pooled from multiple institutions and re-evaluated to further assess quality of innovation. This can be accomplished effectively by using national registries to track long-term outcomes, or maintaining institutional datasets over time. Maintaining the quality of the published literature and allowing the reviewer and reader to understand the study in the context of COI will give him or her the opportunity to judge the quality of the methods and generalizability of results. This will allow for improved safety in the application of the literature to clinical practice, and will improve the integrity of the literature.

Nevertheless, the effects of COI spread into less regulated and rigorous forms of written communication, including social media and the "grey literature". It is important to recognize that disclosure is not the standard in these forms of communication, Given the presence of these and their influence on both providers and patients, it is increasingly important to critically evaluate the information we receive, and inform patients with what they need to make decisions. This will improve the quality of care provided.

Conclusion

Conflicts of interest that affect clinical practice are inevitable in the present day. Neurosurgeon involvement in innovation is valuable for the advancement of the field. Awareness of COI and reporting does not necessarily change practice, so all stages of neurosurgical innovation could benefit from regulatory oversight to maintain ethical, patient-centered, evidence-based practice. Regardless of the level of policy or institution, constant discussion and evaluation of policy is important to ensure that practice remains ethically sound and prevent both financial and non-financial COI from adversely affecting patients. Taking steps proactively and ensuring that practice is done ethically can prevent controversies, maintain public trust, and ultimately improve the quality of neurosurgical research and innovation.

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7

Oversight in Surgical Innovation: A Response to Ethical Challenges

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***Introduction**: Surgical innovation has advanced outcomes in the field but carries inherent risk for surgeons and patients alike. Oversight mechanisms exist to support surgeon-innovators through difficulties associated with the innovation process. **Methods**: A literature review of ethical risks and oversight mechanisms was conducted. **Results**: Oversight mechanisms range from the historical concept of surgical exceptionalism to departmental, hospital, and centralized committees. These fragmentary and non-standardized oversight mechanisms leave surgeon-innovators and patients open to significant risk of breaching the ethical principles at the core of surgical practice. A systematized approach that mitigates these risks while maintaining the independence and dignity of the surgical profession is necessary. We propose an oversight framework that incorporates multiple structures tailored towards the ethical risk introduced by different forms of innovation. **Conclusions**: We summarize ethical risks and current regulatory structures, and we then use these findings to outline an oversight framework that may be applied to surgical practice.*

Introduction

The drive to innovate has resulted in significant improvements in surgical outcomes. Surgical innovation occurs in contexts ranging from individual cases with

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unique anatomical features to clinical trials, though there is no single, universal definition of surgical innovation. Consequently, surgical innovation can present a challenge by blurring the distinction between experimentation and clinical care. The Belmont Report defines innovative care as "practice that departs significantly from the standard or accepted" and posits that innovative care that deviates significantly from the norm should be formally researched with oversight in place.[1, 2]

The distinction of research and clinical motivation rests on their respective motivation: the primary goals of operative innovation in the clinical and research contexts, respectively, are beneficence to optimize patient care and experimental evaluation to generate generalizable knowledge. Experimental techniques intended to test the new technique with equipoise fall into the research category that receives oversight from Institutional Review Boards (IRBs). However, surgical innovation currently falls outside the realm of oversight since it is often intended to benefit an individual patient rather than systematically investigate a procedure. This type of innovation is exemplified by the hypothetical case of an ostomy between the common bile duct (CBD) and hepatopancreatic ampulla to prevent malabsorption for an infant born with type I biliary atresia with preserved proximal CBD.

The current lack of consensus on oversight mechanisms for procedural innovation leaves surgeons and patients vulnerable to significant risk which carry ethical implications for surgical practice.[3] No standardized approach exists to aid surgeons in evaluating the ethical challenges inherent in surgical innovation. This perspective focuses on the ethical challenges associated with surgical innovation and proposes an oversight framework to regulate it.

Table 7.1: Summary of Oversight Mechanisms

Oversight level	*Benefits*	*Drawbacks*
Surgical Exceptionalism	Surgeon knows patient best, professional dignity and autonomy maintained, expedient	Susceptible to individual biases and COIs, interoperator inconsistencies, no support for surgeons
Departmental	Surgeon knows patient best,, Multiple opinions incorporated, professional dignity and autonomy maintained, expedient	Susceptible to institutional biases and COIs, interhospital inconsistencies
Institutional	Multidisciplinary opinions incorporated, surgeon protected by legal and ethical expertise	Interhospital variability, professional independence may be compromised, moderately costly and time-intensive
Regional/National	Multidisciplinary opinions incorporated, sets precedents for entire field, no interoperator and interhospital variability	Subject to biases of the field, highly costly and time intensive, assessment by evaluators removed from patient
IRB	Multidisciplinary opinions incorporated, protocolized, standardized, transparent	Moderately costly and time intensive, assessment by evaluators removed from patient

Mechanisms for Oversight

Various methods to oversee operative innovation have been suggested, ranging from regulation by the operator alone (surgical exceptionalism) to formal evaluation and oversight for every innovation (**Table 7.1**).[2, 4] This range of opinions high-

lights the delicate ethical balance between assuring patient safety without stifling innovation.

Surgical Exceptionalism

Surgical exceptionalism is characterized by regulation of an innovation by the surgeon performing the procedure without formal oversight.[4] Some argue that features unique to the surgical profession - difficulty in measuring surgical technique, reproducing surgical procedures, and achieving consistency between operators - make oversight impossible. This approach maintains surgeons' independence, expedites innovation, and mitigates biases held by the surgical profession. Emergent cases and unexpected complications may necessitate innovation at a moment's notice, which is amenable for this approach. However, it amplifies the effects of a surgeon's own biases and conflicts of interest. This approach presumes rigorous ethical training, which is presently not met by current medical training or continuing medical education.[5]

Departmental and Institutional Oversight

Discussion with colleagues through informal conversation, approval by the chair, or case conferences provide departmental forms of regulation. The results of a policy including department chair approval and outcomes tracking for innovations have been reported at The Hospital for Sick Children with many surgeon-innovators commending its ease of use and noting that it encouraged them to innovate.[6] The benefit of departmental regulation includes rapid introduction of the innovation and preserved independence for the surgeon, who knows the patient's anatomy the best. This approach does not mitigate the surgeon's or institution's potential conflicts of interest, and the degree to which pertinent ethical issues are considered likely vary widely by surgeon and institution.

Institutional ethics committees (IECs) that meet regularly to discuss anticipated alteration of procedures provide increasingly formalized oversight. The standards, scope, and role of such committees differ widely by institution, and no hospitals currently integrate them into routine surgical practice. IECs may contain bioethicists and lawyers amongst other professionals to provide multidisciplinary consultation. They may serve in a consultant role such that the decision-making rests with the surgeon or in a regulatory role where its decision may supersede that of the surgeon. These committees have played larger historic roles in medical, rather than surgical, decision-making in part because surgeons believe that ethical consultants may not truly understand surgical problems.[7] Advantages of this approach are its inclusion of multidisciplinary opinions, the possibility to teach peers, and the systematized consideration of pertinent ethical considerations. Challenges to the IEC method includes differing standards between institutions, a slowed pace of innovation, and decision-making by professionals not directly involved in a patient's care.

Centralized Oversight

Oversight boards organized by regional or national professional societies would provide the most centralized and standardized oversight for innovation. However, no

surgical societies currently provide oversight committees for individuals who seek ethical support for an attempt at innovation. These committees would have the expertise to create committees to offer methodologically consistent and rigorous oversight for individual attempts at innovation. Such committees are currently hypothetical within the surgical community, but similar ones exist in medicine: the American Medical Association's Council on Ethical and Judicial Affairs and other specialty societies have judicial and advisory responsibilities over certain ethics-related decisions. This centralized process would minimize individual bias and adds multidisciplinary knowledge, but may be slow and costly. Furthermore, it may be subjected to bias formed by the culture of current practice. Finally, these committees would consist of members not directly involved with the patient and may not appreciate the uniqueness of the case or patient's anatomy.

Formal Research Protocols

Some operative innovations have been tested in a research setting through clinical trials. Research is conducted with clinical equipoise and appropriate blinding and randomization to generate knowledge for a specific group of patients and requires formal research protocols with IRB oversight. Traditionally, the strongest evidence is provided by randomized control trials, but given low accrual, interpatient anatomic variation, and difference in skills between surgeons, most procedures are evaluated by single-operator/single-institution case series. IECs and IRBs are both institutional entities, but differ in organization and role. IECs are multidisciplinary teams that can aid physicians and surgeons through ethical questions similar to how a subspecialty consulting team may provide daily input on a patient at the request of the primary care team. IRBs are standardized committees that oversee formal investigative research and monitor ethics as well as efficacy. They are nationally mandated and standardized bodies designed to evaluate and oversee all formal research protocols. Their benefits include the multidisciplinary knowledge, minimization of conflict of interest, and nationally standardized implementation of research protocols to ensure safety and autonomy for patients and maintain integrity and accountability in research.[8] Their downsides include relatively slower review, which limits feasibility for emergent cases; significant costs; and oversight by evaluators who are removed from the clinical management of the patient.[9]

Ethical Justification for Formal Oversight

The goal of oversight should be to provide practical structures that address ethical considerations delineated in earlier work: scientific validity, risk-benefit ratio, informed consent, protection of vulnerable populations, justice, and conflicts of interest.[3, 10] Scientific validity and risk-benefit ratio are "scientific factors" since both involve scientific and statistical estimations based on available objective research and expertise. Informed consent, protection of vulnerable populations, justice, and conflict of interest are considered "human factors" because they deal the less tangible subjective areas of interpersonal communication, social justice, and personal biases. The practical justification for this division is that scientific factors are best judged

by colleagues in the same field who are familiar and experienced with the relevant pathology and anatomy. Human factors, on the other hand, benefit from a more multidisciplinary approach that recognizes the legal and cultural contexts behind these ethical principles. These have been expounded in previous literature and are briefly summarized to motivate discussion for novel oversight mechanisms.[11]

Scientific Factors

The scientific validity of an innovation depends on evidence of its safety and efficacy. Randomized control trials and meta-analyses are the gold standard in evaluating the clinical efficacy of an innovation, but the challenges of blinding and randomizing in surgery make conducting these trials difficult. Indeed, the prevalence and quality of RCTs in surgery remains low.[12, 13]

Defining the risk-benefit ratio prior to any attempt at innovation is crucial. Surgical procedures may trade function to restore another function, decrease pain, or extend survival. Thus, precisely defining each patient's values is crucial to align the goals of operative innovation with a patient's own goals. Innovation carries a "learning curve" to reach maximal efficacy and immediate risks may not be apparent and may depend on each patient's anatomy.[14] Long-term risks of operative innovations may be difficult takes years of follow-up to quantify. Novel procedures bring financial burden, and ill-planned innovations risk harming the public reputation of the surgical profession.[15]

Human factors

Informed consent standards mandate that it is the responsibility of the surgeon to ensure that the patient understands the pertinent information necessary to make a choice about whether to proceed with a procedure. The information crucial to informed consent should include the innovative nature of the procedure, evidence to support it, and the surgeon's experience with it.[11] Examples of vulnerable patients include unconscious patients, patients in emergency conditions, patients with refractory disease, and children, prisoners, ethnic minorities, socially marginalized persons, etc..[11] Care should be taken to avoid tendencies, including implicit rationing that excludes certain patients, which may exploit vulnerable patients.[16, 17] Justice within innovation mandates that its risks and benefits are shared equally by society, including all geographic and socioeconomic groups. However, innovation may gravitate towards practices with a culture that encourages innovation and areas with minimal regulation of innovation. Innovative surgeons may attract attention from "in-the-know" patients connected to the medical community. Furthermore, early innovations not covered by insurers may limit representation by patients of lower socioeconomic status.

Conflicts of interest can be divided into financial and non-financial conflicts. Financial conflicts of interest occur when certain devices or surgical tools are preferred due to industry financial incentives. These conflicts are nationally monitored to an extent - the Sunshine Act in the United States requires that all payments from the industry to physicians are registered and open to the public, though does not mandate that physicians report these to their patients.[18] The achievement of innovation

may also come with academic prestige or may be required to continue thriving in competitive fields of research for physicians or institutions.

Table 7.2: Case Examples of Surgical Innovations Appropriate for Different Oversight Levels

Oversight Level	*Example for Non-Emergent Cases*	*Ethical Risks*
Surgical Exceptionalism	Modification of port location to facilitate laparoscopic cholecystectomy in an adult patient with situs inversus totalis who is able to provide informed consent.	No significant risks
Departmental	Approach and location of renal transplantation in renal failure patient with extensive retroperitoneal scarring from previously irradiated sarcoma.	Scientific risks
IEC[a]	Novel combined open/neuroendoscopic approach for a unusual arteriovenous malformation in an obtunded patient without a known advance directive.	Human risks (informed consent)
Regional/National	Transvaginal lysis of peritoneal adhesions for a patient wishing to avoid visible scars by a program with financial ties to transvaginal endoscope manufacturer.	Scientific risks, financial conflict of interest
IRB[b]	Thoracopy vs. thoracotomy for pulmonary lobectomy in severe COPD patient.	--

Oversight as Quality Improvement

Standardized oversight structures can aid in mitigating ethical risks while protecting surgical independence in a quality improvement (QI) structure that shifts cultural practice rather than targets individuals. An ideal oversight framework would serve to accelerate innovation by protecting surgeons who were formerly too apprehensive about ethical and legal risks to innovate while not significantly slowing current surgeon-innovators. We propose a systematic, quality-improvement framework to aid surgeons in the ethical introduction of surgical innovations (Figure 7.1). This framework builds on The Society of University Surgeons Surgical Innovations Project Team's position statement by stratifying different levels of innovation.[19] Surgeons could utilize existing tools to identify an innovation as such and then apply this framework to determine the appropriate level of oversight.[19, 20] This approach would maintain surgical independence and dignity and encourage the surgeon to take ownership in the ethical care of their patient. In general, operative innovations that present greater ethical challenges should warrant increased oversight. Other factors to weigh include the experience of the surgeon and the emergence of the case.

This framework should be adopted in a QI mechanism with measurable outcomes. QI requires transparency; rigorous data collection and analysis; and openness to adjust. Relevant outcomes include surgeons' sense of support supported while innovating, the usability of this framework, and patients' understanding of an innovation. Objective measures include number of innovations performed annually and lawsuits from adverse outcomes or miscommunication. Standardized data collection on the administrative aspects prior to an innovation (ie: ease of committee meeting, adequate time to for a department to deliberate an innovation, etc) could generate valuable information on how to implement this oversight framework efficiently. Prospective data capture from surgical innovations themselves could provide a wealth of information to other surgeons considering similar procedures and may facilitate

collaboration as well as study of an innovation. The mindset of a learning QI system should continually incorporate data analysis to improve the framework's content and delivery. Voluntary, surgeon-led QI initiatives depend on mutual trust and have demonstrated success in other elements of surgical care.[21]

An important initial delineation for this framework is distinguishing research and individual clinical contexts. The distinction of these rests on their respective motivation: the primary goals of operative innovation in the clinical and research contexts, respectively, are beneficence to optimize patient care and experimental evaluation to generate generalizable knowledge. Experimental techniques intended to test the new technique with equipoise fall into the research category that receives oversight from IRBs. An example is single-port laparoscopic cholecystectomy for porcelain gallbladder with considerable malignant potential. Traditional laparoscopy already carries an acceptable risk for this pathology and this single-port approach is not an innovation for an individual patient's unique anatomic or pathologic circumstances, but rather as a challenge to multi-port laparoscopy.

An operative innovation may at the same time be experimental and introduced by the surgeon specifically for a patient thought to derive benefit from it; these cases fall into the innovation for individualized clinical benefit category. Oversight in this category includes surgical exceptionalism, informal discussion with colleagues, formal departmental conferences, IECs, and regional/national ethics committees (**Table 7.1**). The ethical factors that determine the appropriate level of oversight include the aforementioned scientific factors and human factors. Practical considerations unique to surgery such as expertise of the surgeon and emergence of the case also factor into this determination. Illustrative cases are described in **Table 7.2**, though as a caveat, no consensus about what constitutes surgical innovation exists and individuals may vary in scenarios they consider innovation.

The ideal cases for surgical exceptionalism are limited to those in which the presence of any regulation at all is unnecessary or overly burdensome. Such procedures without significant ethical challenges involving efficacy or decision-making will not require further oversight. Relevant caveats to this approach are that surgeon discretion presumes training in identifying innovation and in surgical ethics and that only innovations that do not significantly depart from standard of care warrant no additional oversight since the risk-benefit ratio is not as predictable in innovations that depart from standard. Further, the innovation should be discussed with other members of the surgical and post-operative care teams, including anesthesiologists, critical care physicians, and nursing staff so they can provide input and also anticipate changes required in their care. An example case for surgical exceptionalism is the utilization of a new port location to facilitate laparoscopic cholecystectomy in an adult patient with situs inversus totalis who is able to provide informed consent.

Cases that involve challenges to scientific ethical factors, but not human ethical factors, may benefit from departmental oversight. These innovations may be supported by lower quality pre-clinical evidence or have poorly defined risk-benefit ratios, but there are no risks in the communication between the surgeon and the patient and no conflicts of interest for the surgeon. The surgeon's own colleagues would be best poised to refine the innovation to maximize benefits to the patient, but as the

surgeon knows the patient's anatomy and clinical history the best, the decision to innovate remains with the surgeon and patient. Surgeons with extensive experience with the anatomic features involved in a proposed innovation may be well prepared to undertake an attempt at innovation without oversight by colleagues as their expertise provides them with the best possible assessment of efficacy and safety. Like in surgical exceptionalism, anesthesiologists and post-operative teams should be included. The multidisciplinary knowledge of IECs and centralized oversight committees, which could aid in communicating informed consent or assessing patient vulnerability, are unnecessary since no human ethical factors are challenged. Under this framework, departmental discussion would be appropriate in determining the approach and optimal extent of resection* for a large complex skull base lesion that invades nearby neurovascular structures and is expected to be difficult to remove due to prior irradiation.

Innovations that involve challenges to human ethical factors (with or without scientific ethical factors) step up to oversight by IECs. IECs benefit from a diverse range of opinions due to their multidisciplinary nature and are consequently poised well to manage situations presenting complex ethical challenges. Multidisciplinary institutional committees containing ethicists and lawyers have the expertise to help surgeon-innovators navigate difficult informed consents, ensure the protection of this vulnerable patient, and mitigate conflicts of interest. One weakness of this framework is that IECs differ in role, scope, and make-up by institution. Collaboration by surgical and ethical societies to standardize or create minimal requirements for IECs is necessary to ensure these committees are equally prepared to assess this level of surgical innovation. Major academic hospitals may partner with non-academic centers to ensure their access to IEC expertise. As a caveat, emergent cases that a surgeon deems to warrant an operative innovation may supersede other ethical considerations due to time constraints, so an emergent innovation may warrant a lower level of oversight. For example, a surgeon managing an adolescent with cystic fibrosis complicated by bronchiectasis who presents with penetration multiple gun-shot wounds to the chest may seek a modified conservative approach for repair to maximize salvage of lung parenchyma, but the patient's condition may demand action before an IEC can convene. The surgeon must depend on more expedient forms of oversight such as discussion with colleagues or post-hoc case conferences in these emergent settings.

A more centralized oversight process coordinated by regional or national professional societies is warranted to ensure the ethical introduction of operative innovations that involve an institutional conflict of interest, such as holding financial stakes in a company funding an innovation, in addition to human or scientific ethical challenges. While the members of these centralized committees would have similar multidisciplinary expertise as IECs, they mitigate the effects of institutional conflicts of interest. Centralized committees are entirely hypothetical in surgery, and a major barrier to formation is restructuring professional societies to incorporate them. Patient advocacy organizations could work with state and national governments to help fund these committees. An example case is alveolar bone graft prior to odonotic maturation for cleft palate repair in a child flown in pro bono from an underdeveloped

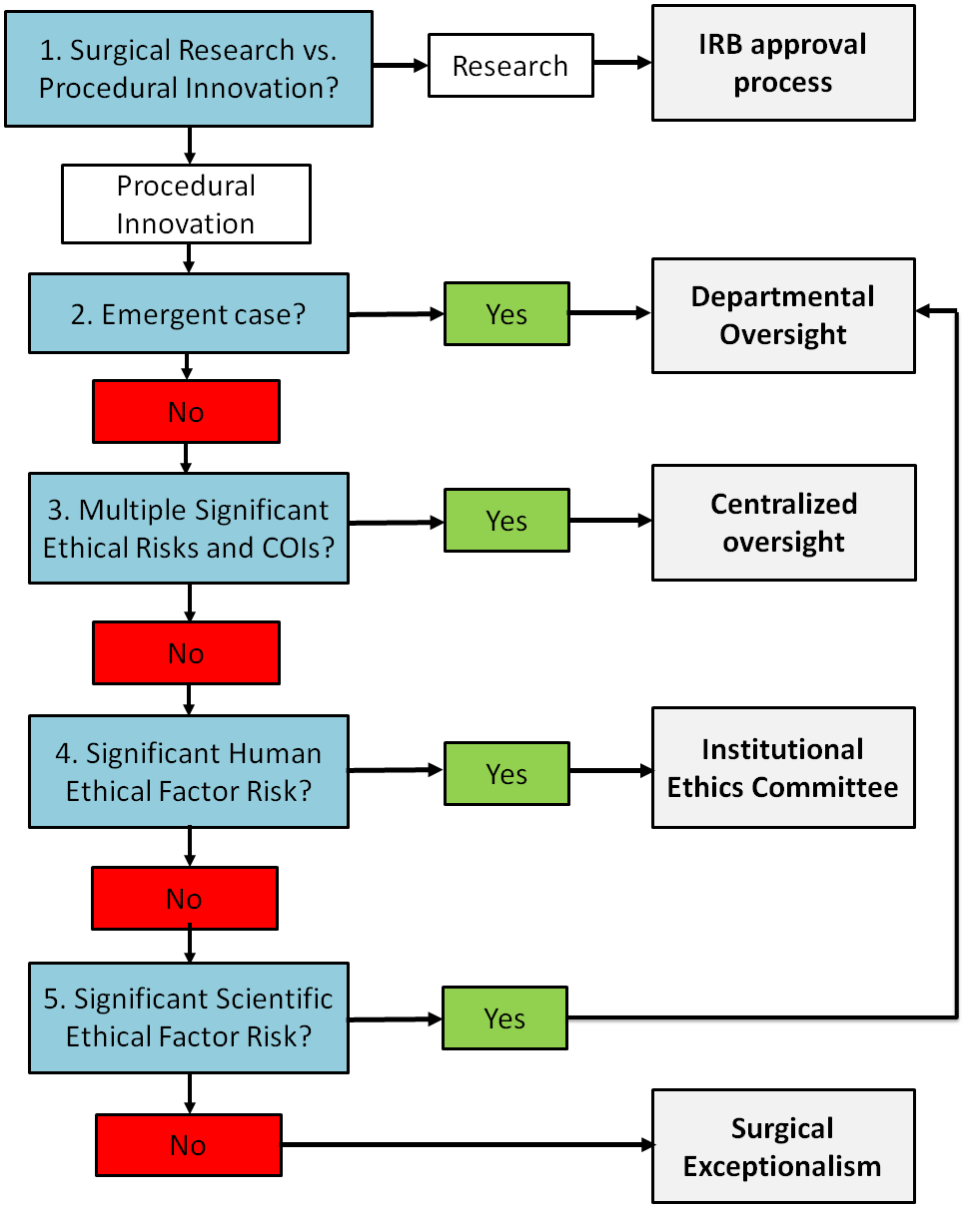
country with the expectation of the department using this case to promote its humanitarian work. It may be reasonable to innovate on this patient early given that the patient may not have future access to medical care; however, there are human risks (justice for patient with less access to care, vulnerable child patient) and scientific risks (very novel procedure, so unclear risk/benefits) at play, as well as the department's benefiting from advertising this humanitarian procedure. Once formed, centralized oversight committees may integrate with IECs by sending unbiased representatives to consult with them to maintain institutional independence and to accelerate decision-making for time-dependent procedures. Again, emergent procedural innovations that would otherwise warrant such oversight may depend on less oversight given time restraints.

Current challenges requiring further exploration include tools for surgeons to identify innovation and conflicts of interest, the development of standardized case conferences and IECs, and infrastructure that integrates oversight seamlessly with surgical care. Data collection on the efficiency and ease of the framework would aid procedures in effective implementation of the framework. Ethical considerations may be complex and surgeon-innovators may seek multiple types of oversight simultaneously. For instance, IRBs do not often contain multiple surgical subspecialists as reviewer, so an IRB-approved study may additionally benefit from departmental oversight of risk/benefit calculations. Multi-institutional IRB-approved studies may similarly benefit from departmental or regional oversight to help weigh these calculations. Different departments may be especially well attuned to the different conflicts of interest and levels of ethical training in their group, which could aid IRBs. IRBs may benefit from inclusion of subspecialist consultants as well. The role of insurers who decide which innovations to cover is important to also consider as they influence which patients receive innovations. The role of insurers in this framework may vary depending on the health care system; for example, a government-run single payer system acts broadly in citizens' interests, so it may conduct process checks for adherence to this framework as a requirement for coverage of innovations.

The ultimate decision on whether to seek oversight currently rests with surgeons. This proposed framework does not reduce a surgeon's independence and ownership over their patients; rather, it aims to protect patients from risk and support surgeons through ethical quandaries to allow them to keep their focus on innovating in the operating room. Previous experience even suggests some regulation may actively promote a culture of innovation through offering assurance and confidence to innovators that they are innovating in an approved ethical manner.[6] This quality improvement framework builds on the pillars of surgical professionalism and education: competence, integrity, humility, and consistency. This framework seeks to align with historic surgical ethos to create a culture of continual self-improvement in a learning environment wherein everyone from patients to surgical interns to renown surgeon-innovators benefits. These proposed levels of oversight provide a consistent and ethically sound method to introduce new innovations. The framework should be introduced with care to ensure all faculty understand its purpose and understand how to use it. In should also accommodate local regulation and oversight, the specific subspecialties in a hospital, and the patient populations' needs. Continuous improve-

ment and adjustments of the framework are necessary to ensure potential benefit to patients.

Figure 7.1: Framework for the Determination of Appropriate Level of Oversight



Conclusion

Current methods to address ethical challenges to operative innovation are inconsistent and open surgeons and patients to risk. Possible oversight mechanisms for operative innovation range from no oversight to formal IRB review. Certain oversight mechanisms may be well suited to regulate an attempt at innovation depending on the type and degree of pertinent ethical challenges to ensure the continued advancement of the field while protecting patients and supporting surgeons.

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8

The ethics of the learning curve in innovative surgery - a systematic review

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***Introduction**: Surgical innovation is essential for improving patient outcomes, but it inherently exposes patients to an increased risk of complications while surgeons master both the procedure and the associated peri-operative care. The purpose of this paper is to evaluate and discuss the literature on the ethics of learning curves in innovative surgery. **Methods**: PubMed and Embase were systematically evaluated for ethical discussions about mastering technical competencies, skills assessment, informed consent, and professional requirements for surgical innovation. Possible manners of addressing the learning curve in an ethical fashion were also evaluated. **Results**: The search strategy yielded 1681 articles of which 38 were included. These articles discussed ethics or the definition of "learning curve", how to deal with the learning curve regarding technical skills, mechanisms of oversight, and professional duties. Most studies included in this paper mainly focus on the technical aspects that are inherent to innovative surgical procedures and rarely discuss other professional requirements. Furthermore, there appears to be no consensus on a definition of the learning curve in an innovative setting. **Conclusions**: To address the learning curve associated with surgical innovation in a morally sound way, the literature shows that surgeons need to meet*

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various mainly technical requirements. We suggest that a broader view that incorporates both technical and professional requirements from the surgeon is necessary. Furthermore, we deem it essential to create a "safe" learning culture within innovative medical centers to minimize associated risks for patients.

Introduction

Without innovation throughout the years, surgical care would be nearly unrecognizable compared to the modern and technologically advanced field that is practiced today. In particular, surgical outcomes have been tremendously improved by the introduction of new techniques and procedures such as use of the bipolar cautery, microsurgery, and, more recently, endoscopic surgery.[38, 42, 46] Clearly, just because a new technique is innovative does not mean it is an improvement over standard practice, and many innovations come with ethical challenges. During the fledgling stages of the implementation of an innovative procedure, the associated learning curve presents one such challenge. Almost by definition, many surgeons may be relatively inexperienced with a brand-new procedure, and their patients may face increased risks of complications as a result. How to balance these risks with the potential benefit of better outcomes for future patients warrants further examination.

Learning curves in surgical innovation can broadly be divided into three phases. The first phase is the performance of a surgical procedure for the very first time.[8] In emergency situations, the surgeon might try something entirely new since reasonable alternatives or an established standard of care are unavailable.[12] This is in contrast to elective procedures, in which there is more time to prepare and practice the new procedure. In the elective setting, the ethical questions surrounding learning curves are therefore perhaps even more challenging since there is the possibility of opting for an established procedure rather than the novel one.

The second phase of learning curves is when an innovative procedure seems to be beneficial to the patient, but still needs further evaluation in order to prove its safety and efficacy.[21] A prospective trial with some type of randomization would be the preferred method to evaluate its efficacy and safety. To conduct a valid trial, however, all surgeons would ideally have the same proficiency level, which is not always feasible. For instance, equal proficiency could be achieved via a form of training before surgeons perform the new procedure, but this may not always be logistically possible. The third and final phase occurs when the innovative procedure has been proven to be beneficial and safe but has not been implemented outside of the initial centers.[37]

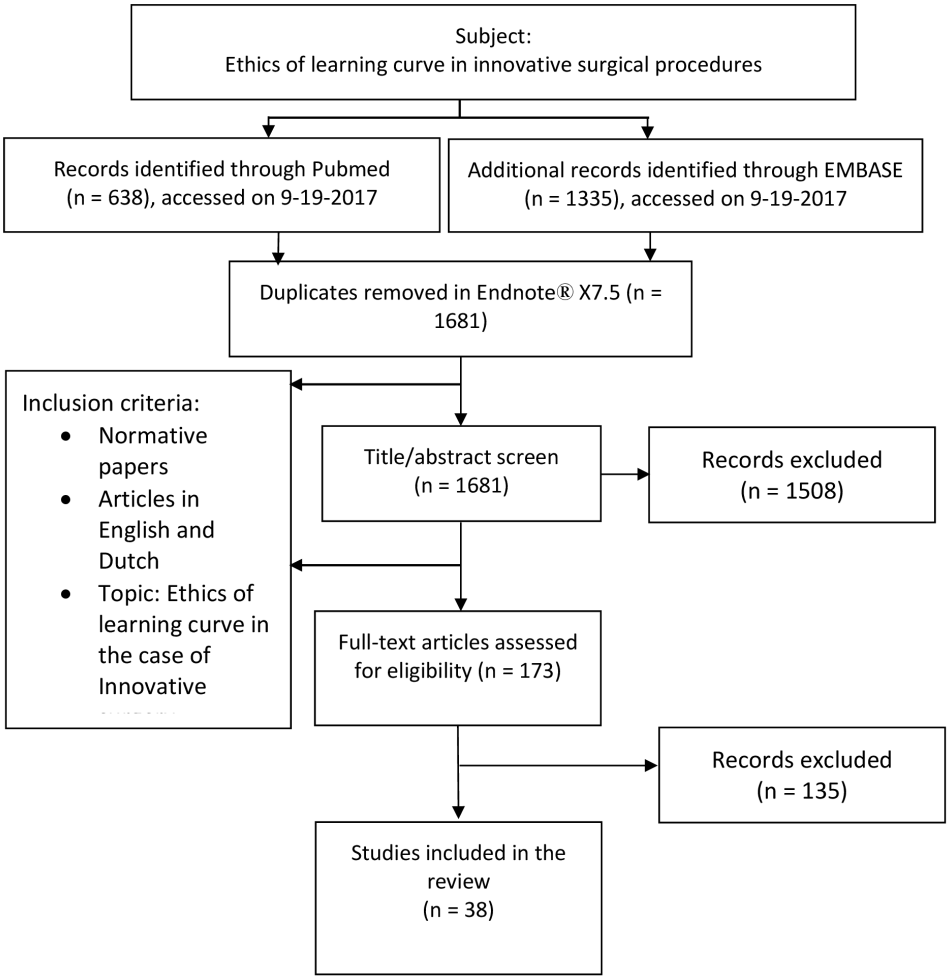
Each stage of innovation comes with unique considerations about the influence of learning curves on patient outcomes. In this systematic review, we evaluate the literature, address the ethical challenges of the learning curve in each phase, and describe methods of evaluation and management of surgeons' progress along learning curves.

Methods

This review sought to answer the following question: "What are the main ethical challenges of the learning curve phenomenon inherent in innovative surgery?"

This study is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[33] PubMed and Embase databases were searched on September 19th 2017. The search strategy was drafted with help from a librarian and is described in **Supplementary table 8.2**. Additional references were identified by hand searching of bibliographies of the retrieved papers. This review is restricted to published literature and language was restricted to English and Dutch. The search was not limited by date of publication.

Figure 8.1: Flowchart



The available title and abstracts of the retrieved studies were screened by two authors, and full texts of the potentially suitable articles were read by two authors. Only studies that provided recommendations, or express an opinion, point of view,

or statement regarding the ethics of learning curve in innovative surgery were included. The resulting flowchart is depicted in **Figure 8.1**. Disagreements were solved by discussion or consultation of the writing team if necessary.

Results

After screening of 1681 titles and abstracts, 38 papers that assessed the learning curve phenomenon were included. These articles discussed ethics or the definition of "learning curve", how to deal with the learning curve regarding technical skills, mechanisms of oversight, and professional duties. The findings are described in the following paragraphs by phase of innovation, starting with the (lack of a) definition of the learning curve.

Learning curves: lack of a clear definition

In the literature, there seems to be no uniform definition of "learning curve" as it applies to innovative procedures.[20, 30, 36] Some have described it as the gradual increase of knowledge and skill that comes with the repeated performance of the innovative procedure and peri-operative patient care.[20, 30, 36] Others define "learning curve" as the gained knowledge and experience that is necessary for successful performance of the surgical procedure.[37]

The influence of learning curves is recognized in several different phases and settings of innovative surgery.[8] Others discussed learning curves only in the setting of performing radically new procedures, such as during the first phase discussed above.[18, 26, 34] Interestingly, only three papers have described how evaluation of learning curves should be incorporated in a research setting, which would apply to the second phase of learning curves.[10, 21, 37] Most authors describe the influence of a learning curve during the third, or implementation phase of the innovative procedure.[3, 4, 23, 32]

In the literature, opinions about learning curves vary greatly. They range from the opinion that they are an unavoidable part of surgical innovation[20, 24] to the view that learning curves are a serious problem that needs to be addressed.[3-5, 14, 18, 20, 23, 31, 32, 47] Some have even described learning curves as a menace to patient safety, although this is not the typical stance taken by authors on this subject.[35]

Managing learning curves

Since innovative surgery is by definition initially performed by surgeons with little to no experience with the procedure in question, the associated learning curve could have unforeseen consequences. For instance, surgeon inexperience could confound and complicate evaluation and interpretation of patient outcomes.[14, 21, 24, 45] Furthermore, in the case of adverse outcomes, it could result in reduced patient trust in the surgeon.[20] Since the scope of the risks of innovative procedures cannot always be fully defined, it is difficult, and in some cases impossible, for the surgeon to completely explain the risks associated with the procedure to the patient.[4] From an educational standpoint, since the attending surgeon in these cases has not completely mastered the procedure, surgical training of residents who are participating may not be completely effective.[18, 30] Approaches for managing these and other aspects of

learning curves in surgical innovation have been described by various authors (**Table 8.1**).[1, 3-5, 8, 11, 13, 14, 18-21, 23, 24, 26, 28-32, 34-37, 44, 45, 47]

Table 8.1: Technical and professional requirements for each phase of innovation

Phase of innovation	*Goal*	*Professional requirements*
Pre-clinical phase	Maximum preparedness for first procedure	• Train through simulation (e.g. cadaveric or computer models etc.) • Evaluate relevant literature and operative videos • Shadow experts
Clinical phase	Independent performance of the procedure	• Involve mentor for guidance • Review video post-operatively • Disclosure of relative inexperience during the informed consent procedure
Post-clinical phase	Maintain and enhance skills	• Participate in mentoring programs • Share experiences and learn from mistakes (e.g. at a conference) • Evaluate personal experience and outcomes with peers • Present personal outcomes in a transparent fashion

Training and technical competency

One of the main professional requirements for surgeons is to be technically capable of performing the procedure. Various methods of training have been proposed in the literature to ensure the technical competency of surgeons performing innovative procedures.[3, 8, 14, 18-20, 26, 31, 32, 34, 37, 45, 47] There are three different time periods when training is appropriate which somewhat correspond to the aforementioned phases of learning curves: the preclinical phase, which involves preparation prior to the procedure, the clinical phase, in which the procedure actually takes place, and the post-clinical phase, in which proficiency of the surgeon is maintained.[37]

Pre-clinical phase

The purpose of the pre-clinical phase of training is to attempt to mitigate the potential negative effects on patient safety of a surgeon's inexperience with a new procedure. In this phase, both cognitive and technical training are essential. In order to achieve adequate preparation, the use of in vivo, in vitro, computer, and cadaver models have been suggested in order to simulate human anatomy during training.[6, 16, 18-20, 32, 34, 37, 41] If possible, the surgeon could also study existing literature and operative videos of similar cases.[26, 36, 37] Finally, gaining first-hand experience from experts, for instance, by visiting an expert center or by doing a fellowship, is suggested to a valuable tool to understand more nuanced aspects of the new procedure.[8, 18, 19, 26, 32, 36]

Clinical phase

The clinical phase of training is comprised of the actual repeated performance of the new procedure, and it begins as soon as the first procedure is done by a surgeon. It has been suggested that, ideally, the first procedure is performed with involvement of a mentor (i.e. a surgeon with greater experience).[18, 19, 26, 43] Although it is not always possible in the case of very new procedures, mentors could answer questions that may arise and offer guidance via back-and-forth communication.[31, 32] Alternatively, some have suggested that reviewing operative videos may be sufficient in certain cases, such as when a new procedure is a slight variation on a familiar one.[18] It has been suggested that an innovative procedure is only cost-effective when carried out with a high case-volume, partially due to the fact that learning curves can influence outcomes.[22] Others have also described possible statistical methods for assessing when a surgical apprentice has gained sufficient experience with innovative procedure.[39] The ultimate goal is for the surgeon to be able to perform the procedure independently, but this could be aided by expert review, when possible, as a final step before full independent performance of the procedure.[8]

Post-clinical phase

After having gained enough experience to successfully perform the new procedure independently, it is vital to maintain and enhance these skills. Some have suggested that this should be carried out in a mentoring program.[18] In any case, it is essential for the surgical community to share gained experience and patient outcomes, perhaps through conferences with this specific aim.[31, 40] By learning from mistakes, identifying problems, and describing risks and limitations of the procedure based on experiences of a broad group of surgeons, outcomes could be improved more quickly and efficiently.[31] This continued improvement and expansion of accumulated knowledge comprises the post-clinical phase of training, with the hope that this knowledge could be used to develop more accurate training modules to assist in the earlier phases of training.[31]

Assessment of the learning curve

There appears to be no standardized method to assess learning curves of innovative procedures. Several ways to monitor learning curves, however, have been described in the literature, including the formation of regulatory entities.[8, 13, 25, 30] Some have suggested that a single expert surgeon may be sufficient for adequate oversight, whereas others have argued that regional, multidisciplinary committees overseeing surgeon progress at multiple institutions would be better.[8, 13, 30, 36] The goals of these committees could be to define standardized requirements for appropriate training, to review fledgling innovative procedures, and to provide accreditation.[8, 36, 44] Others have suggested using the learning curve cumulative simulation, a statistical method aimed at identifying the number of procedures necessary to become competent surgeon.[9, 40]

Additional professional requirements

Physicians are not only expected to be technically skilled experts but also to possess other professional characteristics, such as high standards for ethical conduct. The learning curve associated with innovative surgeries calls for at least

the following two ethical requirements: 1) obtaining adequate informed consent from patients and 2) honest communication of technical competency with peers.[1, 4, 5, 8, 14, 18, 19, 21, 24, 26, 28, 29, 31, 32, 34, 35, 37, 44, 45, 47]

During the informed consent process, transparent communication is essential in order to provide patients with accurate information about the relative inexperience of the surgeon performing the procedure.[1, 4, 5, 14, 20, 24, 26, 28, 29, 32, 35, 47] This information could include a description of the success rate of the surgeon or other quantitative or qualitative forms of describing outcomes, both positive and negative.[1, 18] This disclosure becomes even more important when the surgeon performs the procedure for the first time.[7, 17, 32]

Some view it as an obligation of the surgeon to evaluate their personal outcomes and reflect on their own skill and performance when deciding whether to perform an innovative procedure.[1, 18, 20, 26, 30] This could be aided by keeping detailed records of outcomes with adequate follow-up, which then can be used to improve the training of other surgeons as well as allowing for a more informed self-assessment.[1, 5, 18, 20, 21, 26, 31, 32, 37, 44]

Discussion

In this review, the literature regarding the ethics of the learning curve during surgical innovation was evaluated. Most publications that were included in this synthesis focused on the ethical challenges associated with the technical aspects of a learning curve. The literature does not provide a uniform definition of a surgeon's learning curve for novel procedures, although such a definition would be helpful to facilitate the discussion about said learning curves. We suggest that a definition should incorporate the necessity for the surgeon to master a procedure, which inherently comes with steps that must be taken to progress to the desired skill level. Others have provided a practical alternative definition of the learning curve: a problem that arises when surgeons other than the original innovator start performing the procedure.[4] Whether or not this is the case, the experience of the primary investigator certainly could guide the learning process of other surgeons attempting to master the innovative procedure.[37] One could even argue that the learning curve that attending surgeons face when performing an innovative procedure is similar to residents gaining experience with established procedures, which comes with simulation, mentoring, and supervision. As a result, the learning curves of residents could provide valuable insights that are also applicable to innovative surgery.

There are several essential differences, however, between a resident's learning curve and the learning curve of a fully trained surgeon that performs innovative procedures. First, potential complications and outcomes of the procedures performed by the residents are relatively well-defined and the responsible attending surgeon is well-prepared to take over the procedure if something goes wrong. Furthermore, during the training of residents, the whole surgical team is experienced with the procedure, is familiar with potential complications, and has previously been involved in the training of residents. Conversely, during an innovative procedure, not only the surgeon but also the peri-operative team is inexperienced and unaware of the possible consequences, confounding and impeding the learning process which is more

systematic for residents.

Consequences of learning curves

In the case of performing a radically new procedure, adequate preparation by the whole peri-operative team involved is necessary in order to manage the surgical learning curve. This is especially important since no earlier experience is available to guide decision-making intra- and peri-operatively, which may be considered routine for established procedures. In this scenario, frameworks such as the IDEAL (Idea, Development, Exploration, Assessment, Long-term follow-up) framework may prove helpful, as it describes clear steps that should be taken during development and implementation of innovative procedures.[21] This could be further aided by pre- and post-clinical training, which we deem as imperative to ensure patient safety by minimizing risks. Since each innovative procedure is unique, it requires a carefully tailored training program in order to achieve maximum preparedness. This could be attained through various forms of simulations and/or direct mentoring by an expert surgeon.

Informed consent procedure

The most important aspects of an adequate informed consent procedure with regard to the learning curve are a transparent presentation of the experimental nature of the procedure and the known risks, benefits, and alternatives associated with the procedure.[4] Furthermore, a surgeon should describe his or her relative (in)experience, which we see as an absolute necessity in order to meet the requirements of adequate informed consent: disclosure, decisional capacity, patient understanding of the information, voluntariness, and consent.[47] In reality, however, perhaps out of fear that the disclosure might confuse or distress the patient, present informed consent procedures probably do not meet these criteria.[5] According to a survey among patients and surgeons, honest, descriptive disclosure of the risks and benefits and disclosure of whether the surgeon is performing the procedure for the first time appears to be the best approach.[27]

With regard to preparing for the procedure, most publications focus on meeting technical requirements and regulations for performing the procedure to ensure patient safety. Although some authors do acknowledge that non-technical skills, such as communicative skills, are also important, none provide clear recommendations on how to implement those in the case of innovative surgery. These ”soft skills”, however, may be of key importance when it comes to involving patients in innovation and acquiring adequate informed consent. These skills range from interpersonal skills (e.g. teamwork and communication), cognitive skills (e.g. situational awareness and decision-making) and personal resource skills (e.g. coping with stressful situations).[15] Furthermore, it has been suggested that surgical care is currently too heavily focused on technical skills and achievement and that there should be increased focus on these so-called soft skills, which might better be called professional skills.[2] We believe that this broader view on surgical care is especially important in the case of innovative surgery. Finally, as innovative surgeons will undoubtedly be faced with multiple ethical challenges involving both their professional and personal values, adequate training is necessary to ensure both technical and non-technical competency.

Learning curve assessment

Currently, there is no standard way to assess learning curves of innovative procedures. Even though we think that specific oversight bodies as described above could play a role, an interesting different approach could be critical self-evaluation by the surgeon before, during, and after performing an innovative procedure. This could be done together with an expert or mentor for added insight. A proper understanding of a surgeon's own limitations is also warranted, despite the possibility that this could result in the decision to stop performing the innovative procedure. In this method, characterized by self-reflection, a surgeon's errors and past complications are acknowledged, evaluated, and form a basis for future improvement. One efficient way of achieving this may be through patient databases that help promote adequate follow-up of all outcomes in order to evaluate not only safety but also progression of the surgeon along the learning curve. In the best-case scenario, these databases may even shorten the learning curve and result in prevention of adverse events.

As stated before, transparent communication among performing surgeons is necessary for safe surgical innovation. As outcomes of the procedure may be viewed as a reflection of a surgeon's performance or technical skill, however, many surgeons may be hesitant to openly communicate this information with their peers. Therefore, a key element in improving assessment of the innovative learning curve is the creation of a safe and 'learning' environment in which adverse events can be openly discussed. In this scenario, surgeons may be more willing to share adverse events and negative experiences with their peers, which otherwise may be downplayed or avoided altogether, again shortening the learning curve. Hierarchies within hospitals or academic medical centers may limit communication among peers and should therefore not be influenced by open communication of adverse events in surgical innovation.

Overall, self-reflection, verifiability, and honesty among surgeons form the foundations of this safe environment. As most surgeons follow the mantra "rather mistaken than in doubt" in the real world, however, this may be difficult to achieve.[5] Especially in regard to maintaining patient safety, but also in order to adequately evaluate the learning curve in innovative surgeries, we deem it essential to create a "safe" learning culture within innovative medical centers.

Conclusion

In order to address the learning curve associated with surgical innovation in a morally sound way, the performing surgeon needs to meet various professional requirements. We suggest that a broader view, however, is necessary - one which incorporates a professional attitude from the surgeon while managing and progressing along his or her own learning curve. In the end, it is an ethical necessity to incorporate self-reflection, verifiability, and honesty into a safe culture that promotes continuous learning in an open environment throughout the entire process of surgical innovation.

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Table 8.2: Search strategy

Search engine	*Search syntax*
PubMed	(((Innovative Therapy[MeSH Terms]) OR Invent*[Title/Abstract]) OR Innovat*[Title/Abstract]) AND (((((((Surgical procedures, Operative[MeSH Terms]) OR Surger*[Title/Abstract]) OR Surgical[Title/Abstract]) OR Operative procedur*[Title/Abstract]) OR Operative [Title/Abstract]) OR Operation[Title/Abstract]) OR Operations[Title/Abstract]) AND ((((Ethic*[Title/Abstract]) OR Bioethic*[Title/Abstract]) OR Moral*[Title/Abstract]) OR Ethics[MeSH Terms])
Embase	('experimental therapy'/exp OR 'experimental surgery'/exp OR innovat*:ab,ti OR invent*:ab,ti OR experiment*:ab,ti) AND ('surgery'/exp OR 'surgical technique'/exp OR 'experimental surgery'/exp OR 'surger*':ab,ti 'surgical':ab,ti OR 'operative procedur*':ab,ti OR 'operation':ab,ti OR 'operative':ab,ti OR 'operations':ab,ti) AND ('bioethics'/exp OR 'medical ethics'/exp OR 'ethical theory'/exp OR 'moral*':ab,ti OR 'ethic*':ab,ti OR 'bioethic*':ab,ti)

9

When time is critical, is informed consent less so? A discussion of patient autonomy in emergency neurosurgery

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***Summary**: Neurosurgical interventions often take place in an emergency setting. In this setting, patients often have impaired consciousness or are severely threatened by spinal cord dysfunction and are therefore unable to express their values and wishes regarding their treatment. The limited time available for clinical decision making holds great ethical implications as the informed consent procedure may become compromised. The ethical situation may be further challenged by different views between the patient, relatives and the neurosurgeon; the presence of advance directives; innovative procedures; or if the procedure is part of a research project. In this moral opinion piece, we discuss the implications of time constraints and a lack of patient capacity for autonomous decision making in emergency neurosurgical situations. We also discuss potential solutions to these challenges that might help to improve ethical patient management in emergency settings.*

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Introduction

Time is of the essence for many neurosurgical procedures that often must be done on an emergent basis to mitigate the extent of patient morbidity and mortality.[14] Emergency surgeries have been independently associated with increased post-operative morbidity and mortality when compared with non-emergent procedures.[14] Patients may also have greater expected benefit from the procedure if it takes place sooner rather than later .[19] Additionally, the need to operate as soon as possible creates ethical issues regarding patient autonomy and beneficence. Currently, no formal guidelines or statements exist that specifically describe how to obtain informed consent in an emergency setting for neurosurgery, but British physicians are allowed to act in the best interest of acutely incapacitated patients.[6, 21] The statements of the American College of Surgeons and Association Of Surgeons Of Great Britain Ireland (ASGBI) on emergency surgery indicate that surgeons with appropriate training should be able to provide the necessary emergent care.[2, 4] The ASGBI Good Clinical Practice Guideline does state that surgeons have a legal obligation to obtain informed consent in limited time.[26] While these statements on emergency surgery provide a general emphasis on good clinical practice and acting in the best interest of the patient, they unfortunately do not provide a template for striking a balance between respect for patient's autonomy and beneficence in an emergency scenario. A neurosurgeon is required to obtain adequate informed consent and make sure the patient undergoes the necessary procedure as soon as possible. This may be complicated and is frequently lacking, due to a relative lack of time and the rapidly evolving pathology that limits a patient's capacity to make an informed decision. During this complex process, neurosurgeons must balance the diverse views, choices, and actions of patients based on the patients' personal values and beliefs, that are often not expressed by the patients themselves at time of decision making, while ensuring that the care provided is of the highest standard. In this perspective piece, we discuss the ethical questions that might arise in an emergency neurosurgery related to respect for autonomy and propose methods to address them.

Respect for autonomy in an emergency setting

Respect for the autonomy of the patient during the informed consent process may be compromised during an emergency surgical scenario primarily for two reasons: a lack of time and questionable capacity.

Lack of time

In an emergency setting, patients are often unable to make an autonomous decision because of time constraints.[3, 5] The limited time compromises the ability of the patient to weigh the benefits and risks, to appreciate the gravity of the situation, and to consider all treatment or non-treatment options and divergent outcomes. Patients and their proxies may also be frightened, misunderstand the proposed procedure, and feel pressured to consent in an emergency situation.[1] Therefore, autonomous decision making and informed consent may be compromised in an this acute setting.[5] The lack of time also affects neurosurgeons as they have less time to perform a moral

deliberation and to prepare a surgical plan, and may be faced with increased emotional stress among the surgical team.[17] Decisions to operate (or not) may also be influenced by a fear of malpractice lawsuits, especially when one would refrain from surgery.[28]

Lack of capacity to make autonomous decisions

In addition to a lack of time for informed consent, acute neurosurgical diseases may limit the capacity of a patient to formulate or express an autonomous decision. Four scenarios may arise: 1) the patient has capacity to make an autonomous decision before surgery, 2) the patient lacks capacity to make an autonomous decision and relies on surrogate decision maker, 3) a patient lacks capacity to make an autonomous decision and has an advance directive for medical emergencies, or 4) the patient is comatose or tetraplegic and family members are unavailable (**Table 9.1**).

In the first scenario, communicating and providing informed consent efficiently given a relative lack of time is the main challenge in emergency surgery. This might for instance be the case for a trauma patient with a lower spinal cord injury, who is otherwise alert and orientated, but requires urgent stabilization or decompression. In the second -very common- scenario, a patient that requires emergency surgery has impaired level of consciousness and is no longer capable of autonomous decision making. Hence, decision making relies on a surrogate decision-maker (often a family member) if available. A patient may have previously expressed personal wishes or preferences in case of life-threatening scenarios which can guide decision-making by their representatives. This surrogate decision-maker should decide what the patient would have done with capacity in that scenario. This may aid the decision making-process, but their guidance does not necessarily equate what the patient would have preferred, as these cannot be known for each patient in any given emergency situation.

In the third scenario, the patient has an advance directive for medical emergencies. This can be a living-will that provides directions in specific circumstances and/or a durable power of attorney (DPA) in which the authority of the patient is carried over to another person through a legal document. Living wills offer a clear direction to take for the neurosurgeon, which respects the patient's autonomy. A clear and reasonable wish in a specific circumstance may seem "easy" for a neurosurgeon to follow (e.g. an elderly patient with a severe TBI and living will that states that no surgery should be pursued). However, multiple factors may cloud this decision. The living will may have been drafted at a time when the patient felt differently about their goals and personal views and post-operative outcome may be hard to predict. The neurosurgeon may personally disagree with a living will. Differing cultural and regional backgrounds of the neurosurgeon and patient further complicate the decision to operate due to widely varying expectations, values, and medical practices. For these and other reasons, living wills may have limited implications in neurosurgical emergency scenarios. One survey among neurosurgeon showed that only half of responding neurosurgeons would decline to operate on patients with an advance directive that limits post-operative life-supporting therapy.[25]

A DPA may also provide guidance in the decision-making process for emergency

surgery. A DPA is been appointed by the patient and should be familiar the patient's values and wishes. However, the DPA may be unavailable in an emergency situation and the patient's wishes may have changed since the DPA was appointed. Therefore, the DPA still brings practical concerns and may not offer a solution in all scenarios.

Table 9.1: Four scenarios in emergency neurosurgery.

Scenario	*The patient is able to make autonomous decisions:*	*Other available parties or materials to guide decision-making.*	*Decision-maker.*	*Example.*
1	Yes	Not necessary.	The patient.	An adult patient with a traumatic vertebral fracture that needs urgent stabilization.
2	No	A surrogate decision-maker such as a family member.	The surrogate decision-maker.	A pediatric patient with an epidural hematoma that requires emergent evacuation.
3		An advanced directive: DPA or living will.	The neurosurgeon, guided by the Advanced directive.	An elderly patient that has stated in a living will that no surgical procedure should be pursued but requires emergency evacuation of a subdural hematoma.
4		Not available or enough time does not exist (e.g. patient with unilateral mydriasis and EDH)	The neurosurgeon.	A comatose patient with severe TBI that is brought in by emergency services whose name and family are unknown to the neurosurgeon.

In the final scenario with a patient that is unable to make an autonomous decision and has no available surrogate decision maker or known living will, the neurosurgeon becomes the sole responsible person to make a decision that is in the patient's best interest. This may also be the case when a patient cannot be expected to make a rational decision despite not being cognitively impaired, e.g. a tetraplegic patient. This requires the neurosurgeon to have some appreciation about what a favorable outcome would be for the patient based on their presumed culture and background.

Ethical challenges related to emergency neurosurgery

In emergency settings, lack of time and compromised capacity can challenge respect for autonomy. Here, we discuss how neurosurgeons may balance lack of time, compromised capacity of the patient and respect for autonomy and propose potential solutions to help guide management in these scenarios.

Balance between limited time, incapacitated patients, and respect for autonomy

In emergency situations, the neurosurgeon has to balance informed consent with minimal delay of the surgery. As a result, the formal informed consent procedure may be waived in acutely life-threatening scenarios like an evolving epidural hematoma causing uncal herniation. The ability to act fast maximizes beneficence to potentially incapacitated neurosurgical patients whose prognosis worsens with each minute of inaction. Most situations, however, will offer some – though limited - time to discuss treatment options but will still result in a compromised informed consent. All efforts should be made to obtain informed consent that is as complete as possible from the patient or surrogate decision-maker. Excellent communicational skills are of paramount importance for the neurosurgeon to provide a sufficient explanation in this limited time. The neurosurgical team should ideally try to elaborate on the expected outcome of the procedure including mortality, functional outcome, quality of life, and in particular the chance of survival with severe morbidity. However, this may be hard as most data is derived from large cohort studies that may not provide an accurate prediction of outcome for individual patients.

In the case of a patient that is incompetent to make an autonomous decision, the neurosurgeon should first consult the DPA or surrogate decision maker to guide decision-making. A living will may very well guide this process but should only aid decision-making if it provides a specified plan of action for the medical scenario. As indicated above, the decision to operate ultimately rests on the neurosurgeon's shoulders if no surrogate decision maker, DPA, or living will is available.

Disagreement between patient and neurosurgeon

We argue that neurosurgeons should in general regard the patient capable to make an autonomous decision when determining the patient's decision-making potential for emergent surgery. Only when the neurosurgeon has reasonable doubt regarding the patient's capacity to make autonomous decisions after discussion between multiple members of the neurosurgical team may operating without consent be ethically justified. Choosing to perform surgery without consent may be justified if the patient lacks capacity, has an unknown or unreachable health care proxy, has no living will or DPA prepared, and requires an urgent operation. A psychiatric evaluation could aid assessment of a patient's capacity to make an autonomous decision if time allows for it. This cautious management errs on the side of saving a life when it is not completely clear that a patient has capacity to make an autonomous decision. On the other hand, if a patient is capable to make an autonomous decision and does not change his or her mind over a reasonable amount of time, then the patient's decision should be respected despite potential detrimental outcomes. However, there may be no time to be sure that the patient is consistent in his or her reasoning over a longer period of time and the patient may also have chosen differently if the choice was not presented in an emergency scenario. Prioritizing beneficence over respect for autonomy may be ethically justified if respect or autonomy is viewed as a value or a relative right instead of an absolute right and thus beneficence (e.g. saving the patient's life) is highly likely to strongly outweigh respect for autonomy under the patient's own

value system.[27] In this situation, the neurosurgeon tries to act in the patient's best interest, which could be regarded as experience-based paternalism.[8]

This approach should be applied with caution. It may not justifiable if there is time available to further discuss treatment options with the patient or surrogate decision-makers. The neurosurgeon also risks incorrectly assuming the values and wishes of the patient due to social or cultural differences, which compromises the decision-making process. There may also be uncertainty to what constitutes a good outcome as seen with decompression for malignant middle cerebral artery infarction. [11, 15] Some have argued that in addition to mortality, quality of life and functional outcomes are very valuable to patients and their families, even though early surgery may not result in improved outcomes for malignant middle cerebral artery infarction.[10, 24] A neurosurgeon may also be inclined to operate due to reasons other than provide optimal care, e.g. the fear of malpractice law suits.[28] An appreciation for a patient's legally protected preferences for end-of-life decision-making, such as living wills, should also be followed if they apply to the specific situation. The difficulty in weighing respect for autonomy and beneficence in complicated scenarios highlights the necessity for neurosurgeons to comply with the highest professional standards, be fully informed, and be sufficiently trained to avoid or take paternalistic positions as appropriate.

Conversely, respect for the autonomous decision to forgo surgery may outweigh the beneficence conferred by the surgery when the neurosurgeon wants to pursue surgery. This may be the case when there is minor expected benefit, high risk of poor outcome, and great uncertainty regarding outcomes between surgery or conservative management.

A surgeon may also decide to refuse to offer surgery to the patient, while the patient or the surrogate want an operation. In this instance, the neurosurgeon prioritizes non-maleficence over respect for autonomy. This results in the neurosurgeon not performing a surgery and opt for conservative management even when the patient or surrogate decision-maker do not agree. Ethical justification for this practice requires reasonable certainty regarding the outcome and thorough explanation to the patient or surrogate decision makers. An example is a family demanding decompressive surgery for an elderly patient with a severe traumatic brain injury with expected poor outcome. A neurosurgeon (or the family) may consult a colleague for a second opinion if the patient or surrogate continues to insist on an operation. Furthermore, the neurosurgeon should always try to pursue a treatment plan that respects the values and follows the wishes of the patient as closely as possible whilst ensuring an optimal outcome for the patient.

Emergency neurosurgery in an innovative or research setting

Respect for autonomy in an emergency situation becomes even more challenging when the procedure is innovative or takes place in a research setting. The uniqueness of an emergency case may pressure the neurosurgeon to perform the relatively unproven or innovative procedure. There is no standard within surgery regarding the extent to which a neurosurgeon should discuss the innovative nature of the procedure, the evidence or lack thereof; the associated risks and benefits, unforeseeable

or unknown risks given the experimental and non-validated nature of the procedure, the operating surgeon's learning curve considering his or her experience with the procedure, and alternatives treatment options.[7, 29] Furthermore, given that innovative approaches arguable confer a more extensive consent process, the relative lack of time or patient incompetence to make an autonomous decision may result in a relative lack of understanding and voluntariness.

Currently, operative innovation is not subject to any form of oversight or regulation and is treated as regular care, which may result in a relative lack of disclosure from the neurosurgeon or a form of oversight.[13, 29] This allows the neurosurgeon to innovate when this is deemed necessary to ensure an optimal outcome for a unique patient. However, neurosurgeons should realize that patients that are not able to provide consent in an emergency procedure might have refrained from surgery if they had known it to be innovative. This, therefore, requires a more extensive description of the procedure by the neurosurgeon postoperatively and a disclosure that the procedure was in fact innovative. This should, however, not result in neurosurgeons refraining from innovating in an emergency scenario when necessary.

Innovation may also take place in a research setting which requires specific informed consent. Informed consent in a research setting procedure requires understanding from the patient but also a voluntariness from the patient who will be exposed to potential unexpected outcomes. In some scenarios, e.g. where the patient is comatose, this understanding and voluntariness may be completely absent, and a surrogate decision-maker has to decide on the patient's behalf. One could, therefore, argue that these patients are not suitable research subjects. On the other hand, outcomes of future patients may only be improved through formal research and there may be no other ways investigate certain treatments. The Rescue ICP and RESCUE-ASDH trials demonstrates that formal research in incompetent patients in an emergency setting can be done safely and ethically.[16, 18, 20, 23] In England, a legal representative is allowed to provide consent for an incapacitated patient to participate in a trial.[22] Patients seem to be a survey showed that the vast majority of the public would find it acceptable if a surrogate or their next of kin provided consent for a trial in an emergency setting.[9]

Ethical care for emergency patients

We argue that greater awareness of the meaning and importance of autonomy as well as open communication between the patient and neurosurgeon will ensure that these scenarios are handled ethically. Here we outline several steps may be taken by all parties involved to achieve this involved in emergency neurosurgical care to achieve this in order of applicability.

A mandatory post-operative notification could be an additive to an incomplete informed consent procedure for an emergent case. The patient should be made aware of what the procedure entailed and what the reason was for choosing a particular procedure. This should ideally take place when the patient has recovered to a state that could be considered competent to make an autonomous decision. The representatives or family could be informed earlier if the patient remains cognitively impaired or needs extensive recovery. This encourages open communication between the patient

or the patient's family and the neurosurgeon after the procedure. The neurosurgeon should also explain why the informed consent procedure was completely or partially waived. We believe it is a professional obligation of the neurosurgeon to defend the course of action and discuss potential disagreement with the patient. Currently, it is customary for the neurosurgeon to talk to the patient and the family after surgery, especially if little time was available beforehand. Guidelines could help in this scenario by suggesting what should be communicated at a minimum.

Specific training for obtaining optimal informed consent in an emergency setting and communication with patients in emergency scenarios and afterwards could be included in the neurosurgical (ethics) curriculum. This training could focus not only on what to communicate, but also on how to honestly reflect expected outcomes, and how to encourage patients (and proxies) to express their wishes and values relevant to the decision-making process.

In addition, to create awareness and encourage advance directives, (potential) patients could be notified that the informed consent process may be partially or completely waived in an emergency situation. This could take the form of a notification in the emergency room or a brochure.[12] This notification could also state that the course of action will be explained to the patient afterwards. Such a notification has been implemented by the National Health Services (NHS) in the UK.[21] A downside to this approach is that patients may ignore this notification or that patients will only notice this notification when requiring emergency surgery. There may also be differences between different hospitals, language barriers, and an impossibility to reach all patients such as comatose patients. However, we believe that greater awareness among patients may stimulate them to discuss values and wishes with family and other potential surrogate decision-makers or even provide advance directives. This could result in patients that are more involved in the decision-making process in advance and fasten the decision-making process in possible future emergency scenarios as a result. This knowledge of wishes and values of the patient could improve respect for autonomy in future emergency scenarios.

On a policy level, surgical societies could engage with patient advocates and hospitals to come up with guidelines, statements, or a form of oversight for emergency surgery. These guidelines could reflect the difficulties that may arise and how these may be handled by neurosurgeons. These guidelines could also require neurosurgeons to be trained how to communicate in emergency situations. Communication outside an emergency setting between all parties involved could ensure a more ethical handling of emergency neurosurgery and respect for patient's autonomy. We believe that these policies could improve awareness among patients and could increase the trust patients place in neurosurgeons when they seek emergency care.

Conclusion

Emergency neurosurgery challenges the respect of autonomy of the patient. The emergent nature compromises the respect for autonomy due to a lack of time, especially if the patient lacks capacity to make an autonomous decision. The neurosurgeon needs to possess robust knowledge of the inherent risks and benefits of various emergency scenarios, excellent communication skills to balance the time allotted and

informed consent, and prowess to ethically handle disagreement. The situation may be improved by a post-operative notification, specific training of the neurosurgical team, and greater awareness among patients.

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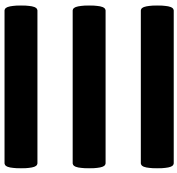

Part 3: Potential for future improvement of innovation in Neurosurgery

10

Innovation in Neurosurgery: less than IDEAL? - a systematic review

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Introduction*: Surgical innovation is different from introduction of novel pharmaceuticals. To help address this, the IDEAL Collaboration (Idea, Development, Exploration, Assessment, Long-term follow-up) introduced in 2009 the five-stage framework for surgical innovation. To evaluate framework feasibility for novel neurosurgical procedure introduction, two innovative surgical procedures were examined: endoscopic endonasal approach for skull base meningiomas (EEMS) and the WovenEndobridge (WEB device) for endovascular treatment of intracranial aneurysms.* ***Methods****: The published literature on EEMS and WEB devices was systematically reviewed. Identified studies were classified according to the IDEAL framework stage. Next, studies were evaluated for possible categorization according to the IDEAL framework.* ***Results****: 576 papers describing EEMS were identified of which 26 papers were included. No prospective studies were identified and no studies reported on ethical approval or patient informed consent for the innovative procedure. Therefore, no clinical studies could be categorized according to the IDEAL Framework. For WEB devices, 6229 articles were screened of which 21 were included. In contrast to EEMS, two studies were categorized as 2a and two as 2b.* ***Conclusions****: 576 papers describing EEMS were identified*

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of which 26 papers were included. No prospective studies were identified and no studies reported on ethical approval or patient informed consent for the innovative procedure. Therefore, no clinical studies could be categorized according to the IDEAL Framework. For WEB devices, 6229 articles were screened of which 21 were included. In contrast to EEMS, two studies were categorized as 2a and two as 2b.

Introduction

Today, it is unusual to perform neurosurgical procedures in most countries without access to an operative microscope, state of the art neuro-navigational systems, or even hemostatic agents such as a bipolar electrocautery device. In fact, technological innovation has been the hallmark of neurosurgery, and the vast majority of procedures that are currently considered routine would not be possible at all without innovation. However, not all innovation is an improvement over the technology it seeks to supplant. Evidence of patient outcome superiority is often lacking or nonexistent in the real-time of innovation. In neurosurgical disease, low incidence and high burden may further hinder systematic evaluation of any new technique. Regardless of these difficulties, it is vital that new technology and procedures undergo a strategic and ethical clinical introduction.[1] As surgical innovation does not typically follow the same introductory path as novel pharmaceuticals, the IDEAL Collaboration, formed by surgeons and methodologists, introduced the IDEAL (Idea, Development, Exploration, Assessment, Long-term follow-up) framework in 2009 and have published several updates since.[2-6] The goal of the collaboration is to improve surgical research, especially research surrounding innovation, and to overcome obstacles and methodological problems inherent to surgery.[2,7]

The IDEAL framework describes five stages through which interventional therapeutic innovations typically pass, together with the characteristics and study design of each stage (**Table 10.1**, adapted from McCulloch et al.).[2-6] Any study involving non-human pre-clinical assessment of a novel technique, including simulator or animal studies, is regarded as stage 0. Stage one describes a proof-of-concept study in the first human patient. Stage 2a consists of a prospective study in up to thirty patients conducted by surgeons responsible for the earlier stage(s). Involving surgeons with no prior experience in a larger prospective study usually takes place in stage 2b to assess learning curve and further develop the procedure. In stage 3, the procedure should be stable and is investigated in a randomized controlled trial (RCT) that compares outcomes of the innovative procedure with the gold standard. Assessment of rare and long-term outcomes takes place in stage 4 (**Table 10.1**).[2,7]

To assess whether the IDEAL framework has been used two different neurosurgical procedures were evaluated: endoscopic endonasal approach for skull base meningiomas (EEMS) and the use of Woven Endobridge (WEB device, ©Sequent Medical) for endovascular treatment of intracranial aneurysms. Traditionally, skull base meningiomas are resected using an open transcranial microscopic approach.[8] However, recently, EEMS has been introduced and has gained some traction in neurosurgical literature.[8] The WEB device is a new option for intracranial aneurysm-treatment, consisting of an unfoldable, detachable metallic mesh that is placed into the aneurysm neck leading to flow disruption.[9] The WEB device was especially de-

veloped for bifurcation and wide neck aneurysms as an alternative to traditional clipping or coiling.[9] Since the two innovations, one a device and the other a procedure, are used in different fields of neurosurgery and were recently introduced, we chose these two as examples for neurosurgical innovations in general.

In this review, published literature on these two procedures was evaluated to assess whether they were introduced according to the stages of the IDEAL framework.

Table 10.1: The IDEAL Framework

	1: Idea	2a: Development	2b: Exploration	3: Assessment	4: Long-term study
Purpose	Proof of concept	Development	Learning	Assessment	Surveillance
Number and types of patients	Single digit, Highly selected	Few; selected	Many; may expand to mixed; broadening indication	Many; expanded indications	All eligible
Number and types of surgeons	Very few; innovators	Few; innovators and some early adaptors	Many; innovators, early adaptors, early majority	Many; early majority	All eligible
Output	Description	Description	Measurement; comparison	Comparison; Complete information for non RCT participants	Description; audit; regional variation; quality assurance; risk adjustment
Intervention	Evolving: procedure inception	Evolving; procedure development	Evolving; procedure refinement; community learning	Stable	Stable
Method	Structured case reports	Prospective development studies	Research database; explanatory or feasibility RCT	RCT with or without additions/modifications; alternative designs	Registry; routine database; rare-case reports
Outcomes	Proof of concept; technical achievement; Disasters; dramatic successes	Mainly safety; technical and procedural success	Safety; clinical outcomes; short-term outcomes; patient centered outcomes feasibility outcomes	Clinical outcomes; middle-term and long-term outcomes; patient-centered outcomes; cost-effectiveness	Rare events; long-term outcomes; quality assurance
Ethical approval	Sometimes	Yes	Yes	Yes	No

Adopted from McCulloch (2009)[2]

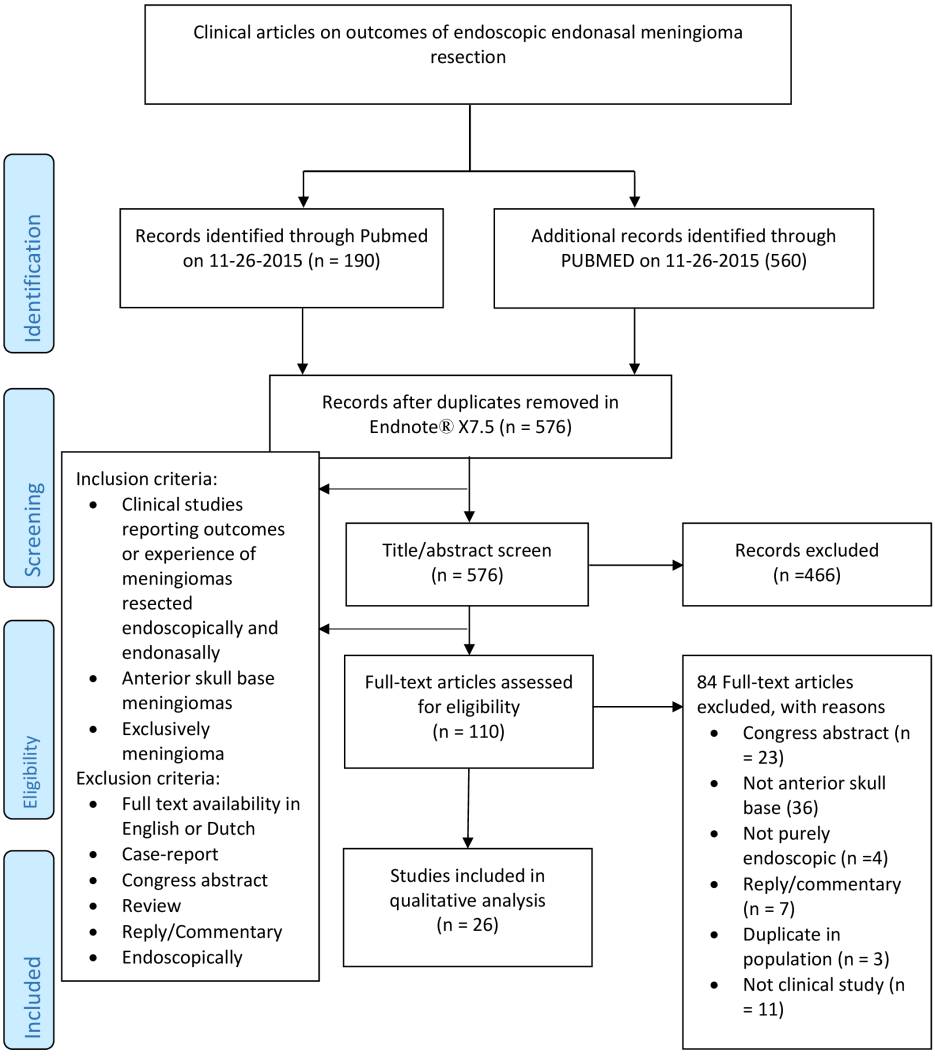
Methods

Search strategy and paper selection

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[10] The literature search for EEMS was conducted in PubMed and Embase up to 11-26-2015, using the following keywords: endoscopy, neurosurgery, endo- and transnasal and meningioma. search strategy provided in Supplemental Table 10.4 and 10.5. This search strategy resulted in 576 unique papers. In addition, bibliographies of included papers were screened for relevant papers. For WEB devices, a search was conducted in the same search engines on 05-29-2016 using the keywords: WEB device, endovascular treatment, intracranial aneurysm as depicted in Supplemental Digital Content Table 1b. This resulted in 6229 articles. These papers were supplemented by hand searching of the bibliographies of the papers retrieved by the electronic search. This review was restricted to published data. Only papers written in English, Dutch, French, or German were considered for this review. The search was not limited by date of publication. Titles and abstracts of retrieved citations were screened by two authors, and

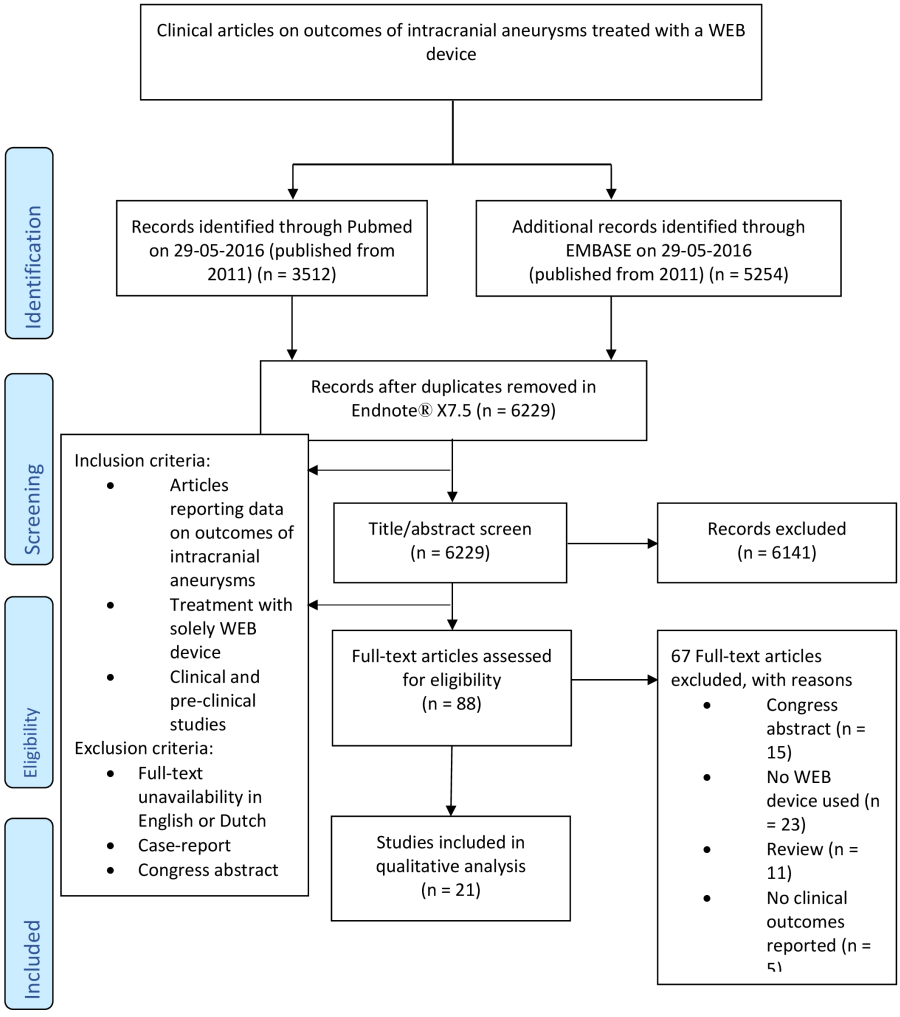
potentially suitable studies for EEMS were read in full by IM and SD and for WEB device by IM and JS. We included papers that solely focused on EEMS as depicted in **Figure 10.1**.[10] For WEB devices we included papers reporting outcomes of treated aneurysms as described in **Figure 10.2**.[10] Disagreements were solved by reviewer consensus.

Figure 10.1: Flowchart



Flowchart of study selection process of included articles on endoscopic endonasal meningioma resection*

Figure 10.2: Flowchart



Flowchart of study selection process of included articles on WEB device

Study assessment

Relevant studies were reviewed full text to determine if a study could be classified according to an IDEAL stage by two authors (IM SD for EEMS and IM JS for WEB devices).[2] The following criteria were used to classify studies according to the five stages. Pre-clinical studies were classified as stage 0 and proof of principal in 1 patient was regarded as stage 1 if informed consent had been obtained.2 Studies were classified as stage 2 if ethical approval for a prospective study and informed consent for an innovative procedure from included patients had been obtained. Studies with up to 20 patients were classified as stage 2a, and those with more than 20 patients as stage

2b. Studies that compared EEMS or WEB devices with the current gold standard in a prospective fashion were regarded as stage 3. As an RCT may not have been feasible for ethical or pragmatic reasons, we also evaluated studies with different designs.[3,4]. Long term follow-up studies were categorized as stage 4. In addition to study design, ethical approval and informed consent, all studies were evaluated for reporting surgical or radiological outcomes for EEMS and WEB devices studies, respectively. Disagreements were solved by consensus discussion.

Results

For For EEMS, 576 abstracts and titles were screened, 110 were examined full-text and 26 papers were included (**Figure 10.1**).[11-36] Two cadaveric studies were categorized as stage 0.[11,12] No studies were categorized as stage 2, as none of the included studies reported outcomes of a prospective study with adequate informed consent.[13-36] Even though four studies compared EEMS with an open transcranial approach, they did not do this in a prospective fashion and no RCTs could be identified.[14,17,18,27] Furthermore, there were no studies that examined long-term outcomes and therefore no studies were categorized as stage 4 (Table **Table 10.2**). All other studies could not be categorized into an IDEAL stage.

For WEB devices 6229 abstracts and titles were screened, 88 articles were examined full-text and 21 papers were included (**Figure 10.2**).[9,37-56] preclinical studies using rabbit models were classified as stage 0.[37,38] One study that acquired informed consent for treatment of two patients was categorized as stage 1, but did not describe the clinical problem that needed a solution.[9] Two studies with ethical approval for a prospective study and informed consent of included patients, were categorized as stage 2a.[39,57] The studies with larger populations that reported the outcomes of the WEBCAST trial and the French observatory trial were categorized as stage 2b.[53,54] All other studies could not be categorized into an IDEAL stage and no studies were categorized as stage 3 or 4 as no comparison was made with other treatment modalities and no long-term outcomes were evaluated (**Table 10.3**).

Discussion

The results of this systematic review demonstrate that both the endoscopic endonasal transsphenoidal approach for resection* of skull base meningiomas and WEB devices were not introduced according to the IDEAL Framework. Not only could not all IDEAL framework stages be identified, some of the early pre-clinical studies (stage 0) were performed long after the description of the first-in-man studies (for EEMS) or after publication of prospective studies (WEB devices).[11,12,37,38] Perhaps unsurprisingly, only five clinical studies could be categorized into an IDEAL stage. WEB device studies followed the IDEAL Framework more closely than EEMS, but only up to stage 2b.[9,39,50,53,54] In addition, only six WEB device studies acquired ethical approval for a prospective study in line with the IDEAL framework.[39,45,50,51,53,58] No study reported patient selection for EEMS compared to five WEB device studies.[45,47,50,53,54] Furthermore, no studies were categorized as stage 3 as no clinical study (of either procedure) was a prospective comparison with

Table 10.2: IDEAL Framework recommendations and Endoscopic Endonasal Meningioma Surgery

Author (year of publication)	**participants (N=)**	**Ethical approval for prospective study**	**Informed consent for innovative procedure**	**Described surgical outcome**	**Randomized controlled trial**	**Awarded IDEAL stage**
Cavallo et al. (2005)	0	NA	NA	NA	NA	0
Jacquesson et al. (2015)	0	NA	NA	NA	NA	0
Alexander et al. (2010)	1	N	N	Y	N	None
Bowers et al. (2011)	27	N	N	Y	N	None
Chowdhury et al. (2012)	6	N	N	Y	N	None
Cook et al. (2004)	3	N	N	Y	N	None
De Almeida et al. (2015)	20	N	N	Y	N	None
De Divitiis et al. (2008)	51	N	N	Y	N	None
De Divitiis et al. (2008)	11	N	N	Y	N	None
Fernadez-Miranda et al. (2012)	1	N	N	Y	N	None
Gadgil et al. (2013)	5	N	N	Y	N	None
Gardner et al. (2008)	35	N	N	Y	N	None
Julian et al. (2014)	1	N	N	Y	N	None
Khan et al. (2014)	46	N	N	Y	N	None
Koutourousiou (2014)	75	N	N	Y	N	None
Koutourousiou (2014)	50	N	N	Y	N	None
Mortazavi et al. (2015)	27	N	N	Y	N	None
Ogawa et al. (2012)	19	N	N	Y	N	None
Ottenhausen et al. (2014)	20	N	N	Y	N	None
Padhye et al. (2012)	15	N	N	Y	N	None
Prevedello et al. (2007)	1	N	N	Y	N	None
Van Gompel et al. (2011)	13	N	N	Y	N	None
Wang et al. (2009)	7	N	N	Y	N	None
Wang et al. (2010)	12	N	N	Y	N	None
Wang et al. (2015)	1	N	N	Y	N	None
Webb-Myers et al. (2008)	1	N	N	Y	N	None

Legend:The Y (Yes) means the study meets the IDEAL framework recommendations.The N (No) means the study did not meet the IDEAL framework recommendations, NA: Not applicable

Table 10.3: IDEAL Framework recommendations and the WEB device

Author (year of publication)	**Participants (N=)**	**Ethical approval for prospective study**	**Informed consent for innovative procedure**	**Described radiological outcome**	**Randomized controlled trial**	**Awarded IDEAL stage**
Ding et al. (2011)	24 (rabbits)	NA	NA	NA	N	0
Rouchaud et al. (2016)	80 (rabbits)	NA	NA	NA	N	0
Ambrosi et al. (2015)	10	Y	Y	Y	N	2a
Behme et al. (2015)	52	N	N	Y	N	None
Caroff et al. (2014)	6	N	N	Y	N	None
Caroff et al. (2015)	98	N	N	Y	N	None
Clajus et al. (2016)	108	N	Y*	Y	N	None
Colla et al. (2013)	4	N	N	Y	N	None
Gherasim et al. (2015)	10	Y	N	Y	N	None
Kabbasch et al. (2016)	43	N	N	Y	N	None
Klisch et al. (2011)	2	N	Y	Y	N	1
Lawson et al. (2016)	23	N	N	Y	N	None
Lescher et al. (2016)	22	N	N	Y	N	None
Liebig et al. (2015)	47	N	N	Y	N	None
Lubicz et al. (2013)	19	Y	Y	Y	N	2a
Papagiannaki et al. (2014)	83	Y	N	Y	N	None
Pierot et al. (2013)	33	N	N	Y	N	None
Pierot et al. (2015)	45	N	N	Y	N	None
Pierot et al. (2016)	51	Y	Y	Y	N	2b
Pierot et al. (2016)	62	Y	Y	Y	N	2b
Van Rooij et al. (2016)	32	N	N	Y	N	None

Legend:The Y (Yes) - symbol means the study met the IDEAL framework recommendations.
The N (No) - symbol means the study did not meet the IDEAL framework recommendations.
*Informed consent was only obtained in cognitively intact patients

the gold standard or was an RCT.

We believe that this is not unique to these two procedures specifically, or to neurosurgery in general. For instance, a study investigating literature on laparoscopic colonic polyp resection* found that its introduction into widespread use also did not follow the stages and recommendations of the IDEAL framework.[59]

The introduction of novel neurosurgical techniques that result in a paradigm

change, i.e. the first endovascular treatment of aneurysms, could be introduced according to some predefined framework such as IDEAL. However, in reality, novel surgical techniques are often the result of small stepwise changes to existing approaches (e.g. EEMS and the transcranial approach to pituitary adenomas). This makes it challenging to introduce innovations as EEMS according to all requirements of the IDEAL framework. Adherence to the IDEAL framework might not only be challenging because of small stepwise changes of existing approaches but also because of a lack of a universally accepted definition of neurosurgical innovation in general.

A major change in endonasal surgery was the introduction of the endoscope, in particular for pituitary adenomas.[60] With expansion of endoscopic technique and experience, a wider spectrum of tumors became resectable through the endonasal approach. However, in retrospect, one could argue that EEMS is indeed a valuable alternative to a classic craniotomy for specific indications.

The WEB device is also example of expanding endovascular experience, and because of new endovascular devices a wider array of pathologies is treatable. Compared to EEMS, WEB devices were studied in a prospective fashion with patient informed consent.[39,50,53,54] However, the WEB device is already used clinically despite lack of comparison with other treatment options (a stage 3 study).[42,43,56] The important question is whether this new technique could have been rigorously compared to established techniques prior to wide-spread adoption.

Overall, this review suggests that neurosurgical innovation (at least for the two procedures evaluated here) has not historically followed the IDEAL framework. On the one hand, this could simply be caused by a lack of awareness of the framework. On the other hand, a different distinct possibility for this could be related to feasibility. The IDEAL collaboration recognizes that, in order to improve the quantity and quality of surgical research, these proposals/recommendations would have to be practical and adapted to the process of innovation.[2] Indeed, the IDEAL Collaboration supports several recommendations for specific (alternative) study designs and reporting standards at different stages of the framework.[2-4] These alternatives could contribute to the quantity and quality of neurosurgical research.

At the innovation stage (stage 1), the recommendations include online registries for first-in-man innovations. No reports on the entry of a study in a registry were found in our review. Often in neurosurgery innovations take place in an acute setting, and only in retrospect is there clarity with regards to the innovation itself. However, it is possible that future innovations could be entered in a registry, especially in the case of new devices like the WEB device. Registries could help reduce positive reporting bias inherent to new innovations. Reports of both successes and failures of new technology are useful for ethical innovation.[61]

At the second development stage recommendations include: prospective development studies, protocol and study registries for prospective development studies in surgery and development of agreed reporting standards and definitions for key outcomes.[2,7] These recommendations were not met for the introduction of EEMS and by only four studies for WEB devices.[39,50,53,54]

Again, not all of these recommendations may be possible in neurosurgery. However, protocol and prospective study registries are feasible in the neurosurgical field,

and could help ensure that clinical results of all patients are transparent and methodologically sound. Furthermore, novel techniques could be reported using professionally accepted reporting guidelines for prospective (and if inapplicable, retrospective) studies that favor clear interpretation of the study design and study results. Also, open comparison of individual studies and applicability of the reported outcomes would be useful. Key, patient-centered, outcomes for various pathologies result in research with comparable and clinically meaningful results.

All studies described the surgical outcomes, and this is outstanding. One next step could be to unify informed consent and outcomes reporting, which should include both positive and negative findings, for emerging innovative procedures. Furthermore, one could argue this process should be done in a more uniform manner across the neurosurgical field. One method might be the use of centralized regulation as seen with medical device approval by the Food and Drug Administration (FDA).[62,63] Alternatively, institutions or neurosurgical societies could create guidelines for reporting of trial registration, prospective design, and patient registries, effectively following the IDEAL framework to a certain extent.[5] Nevertheless, informed consent and ethical approval for a prospective study is, we believe, something that should always be feasible when evaluation a new neurosurgical procedure.

No prospective randomized studies or RCTs, the 'default option' at the third or exploration stage of the IDEAL framework, were identified.[2] This may be one area of the IDEAL framework that is not completely feasible in all types of neurosurgical innovation. As discussed, innovation occurs by incremental but gradual changes over a prolonged period of time, and an RCT may not be the preferred study design for numerous reasons: 1) It is ethically challenging and practically impossible to compare EEMS to an open approach as the endonasal approach is not applicable to all patients; 2) The number of patients with skull base meningiomas is relatively small, which makes it difficult to recruit enough patients for proper statistical analyses; 3) The difference in outcomes between an open and endonasal approach might be small and therefore difficult to prove, especially with point 2 in mind; 4) There could be a lack of clinical equipoise; 5) Surgeons might not be willing to participate because of personal treatment preference or experience;[64] 6) Surgeons have different skill levels; 7) The location, extend and size of meningiomas varies, complicating inter-patient comparability and randomization, again complicated by point 3; 8) Concomitant factors can change during the trial, e.g. innovation in anesthesiology and perioperative care;[65,66] 9) Improvement of endoscopic endonasal meningioma surgery is a constantly evolving process with differences in every center, which contributes to the often reported difficulty in standardization for innovative surgical procedures, it is inefficient to conduct a RCT for every incremental technological advance, and the incidence of these lesions is quite low.[66] For these reasons, a "classical" RCT in low-volume-highly-complex-cases as with skull base meningioma resection*s or similar procedures might not be feasible. However, the IDEAL collaboration endorses various alternatives to this trial design at the third stage. These include case-matching studies and controlled interrupted-time series designs, but also modified RCTs with Baysean modifications to recruitment, randomization, or analysis.[2] These study designs might be useful in neurosurgical innovation. Espe-

cially the introduction of prospective research databases and collaborative studies, endorsed by the IDEAL collaboration, seem valuable for low-volume-highly-complex surgeries as skull base meningioma resections. Also, the recommended additions to the RCTs that include learning curve evaluation, quality control and compliance measures, could be feasible and helpful for innovations as EEMS.

Even though an RCT for WEB devices could be challenging, especially because of the above-mentioned reasons 3-9, an RCT is possible and could have been conducted prior to wide-spread European adoption.[9] However, in the absence of a traditional RCT, a Baysian RCT, or registry could have also been helpful to establish its efficacy and safety. In fact, application of all stages of the IDEAL framework in a more strategic fashion could be possible in technological innovations like the WEB device. To date, the WEB device appears to be efficacious and safe, but a more rigorous and transparent process for introduction of this type of technology could potentially help prevent deleterious outcomes, as seen with the Poly Implant Prothèse (PIP) breast implants and metal-on-metal hip prostheses.[67-69] Currently, proof of safety and efficacy is required by the FDA for Class III devices (the most invasive devices), but this is not standardized.[62,63] Therefore, a change in regulation that results in a closer adherence to the IDEAL framework could lead to a more uniform implementation.[5] At the fourth or long-term study stage, the emphasis is on rare and long-term outcomes. We did not identify any (stage 4) studies reporting long term outcomes of EEMS or WEB devices. We believe that in addition to a closer adherence to the 'IDEA' part of the IDEAL framework, attention for the long-term outcomes of innovations such as EEMS or WEB devices would greatly benefit innovation in neurosurgery. Registries are an appropriate study design for this purpose, although representativeness of the data is a potential limitation. Efforts made to ensure that data entry is complete helps strengthen the representativeness of the registry.[2] Reporting fatigue can compromise comprehensive data collection, and therefore, the development of concentrated, outcome relevant registries are optimal. Also, the use of registries with patient informed consent for surveillance of specific established techniques in neurosurgery is desirable, especially for use of new materials like the WEB device. In general, innovation in low-volume-highly-complex (neuro)surgical cases might benefit from alternatives to traditional RCTs. For example, in a "cohort multiple RCT" some, but not all, patients are randomly assigned to a specific treatment and are followed-up regularly over time, blending a RCT with a observational study with some of their respective benefits.[70-72] A potential stage 3 study on a low-volume-highly-complex surgical innovation could include the following: 1) patient informed consent; 2) ethical approval; 3) strict definition (and registration) of indications for treatment 4) prospective observational design; 5) registration in a trial registry; 6) random allocation of a standard treatment group or the well-defined innovative procedure; 7) regular follow-up on relevant outcomes to patients; 8) reporting of all outcomes and 9) collaboration of multiple centers.

This, however, does not address the issue of which innovative procedures merit such a study. "Big data" could fill the gap with regards to identification of trial-worthy innovations. The use of the electronic medical record, the digitization of patient outcomes, and the computational capacity now available to the typical researcher,

has opened the door detailed and comprehensive analysis of pre-trial data. Indeed, these types of large data sets could become a new level of evidence in and of itself, if an RCT is not feasible.[73]

Conclusion

The introduction of EEMS and WEB devices did not follow the stages as described by the IDEAL framework. The introduction of WEB devices followed the IDEAL Framework more closely, but only up to stage 2b. We believe this is not unique to neurosurgery or to these techniques, and it simply may not be feasible to follow this framework in its current iteration for all types of innovation. Despite this, informed consent, ethical approval, and rigorous outcomes reporting are important elements of the IDEAL framework which could serve to improve the quality of both experimental and alternative neurosurgical study designs. Alternatives to traditional RCTs and the use of "big data" could be useful modifications of the IDEAL framework. We believe that neurosurgical innovation and research could be improved by following a framework such as (a modified version of) IDEAL. This would improve evidence-based practice and potentially patient outcomes. After all, methodologically sound prospective studies, which require informed consent, ethical approval, and equipoise, are feasible in neurosurgery.

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Table 10.4: Search strategy for endonasal meningioma resection*

PubMed	((endoscopic*[Title/Abstract]) OR endoscopy[MeSH Terms]) AND ((((neurosurg*[Title/Abstract]) OR surg*[Title/Abstract]) OR Neurosurgical Procedures[MeSH Terms]) OR neurosurgery[MeSH Terms]) AND (((endonasal*[Title/Abstract]) OR transnasal*[Title/Abstract]) OR transsphenoidal*[Title/Abstract]) AND ((meningiom*[Title/Abstract]) OR meningioma[MeSH Terms]))
Embase	('endoscopy'/exp OR endoscop*:ab,ti) AND ('neurosurgery'/exp OR neurosurg*:ab,ti OR surg*:ab,ti) AND (endonasal*:ab,ti OR transnasal*:ab,ti OR transsphenoidal*:ab,ti) AND ('meningioma'/exp OR meningi*:ab,ti)

Table 10.5: Search strategy for WEB devices

PubMed	Search (((((WEB[Title/Abstract]) OR Woven Endobridge[Title/Abstract])) OR ((((("Endovascular Procedures"[Majr:NoExp]) OR "Embolization, Therapeutic"[Majr:NoExp])) OR ((((endovascular[Title/Abstract]) OR intravascular[Title/Abstract])) AND (((((((technique*[Title/Abstract]) OR procedur*[Title/Abstract]) OR treatment[Title/Abstract]) OR surgery[Title/Abstract]) OR therapy[Title/Abstract]) OR flow disrupt*[Title/Abstract]) OR Embolization[Title/Abstract])))))) AND ((((((aneurism*[Title/Abstract]) OR aneurysm*[Title/Abstract])) AND ((((((cerebral[Title/Abstract]) OR ruptured[Title/Abstract]) OR unruptured[Title/Abstract]) OR brain[Title/Abstract]) OR intracranial[Title/Abstract]))) OR intracranial aneurysm[MeSH Terms]) Filters:Publication date from 2011/01/01 to 2017/01/01
Embase	(('web':ab,ti OR 'woven endobridge':ab,ti) OR ((endovascular:ab,ti OR intravascular:ab,ti) AND (technique*:ab,ti OR procedur*:ab,ti OR treatment:ab,ti OR surgery:ab,ti OR therapy:ab,ti)) OR ('endovascular aneurysm repair'/exp OR 'neurovascular embolization device'/exp OR 'device embolization'/exp OR 'artificial embolism'/exp)) ->8 AND (((aneurism*:ab,ti OR aneurysm*:ab,ti) AND (cerebral:ab,ti OR ruptured:ab,ti OR unruptured:ab,ti OR brain:ab,ti OR intracranial:ab,ti)) OR 'brain artery aneurysm'/exp OR 'intracranial aneurysm'/exp) AND [embase]/lim AND [2011-2016]/py

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Learning health systems for innovative neurosurgery – an ethical obligation?

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Introduction

Neurosurgical innovation and continuous evaluation and improvement of neurosurgical procedures are essential to ensure the best level of care for current and future patients. This however, poses a challenge to current neurosurgical practice, as the use of powerful research designs, such as the randomized controlled trial (RCT) are often infeasible for procedures that are now widely considered to be effective.[4,20] This stresses the need for alternative methods to evaluate and compare the efficacy of novel and existing neurosurgical procedures.

In 2007, the Institute of Medicine – an American institution that provides independent analysis and advice in complex problems related to medicine – proposed the learning health systems (LHS), health care systems in which "knowledge generation is so embedded into the practice of medicine that it is the natural outgrowth

This paper is currently under review

and product of the healthcare delivery process and leads to the continuous improvement of care".[22,2] Key components of the LHS include the search for alternatives to the RCT, implementation of system databases and universal electronic health records, and increasing public and professional understanding of the nature of evidence-based medicine. Whereas LHS aim to facilitate continuous learning activities by integrating clinical research and clinical care, some have noted that too much focus on learning may conflict with a patient's best interests.[2] In this opinionated piece, we discuss how the LHS and associated ethics framework could improve the evaluation of novel and existing neurosurgical procedures, while minimizing potential risks associated with blurring the traditional boundaries between research and care.

Learning health systems in innovative neurosurgery

Alternative trial design

The randomized controlled trial (RCT) is widely regarded as the most powerful research design, and in an ideal world, all neurosurgical trials would be conducted with a form of randomization.[29] In contrast to the introduction of novel pharmaceuticals, however, novel neurosurgical procedures often develop gradually, resulting from an accumulation of minor changes to an established procedure, which are then identified as "novel" in retrospect.[21] For example, endonasal endoscopic pituitary resection* could be seen as a procedure that gradually evolved from microscopic resection*, rather than as a complete new entity.[13] This gradual development often results in "believers", who early adopt the novel procedure, and "sceptics", who will adopt the novel procedure once the long-term outcomes have become available. This may be the reason that endonasal resection* has replaced microscopic resection* in most centers, but not everywhere. Also, many novel neurosurgical procedures are not systematically evaluated during the early developmental stages, which results in a lack of robust evidence, further fueling the debate.[21] Early believers may find it unethical to expose their patients to the shortcomings of the traditional standard of care, whereas the sceptics do not want to expose their patients to potential detrimental complications. Due to this perceived lack of clinical equipoise, it is often very challenging to start an RCT.

From an LHS perspective, several alternatives have been proposed to the randomized controlled study design to evaluate clinical care and innovation, including the cluster randomized trial (CRT).[22] CRTs do not require randomization at patient level but allow participating institutions to perform their preferred standard of care, enabling comparison of practices between different centers. Despite its advantages, a CRT may not to be as effective as an RCT as far greater numbers of patients are required. In addition, centers participating in the CRT would, ultimately, have to change their practice to the superior practice identified at another center at some point.

Another alternative to the RCT is comparative effectiveness research (CER), which allows for the evaluation of chain care to identify superior strategies with regard to patient outcome.[19] Non-experimental CER uses variability in treatment for comparison in real-world conditions and is increasingly used in medicine to compare the

outcomes of different treatments. Examples include the ongoing CENTER-TBI study and a UK trauma registry study that demonstrated the effectiveness of managing patients with severe TBI in neurosurgical centres.[24,19] Pragmatic randomized trials offer another potentially important methodological approach to CER (so-called experimental CER). Probably the most attractive attribute of pragmatic randomized trials is that they aim to balance internal validity and external generalizability, whilst at the same time maintaining the benefits of randomization. An example is the acute subdural hematoma (RESCUE-ASDH) trial.[10]

The above-mentioned research designs may allow neurosurgeons to continue improving their practice and procedures without implementing changes that would have been imposed by an RCT. This makes the perceived lack of clinical equipoise less of a challenge. Naturally, the CER study design has several limitations as it strongly depends on outcomes that are deemed relevant and robust statistical techniques in order to deal with the bias that arises from the absence of randomization. Moreover, there is currently little experience with these research designs in neurosurgery. Nevertheless, it seems preferable to supplement evidence from RCTs with high-quality nonrandomized studies.[22] Therefore, these alternatives could improve evidence-based neurosurgical care but warrant more experience.

Structured data sharing and collection

All potential innovations in neurosurgery require extensive evaluation based on valid data. Despite the variability inherent to many neurosurgical procedures, there is, of yet, no method to systematically register surgical details and patient outcomes for inter-surgeon and inter-center comparisons. Adequate registration and sharing of this data would potentially enhance the generation of evidence by comparative effectiveness research. In addition, ethical problems may arise when research findings are not shared among institutions. For instance, the beneficial results following a minor adaptation to an established procedure may just be verbally transmitted among neurosurgeons within the same institution, without providing the results to the international neurosurgical community, potentially leading to an unjust distribution of beneficial findings. This is especially true for negative research findings, which are often not published (also known as publication bias).[30]

The LHS fosters the implementation of large system databases and universal electronic health records, thereby providing a platform for continuous learning based on clinical decision-making. The LHS regards data as public domain and a central source for advancing knowledge and care. For neurosurgery, this could include systematic registration of information relevant to neurosurgery such as presenting neurological symptoms, imaging details, tumor-related factors, surgical details, complications, costs associated with care, and patient reported outcome measures. Several efforts to share data generated during neurosurgical practice have been made.[12,23,6,28,27] The resulting databases, however, significantly vary in the variables collected, collectors, reliability, and completeness of data, and miss disease-specific variables relevant to neurosurgery.[12] As a result, these datasets currently do not allow for evaluation of learning curves or comparison between different centers, stressing the need for continuous improvement of data registration and sharing to provide valuable insights

that might benefit patients. Nevertheless, differences in outcomes between different institutions can sometimes be evaluated through databases that do not primarily collect neurosurgical data as seen with data from the Trauma Audit and Research Network that was evaluated for traumatic brain injury.[17] One major issue in routine data registration and sharing is that patients have to be informed that they are part of a system in which their data are routinely collected and learned from, and that they consent to this. This makes patient engagement is essential in an LHS.[5]

Patient participation

It can be ethically sensitive to obtain informed consent for data registries[11], which would requires full disclosure, a patient that is capable to make autonomous decisions, and voluntariness.[1] Patients and neurosurgeons may be compelled to do whatever it takes to prolong survival and palliate suffering and may stimulate patient patients to consent to participating in a research activity. The informed consent process may further be complicated when the disease affects the decision-making capacity of the patient, as frequently seen in glioma patients.[8] Neurosurgery is also a highly specialized discipline that is culturally surrounded by prestige.[8] This may give rise to a form of self-coercion, where patients choose to participate in a research activity because they think their doctor believes it is in their best interest.[3] Patients participating in clinical research often misconceive a research activity to be a form of clinical care tailored to their individual medical needs (the so-called "therapeutic misconception").[18] Patients may expect to receive certain benefits from participating in a trial or an observational treatment comparison, while only future patients are likely to experience benefit.[14] The neurosurgeon may also not be aware that an adjustment of a procedure to a patient's specific needs may be considered research by others which further complicates this misconception. The overly optimistic expectancy of a certain research activity is particularly prevalent in neurosurgical innovation, where media reports are generally biased towards success stories, rather than the potential risks involved.[8,25] The opposite may also occur when doctors overemphasize the potential risks associated with a research activity to counteract a patient's optimistic expectations.

The LHS may help to overcome these challenges by "improving public understanding of the nature of evidence-based medicine and the importance of supporting progress toward medical care that reflects the best evidence".[22] Increased public awareness of the nature of evidence-based medicine could potentially lessen the "therapeutic misconception" and smoothen the informed consent process, as informed patients would be able to take a general stance toward participating in research activities before the circumstances arise. Communication to the public is of special importance because the introduction of an LHS is not possible without the trust of patients and referrers, especially when it would mean that patients also have obligations to contribute to improving the quality of care, and cannot always dissent to participation (for instance to be part of a registry).[7,26] In addition, the LHS encourages health care workers to adopt an open attitude towards evidence generation and self-reflection, thereby minimizing the influence of personal interests on the informed consent procedure.

Discussion

Although the LHS may provide a promising way to facilitate neurosurgical innovation and the continuous evaluation of neurosurgical procedures, neurosurgeons should be aware that tempering the traditional divide between clinical research and clinical care may give rise to ethical challenges. Over the last few decades, clinical care and clinical research have been strictly separated.[14] Due to its aim to create generalizable knowledge, research is generally not aiming to benefit a specific individual, and therefore requires specific ethical consideration and regulation in order to prevent individual patients from being exposed to disproportionate risks. To bridge the traditional divide between clinical and research ethics, a new ethics framework has been proposed by Faden and colleagues.[7] The framework aims to stimulate the transformation to an LHS, while ensuring that learning activities within such system are conducted in an ethically appropriate manner. Importantly, it rejects the notion that clinical research and care are ethically distinct entities, and instead provides a set of moral obligations to guide ethically sound research conducted within an LHS.[7,14] This set of moral obligations significantly departs from traditional bioethics in two ways: it places a moral emphasis on learning for both healthcare professionals and patients, even though some have argued that a moral obligation to patients may be problematic.[15] In addition, the framework sets a moral obligation to address unjust distribution of (research) burdens within the healthcare system.[7]

Even though some regard the lack of regular evaluation of (standard) care as a potential hazard to patients, [7] an LHS may entail the risk of placing too much focus on innovation instead of ensuring patients' safety and autonomy. The moral obligation to learning includes both patients and healthcare professionals and holds that everyone involved in healthcare – both on the receiving and the providing end – has the moral responsibility to contribute to learning activities in order to enhance clinical practice "or the value, quality, or efficiency of the systems, institutions, and modalities through which health care services are provided" to the benefit of future patients.[7]

This approach may somewhat temper traditional guidelines of ethical oversight and consent, thereby stimulating continuous learning activities to take place through the implementation of large system databases and data sharing. In addition, active engagement with full disclosure from the neurosurgical community is necessary to respect the autonomy of patients. This could be achieved through a partially standardized disclosure and patient education to make patients active participants in the improvement process. This would require a culture of transparency, open communication, and active engagement towards patients to ensure patients continue to place their trust with the neurosurgeon.

The moral obligation to address unjust inequalities, proposed by Faden et al., may also help to overcome some of the other challenges of evaluating neurosurgical procedures, namely vulnerability and injustice. Neurosurgeons should realize their responsibility to assess whether risks and burdens of a learning activity fall disproportionally on patients that are already disadvantaged.[7] For instance, brain tumor patients that have to undergo a resection* are particularly vulnerable due to the severity and nature of the disease and treatment. The obligation to justice will help to ensure that the burdens of a learning activity will be fairly distributed among these patients, rather

than placing the burden primarily on the most desperate and refractory individuals.[8] Moreover, the obligation to justice also holds that the learning activity will not disproportionally disadvantage patients that are already socially or economically deprived. We believe that this warrants careful handling by the neurosurgical community and an appropriate form of oversight. It should also be noted that the current initiatives towards an LHS in surgery have not resulted in a potentially increased risk of worse outcomes for patients as all databases only introduced a standard method of prospective registration and evaluate a surgical innovation.[12]

Appropriate oversight

Any form of medical research warrants a form of oversight. As opposed to clinical care, research is generally less beneficial to the individual patient and requires specific ethical consideration and oversight to prevent individual patients from being exposed to disproportionate risks. Several frameworks for ethical surgical research have been suggested, such as the IDEAL Framework which upholds the RCT as the golden standard, but opens a door for alternative trial designs as well.[20] The strict distinction between research and clinical care may pose a challenge to evaluating neurosurgical innovations, as any depart from current practice could be regarded as research and may warrant a form of oversight. Neurosurgical innovation often takes place in the gray area between formal research and clinical care, as innovations may have come about as a result of an alteration to a procedure for a specific patient that turned out to be beneficial and implementable to other patients. Innovations may also come about by extending the reach and pathologies for certain surgical innovations, as seen with endoscopic endonasal resection* of anterior skull base meningiomas.[21] There is currently no oversight in place for this gray area. However, it has been suggested that this should depend on the level of potential risk to patients, with less oversight when risks are low, and more rigorous oversight with increasing risks.[16] We believe it to be impractical to mandate IRB approval for every innovative procedure aimed to improve the outcome of an individual patient. On the other hand, innovations that have gained traction among the neurosurgical community and may be applied to other patients should be evaluated with some form of oversight to ensure safety to patients and methodologically sound evaluation. This innovation could at some point be subjected to formal research as suggested by the IDEAL Framework.[20] However, innovation in neurosurgery may also be subjected to different forms of oversight, such as the neurosurgical department, neurosurgical societies, surgical colleges, or dedicated institutional boards.[9] We believe that oversight in an LHS should be tailored to neurosurgery with great involvement of the neurosurgical community and patient advocacy groups to balance safety of patients and continuous innovation and that the amount of oversight should be guided by the estimated risk of the innovation.

Conclusion

The LHS and its associated ethics framework holds the potential to overcome several challenges associated with neurosurgical innovation. These solutions are primarily formed by alternative trial designs, structured data sharing and collection, and

increased patient participation. Implementation of the LHS, however, comes with ethical challenges specific to neurosurgery that include respect for autonomy, justice to patients and appropriate oversight.

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General discussion

The various parts of this thesis show that innovation in neurosurgery generally does not occur systematically and often only becomes apparent in hindsight. This lack of systematic innovation is unethical as patients face unjustifiable risks due to a lack of informed consent, outcome evaluation, and oversight. These unjustifiable risks highlight the need for a more systematic approach to neurosurgical innovation that has the interests of patients close at heart. This approach should involve methodologically sound research, evaluation of outcomes, informed patients, and adequate oversight. Some have proposed frameworks such as the Idea, Development, Exploration, Assessment, Long-term study (IDEAL)[8] Framework and learning health systems (LHS)[1] that aim to provide guidance in innovative surgery and encourage learning from every patient, respectively. Still, these frameworks are not adjusted to neurosurgery, introduce new ethical concerns, and require tremendous efforts to realize. Here, a system is proposed that aims to ethically improve neurosurgical innovation. This system is based on the IDEAL Framework[8] and LHS[1] and envisions the collection of large-scale, high-quality data, methodologically sound research, and proper valuation of systematic ethical neurosurgical innovation.

Data collection

Currently, high-quality data is only obtainable through expensive studies, such as RCTs and prospective cohort studies. Although these studies may provide valuable answers for neurosurgeons, many answers still come with several limitations. These issues may be related to inclusion criteria, treatment variation, and a lack of follow-up. Improved data collection may be beneficial by providing more granular data based on a greater variety of patients followed for longer periods.

One possibility may be the automatic collection of prospective high-quality data on patients through the modification of current electronic medical record (EMR) systems. The EMR systems that neurosurgeons currently use are primarily designed for monitoring the medical status of a patient (in written form), billing, and providing legal security, but, critically, not research.[4,7,10] An EMR system that also provides well-sorted data on patients and outcomes will be more convenient to analyze. Neurosurgeons can also use these newly generated data to compare outcomes in different clinical settings and interventions. Large-scale systematic data collection will also allow neurosurgeons to obtain more data from patients suffering from diseases that require neurosurgical intervention, especially when the disease is rare. For instance, well-sorted data on cognitive outcomes of subarachnoid hemorrhage patients treated with novel medical devices may provide key insights regarding effectiveness, practice variation, and long-term outcomes. Such a system currently does not exist and will require tremendous efforts to construct and maintain. There are currently no incentives or demands for such a system to be created. Ideally, these EMR systems

would be introduced on a national level to increase the availability of data further. Such an EMR system will aid research on neurosurgical patients as most treated diseases are rare and hard to study on a large scale. Parts of the data gathered may also be shared with researchers outside the healthcare system in a de-identified manner, perhaps similar to the UK Biobank[3], to increase the amount and quality of publicly available data. These data sets will also be crucial to train artificial intelligence (AI) algorithms, perform large-scale (genetic) research, and study the effects of practice variations, among many other topics.

All relevant parties need to be involved to introduce an EMR with these capabilities effectively and aware of ethical challenges that may arise. Ethical issues may, for instance, arise due to compromised patient autonomy, compromised privacy, and vulnerable patient populations. These challenges may be comparable to challenges that come with an LHS which is why the framework suggested by Faden et al. may offer solutions through obligations for all parties involved.[5] Every patient needs to be adequately informed about the data that will be collected and provide consent for how much data is collected, the duration of data storage, and the use of the data to uphold the ethical obligation to respect the rights and dignities of patients. This consent process should be a simple and straightforward procedure to make it easy for well-informed patients to join. The neurosurgical community needs to actively encourage patients to participate and educate them on what active participation entails and how this will help neurosurgeons improve future care. Naturally, patients have the right to decline participation but also have the ethical obligation to "contribute to the common purpose of improving the quality and value of clinical care and health care systems".[5] Still, even marginal changes in the number of participating patients can significantly improve the amount of available data on a national scale. The creation of an EMR with such capabilities also introduces privacy-related ethical risks due to the potential of data theft. The neurosurgical community has the obligation to avoid posing non-clinical risks and burdens on patients. All parties involved, therefore, need to put all possible security measures in place to prevent sensitive data from reaching external parties. Data that are automatically collected for innovation when neurosurgical patients are vulnerable (e.g., incapacitated patients due to neurotrauma) need to be carefully stored and removed when asked by the patient at a later timepoint. Neurosurgeons should also make sure that otherwise vulnerable patient populations, such as ethnic minorities, understand the implications of an EMR with the aforementioned capabilities.

An EMR with enhanced research capabilities that is implemented whilst all parties accept their respective obligations will enable the neurosurgical community to fulfill its ethical obligation to provide optimal care that is based on continuous learning to each patient.

Research quality

Research that follows the highest ethical and methodological standards will provide more clinically relevant answers. Neurosurgeons could improve the quality of the research in neurosurgery in several ways.

First, education on ethically and methodologically sound research should be a

core part of neurosurgical training programs. Second, studies that follow the highest possible standards will ensure relevant answers based on fair comparisons that allow for adequate appraisal. Standardization and registration of protocols, trials, and publications will help achieve these goals. All parties involved should avoid an unacceptable increase in bureaucracy and should be on board when increasing regulation through registration.

Third, the neurosurgical community could also be thought about the value of soft skills to improve ethical research (e.g., communication, conflict resolution, and creative thinking). Although many of these soft skills are being taught during residency and are applied by neurosurgeons every day, a greater focus and more dedicated training could further improve innovative neurosurgical care. Developed soft skills will enhance teamwork, patient communication, disclosure of COIs, and teaching skills, which are an absolute necessity for ethical innovation in neurosurgery. These practice improvements and abilities will ensure continued respect for patient autonomy and patient involvement.

The neurosurgical community also needs to allocate adequate resources, setup dedicated innovation teams, and collaborate with other innovation teams and people with different expertise (epidemiology, AI, imaging, among others). Patients should also be made part of innovations teams and may come up with initiatives. External parties such as governmental organizations and health insurers may also be involved to gain more support and provide valuable input on achievability, funding strategies, and scalability. External recognition (e.g., through rankings), increased compensation, and greater appreciation by patients may stimulate neurosurgical teams to conduct ethically and methodologically sound research and thereby accelerate meaningful innovation.

Valuation of innovation

Traditionally, value in health care is defined as outcomes relative to their cost.[9] Innovation that is conducted and implemented ethically and effectively may result in more value than the current standard of care. The amount of created additional value over the current standard of care can be used as a metric to evaluate the quality, quantity, efficacy, and efficiency of neurosurgical innovation. The IDEAL collaboration regards innovative techniques and devices that differ from the gold standard because they are altogether new, are applied to a new anatomical location, or are applied to a new patient group as a surgical innovation.[6] Innovation in neurosurgical care that does not meet this definition can still result in value creation for patients through for instance quality improvement and comparative effectiveness research. For instance, waste reduction in the neurosurgical operation room can create value by cost reduction.[2] Therefore, the following definition of neurosurgical care innovation is proposed: *The creation of more value than the current (gold) standard of neurosurgical care*. The amount of created value will depend on the magnitude and the scale of the innovation. The potential to create substantial additional amounts of value over the current standard may stimulate neurosurgical departments to learn from every patient. Even a minor innovation may result in a small yet meaningful amount value when implemented at scale. This will allow all parties of all sizes to

conduct neurosurgical care innovation and create value.

Ethical neurosurgical care innovation will require adequate evaluation, reporting, implementation, oversight, and financial compensation. Neurosurgical innovation teams, improved education of the neurosurgical community, and aforementioned EMR could ensure adequate evaluation, reporting, and implementation of neurosurgical care innovations. The created value needs to be carefully evaluated and reported on to avoid pseudo value creation. The measurement of created additional value will be challenging and will depend on the magnitude and scale of the innovation. Outcomes may be measured in for instance survival, complication rates, readmission rates, Quality-Adjusted Life Years (QALYs), and Disability-Adjusted Life Years (DALYs) in relation to their respective costs. It will be hard to determine the ideal metric for each innovation. It will require an external party formed by neurosurgeons, patients, and hospital managers, among others, that determines which metric(s) are appropriate. This external party can also determine whether the innovation has genuinely resulted in additional value over current care. This external party could also be made responsible for providing adequate oversight, the amount of which should be determined by the magnitude of the anticipated ethical risk that comes with the innovation. Guidelines on methodological standards put forward by the external party could help innovation teams meet these standard during the innovation process.

The creation of value through ethical neurosurgical care innovation must be adequately financially compensated to provide incentives to all parties involved. Hospitals and neurosurgical departments should be paid for value creation as well as for sharing the innovation as an innovation that results in value creation should never be monopolized. Alongside grant mechanisms, a certain amount of created value should result in a predefined amount of financial reimbursement. The compensation needs to be substantial to motivate all parties involved. Patient advocacy groups, neurosurgical societies, the governmental agencies, and health care insurers could provide necessary funds and may prioritize specific patient populations, determine relevant value metrics, and select particular procedures. This compensation mechanism will result in a more focused and productive innovation that all parties support as well as an additional revenue source for neurosurgical departments. This new form of reimbursement requires adequate oversight to make sure that risks patients are limited, will result in both improvement of care and cost reduction, and ensures that generated knowledge is actively shared. This new reimbursement system may also provide an alternative to traditional forms of competition in innovation and thereby stimulate innovation. This competition, however, should never compromise outcomes for patients and should be a continuous focus of oversight. Naturally, not all attempts at neurosurgical care innovation will result in increased value and compensation. A minimum amount of compensation could be made available to innovation groups that adhere to the highest ethical standards but fail to create additional value to avoid pseudo value creation and stimulate unbiased analysis and reporting of results.

Ethical neurosurgical care innovation as described above is an innovation itself as it is a deviation from the current manner of neurosurgical care improvement. The introduction of ethical neurosurgical care innovation, therefore, needs to be carefully planned, systematically introduced, continuously evaluated, and adjusted

where necessary. The probability of success of ethical neurosurgical care innovation depends on dedication and motivation from all parties involved, sufficient funding, and the willingness of patients to participate. Improved education, a greater focus on soft skills, improved collaboration, and efficient communications may further increase the probability of improved patients outcomes through ethical neurosurgical care innovation.

In conclusion, ethical neurosurgical care innovation may increase and accelerate value creation over the current standard of care in neurosurgery. Ethical neurosurgical care innovation needs to be carefully introduced, financial compensated, guided by external parties, and subjected to adequate oversight. This will, hopefully, improve outcomes for neurosurgical patients in the most efficient manner.

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Summary

In this Ph.D. thesis, *Innovation in Neurosurgery*, the current status of neurosurgical innovation, related ethics, and potential manners of improvement are discussed. Neurosurgical innovation has brought about a tremendous improvement in outcomes for patients. Nevertheless, many patients still face a poor prognosis when presented with a diagnosis that warrants a neurosurgical intervention. Further improvement of outcomes will require continuous innovation. This thesis shows that manner of innovation in neurosurgery has hardly changed over the past decades, which results in ethical challenges but also offers opportunities.

Part I showed that many neurosurgical innovations and medical devices were not introduced systematically. Furthermore, knowledge of long-term outcomes is generally limited. **Chapter 1** described that the Woven EndoBridge (WEB) device might show promising results, but also that long-term consequences remain unknown and warrant careful use of this device. **Chapter 2** described that retreatment for intracranial outcomes is associated with relatively poor outcomes for all available retreatment modalities. **Chapter 3** showed that endoscopic endonasal meningioma resection is not superior to traditional transcranial microscopic surgery. Most of the identified studies are retrospective in nature, may suffer from selection bias, and are generally of low quality. This lack of high-quality data is typical for most neurosurgical research. In **chapter 4**, the potential of the randomized control trial (RCT) was evaluated for applicability in neurosurgery. **Chapter 4** showed that many RCTs in neurosurgery are of low quality and are poorly registered. RCTs in neurosurgery may be significantly improved through registration of study protocols, complete follow-up, and improved design.

In **part II** specific ethical issues related to neurosurgical innovation were evaluated. **Chapter 5** described the various ethical issues that arise during the introduction of innovative medical devices due to current regulation. These ethical issues are very relevant as neurosurgeons use many medical devices during every neurosurgical procedure. Collaborations between neurosurgeons and medical device manufacturers are an absolute necessity for producing effective new medical devices but may result in conflicts of interest (COI) for the parties involved. There is no law that requires disclosure of COIs to patients. **Chapter 6** described that neurosurgeons have an ethical obligation to provide adequate disclosure to patients regarding potential COIs. This disclosure should be standardized and involve a description of personal experience with the device and financial interests. Medical journals must also continue to demand adequate disclosure of COIs when publishing papers describing experience with medical devices. This disclosure will provide the readership with the ability to appraise the described findings adequately. **Chapter 7** showed that no framework or oversight is in place for ethically sound operative innovation. This chapter described a framework where the severity of oversight for operative innovation increases with

the increased ethical risk a particular surgical innovation may bring. It is suggested that communication among peers and that collaboration between all parties involved will be essential for the ethical introduction of operative procedures. Operative innovation also naturally comes with a learning curve (**chapter 8**). There is currently no clear definition of the learning curve in innovative surgery. A focus on soft skills and communication with patients is necessary for ethically sound handling of the learning curve that comes with surgical innovation. Innovation may also happen in an emergency setting which holds important implications related to informed consent due to limited time to discuss treatment options and potential outcomes (**chapter 9**).

Part III focused on potential ways to improve the ethical situation of innovation in neurosurgery. **Chapter 10** described the feasibility and applicability of the Idea, Development, Exploration, Assessment, Long-term study (IDEAL) Framework for the ethical and systematic introduction of novel surgical procedures for neurosurgery. **Chapter 10** showed that the widely applied WEB device and the endoscopic endonasal approach for anterior skull base meningiomas were not introduced according to the IDEAL Framework. The neurosurgical patient population lends itself poorly for innovation that follows the IDEAL Framework. Low incidence of the disease, interpatient variability, and lack of equipoise make an RCT, the gold standard upheld by the IDEAL Framework, generally hard to conduct. Alternative trial designs and registries could form an alternative and provide relevant answers when feasible. In **chapter 11** the feasibility and ethical justification of the LHS for neurosurgery were discussed. The focus on learning may also place unnecessary ethical risks on patients. Furthermore, the data collection on a large scale may compromise the respect for autonomy and forms a major ethical risk. On the other hand, continuous learning and large-scale data collection may also significantly improve patients' outcomes due to research on a larger scale and improved access to quality data on rare diseases. It will require the collaboration of all parties involved to introduce LHS ethically into neurosurgery.

The **general discussion** described a framework for ethical and systematic neurosurgical innovation based on improved data collection, research quality, and valuation of innovation. Introduction of an electronic medical record system that collects high-quality data will help achieve these goals. Education of the neurosurgical community about research methodology and soft skills may improve research quality. Finally, all parties involved that innovate in systematic and ethical innovation fashion and thereby improve patient outcomes create value, which needs to be adequately rewarded. All these measures will require dedication from all parties involved as well as adequate funding.

In conclusion, ethical and systematic neurosurgical innovation requires dedication from all parties involved and needs to be adequately rewarded. Overall, we owe it to our patients to improve their outcomes through ethical innovation.

Nederlandse samenvatting

In dit proefschrift, genaamd *Innovation in Neurosurgery*, worden de huidige status, ethiek en mogelijke manieren van verbetering van neurochirurgische innovatie geëvalueerd. Neurochirurgische innovatie is essentieel geweest voor de verbetering van uitkomsten voor patiënten. Echter, veel patiënten die een neurochirurgische interventie behoeven, hebben nog steeds een matig tot slechte prognose. Een verdere verbetering van uitkomsten van patiënten vergt dus continue neurochirurgische innovatie. Dit proefschrift laat zien dat de manier waarop neurochirurgische innovatie plaatsvindt nauwelijks is veranderd gedurende de laatste decennia. Dit gebrek aan verandering brengt vele ethische dilemma's, maar biedt ook kansen.

Deel I van dit proefschrift liet zien dat vele neurochirurgische innovaties en medische hulpmiddelen niet systematisch worden geïntroduceerd. Daarnaast is de kennis over langetermijnuitkomsten doorgaans zeer beperkt. **Hoofdstuk 1** beschrijft dat de Woven EndoBridge (WEB) device voor de behandeling van intracraniele aneurysmata veel belovende uitkomsten heeft. Echter, kennis over langetermijnuitkomsten is beperkt en maakt voorzichtig gebruik van dit medisch hulpmiddel noodzakelijk. In **hoofdstuk 2** wordt beschreven dat de herbehandeling van intracraniële aneurysmata doorgaans gepaard gaat met relatief matige uitkomsten voor alle beschikbare therapieën. Middels de in **hoofdstuk 3** beschreven analyse werd aangetoond dat de endoscopische endonasale resectie van meningiomen niet superieur is aan de conventionele transcraniële resectie. De meeste geïncludeerde studies in de analyse waren retrospectief en meestal van lage kwaliteit. Ook was er in veel gevallen sprake van selection bias. Dit gebrek aan studies van hoge kwaliteit is typerend voor neurochirurgisch onderzoek. In **hoofdstuk 4** wordt de evaluatie van de randomized control trial (RCT) voor neurochirurgie beschreven. RCTs in de neurochirurgie zijn vaak van lage kwaliteit en worden matig geregistreerd. RCTs binnen de neurochirurgie kunnen verbeterd worden door registratie van studieprotocollen, completere follow-up en verbeterd design.

In **deel II** van dit proefschrift werden specifieke ethische dilemma's met betrekking tot neurochirurgie beschreven. **Hoofdstuk 5** beschrijft dat verscheidene ethische dilemma's ontstaan door de huidige wetgeving omtrent medische hulpmiddelen, die dagelijks door neurochirurgen worden gebruikt. Het is essentieel voor neurochirurgen om samen te werken met fabrikanten van medische hulpmiddelen om veilige en bruikbare producten op de markt te brengen. Echter, dit kan leiden tot belangenverstrengeling voor alle betrokken partijen. Er is op dit moment ook geen regelgeving die openbaring van mogelijke belangenverstrengeling voor artsen afdwingt. In **hoofdstuk 6** wordt beschreven dat neurochirurgen een ethische verplichting jegens hun patiënten hebben om potentiele belangenverstrengelingen bekend te maken. Deze bekendmaking wordt idealiter gestandaardiseerd en dient een beschrijving te bevatten van de persoonlijke ervaring met het medisch hulpmiddel en eventuele

financiële belangen. Medische tijdschriften dienen ook door te gaan met het eisen dat financiële belangen bekend worden gemaakt door auteurs om lezers de mogelijkheid te geven de gepresenteerde vindingen op waarde te schatten. **Hoofdstuk 7** beschreef dat er momenteel geen raamwerk of toezicht is dat ethische operatieve innovatie waarborgt. In dit hoofdstuk wordt een raamwerk beschreven voor ethische chirurgische innovatie waarbij de mate van toezicht toeneemt als het ethische risico van de chirurgische innovatie toeneemt. Hiervoor is samenwerking tussen alle betrokken partijen essentieel. Operatieve innovatie komt altijd met een leercurve die ook ethische dilemma's met zich meebrengt. In **hoofdstuk 8** wordt beschreven dat er momenteel geen heldere definitie is voor de leercurve bij neurochirurgische innovatie. Een grotere focus op softskills en communicatie met patiënten is essentieel voor ethische neurochirurgische innovatie die de onvermijdelijke leercurve in acht neemt. Neurochirurgische innovatie kan ook plaatsvinden in een spoedsetting waarbij er weinig of geen tijd is voor het bespreken van behandelingsopties en het verkrijgen adequate geïnformeerde toestemming van de patiënt. De ethische dilema's die dit meebrengt worden beschreven in het (**hoofdstuk 9**).

In **deel III** van dit proefschrift worden verscheidene manieren beschreven waarop neurochirurgische innovatie kan worden verbeterd vanuit een ethisch oogpunt. **Hoofdstuk 10** beschrijft de mogelijkheid en toepasbaarheid van het Idea, Development, Exploration, Assessment, Long-term study (IDEAL) Framewok voor ethische en systematische introductie van nieuwe chirurgische technieken voor neurochirurgie. **Hoofdstuk 10** toonde aan dat de WEB device en endoscopische endonasale resectie van meningiomen niet systematisch zijn geïntroduceerd volgens het IDEAL Framework. Het is lastig om neurochirurgische technieken te introduceren middels een RCT, zoals beschreven in het IDEAL Framework, wegens zeldzame ziektebeelden, grote variëteit binnen patiënten populaties en een gebrek aan klinische equipoise binnen de neurochirurgische gemeenschap voor vele vraagstukken. Onder andere alternatieve trial designs kunnen helpen om toch relevante antwoorden op prangende vragen binnen de neurochirurgische gemeenschap te genereren. In **hoofdstuk 11** wordt de haalbaarheid en ethische rechtvaardiging van learning health systems (LHS) voor neurochirurgie beschreven. De focus op continu leren die de LHS brengt kan een onnodig ethisch risico plaatsen bij patiënten. Daarnaast kan het op grote schaal verzamelen van data de autonomie van patiënten beperken. Aan de andere kant, continu leren en het op grote schaal verzamelen van data kan ook de uitkomsten van patiënten met zeldzame ziektebeelden verbeteren door betere toegang tot data van voldoende grootte. De LHS binnen de neurochirurgie heeft dus veel potentie voor het verbeteren van uitkomsten, maar een ethische introductie vereist een samenwerking van alle betrokken partijen.

In de **algemene discussie** wordt een raamwerk beschreven voor ethische en systematische neurochirurgische innovatie gebaseerd op verbeterede data verzameling, kwaliteit van onderzoek en waardering van innovatie. De introductie van een elektronisch patiëntendossier dat automatisch data verzamelt van hoge kwaliteit is hiervoor essentieel. Daarnaast kan de educatie over onderzoek methodiek en softskills aan de neurochirurgische gemeenschap de onderzoekskwaliteit verbeteren. Alle partijen die systematisch en ethisch innoveren, creëren waarde voor patiënten. Deze waar-

decreatie dient adequaat beloond te worden. Alle hierboven genoemde maatregelen vereisen betrokkenheid en inzet van alle belanghebbende partijen om te kunnen worden gerealiseerd.

Concluderend, ethische en systematische neurochirurgische innovatie vereist inzet van alle betrokken partijen en dient adequaat te worden beloond. We zijn het immers aan onze patiënten verplicht om hun uitkomsten middels ethische innovatie te blijven verbeteren.

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Curriculum Vitæ

Ivo S. Muskens

Ivo S. Muskens, MD, was born on October 11, 1991 in Utrecht. He went to the Christelijk Gymnasium in Utrecht for high school, where he graduated cum laude in 2010. A passion for working with people, a keen interest in the workings of the human body, and a desire to help others made Ivo decide to go to medical school at Utrecht University. While in medical school, Ivo joined the Utrecht Studenten Corps, a fraternity, and the Utrechtse Studenten Rugby Society, a rugby club for students. After several rotations, Ivo realized that, out of all the medical specialties, his passion lay with neurosurgery. He started a fruitful collaboration with neurosurgeon Dr. Broekman, MD PhD LLM. Subsequently, he decided to join her for a year in Boston to perform research at the Department of Neurosurgery of the Brigham and Women's Hospital, part of Harvard Medical School, in Boston, MA. The research during this period focused on the ethics of neurosurgical innovation and formed the basis of this thesis. After obtaining his MD in 2017, Ivo was offered a postdoctoral position at the University of Southern California in Los Angeles, CA, with prof. Joseph Wiemels, PhD. The research during this postdoc focused on the identification of genetic and non-genetic risk factors for pediatric cancers, pediatric glioma in particular. After his postdoc, Ivo realized he wanted to make an impact at a higher level in the healthcare landscape and joined Gupta Strategists, a consultancy, in Amsterdam as a consultant.

List of Publications

List of publications included in this thesis

1. **Muskens IS**, Senders JT, Dasenbrock HH, Smith TR, Broekman ML (2017) The Woven Endobridge Device for Treatment of Intracranial Aneurysms: A Systematic Review. World Neurosurg 98:809-817 e801. doi:10.1016/j.wneu.2016.11.020

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