Comparison of Complications, Trends, and Costs in Endoscopic vs Microscopic Pituitary Surgery: Analysis From a US Health Claims Database

Anthony O. Asemota, MD, MPH
Masaru Ishii, MD, PhD
Henry Brem, MD
Gary L. Gallia, MD, PhD

Department of Neurosurgery, Johns Hopkins Hospital, Baltimore, Maryland

Correspondence:
Gary L. Gallia, MD, PhD,
Department of Neurosurgery,
Johns Hopkins Hospital,
Baltimore, MD 21287.
E-mail: ggallia1@jhmi.edu

Received, August 31, 2016.
Accepted, May 25, 2017.
Published Online, July 25, 2017.

BACKGROUND: Microsurgical and endoscopic techniques are commonly utilized surgical approaches to pituitary pathologies. There are limited data comparing these 2 procedures.

OBJECTIVE: To evaluate postoperative complications, associated costs, and national and regional trends of microscopic and endoscopic techniques in the United States employing a nationwide database.

METHODS: The Truven MarketScan database 2010 to 2014 was queried and Current Procedural Terminology codes identified patients that underwent microscopic and/or endoscopic transsphenoidal pituitary surgery. International Classification of Diseases codes identified postoperative complications. Adjusted logistic regression and matched propensity analysis evaluated independent odds for complications.

RESULTS: Among 5886 cases studied, 54.49% were microscopic and 45.51% endoscopic. The commonest surgical indications were benign pituitary tumors. Annual trends showed increasing utilization of endoscopic techniques vs microscopic procedures. Postoperative complications occurred in 40.04% of cases, including diabetes insipidus (DI; 16.90%), syndrome of inappropriate antidiuretic hormone (SIADH; 2.02%), iatrogenic hypopituitarism (1.36%), fluid/electrolyte abnormalities (hypoosmolality/hyponatraemia [5.03%] and hyperosmolality/hypernatraemia [2.48%]), and cerebrospinal fluid (CSF) leaks (CSF rhinorrhoea [4.42%] and other CSF leak [6.52%]). In our propensity-based model, patients that underwent endoscopic surgery were more likely to develop DI (odds ratio [OR] = 1.48; 95% confidence interval [CI] = 1.28-1.72), SIADH (OR = 1.53; 95% CI = 1.04-2.24), hypoosmolality/hyponatraemia (OR = 1.17; 95% CI = 1.01-1.34), CSF rhinorrhoea (OR = 2.48; 95% CI = 1.88-3.28), other CSF leak (OR = 1.59; 95% CI = 1.28-1.98), altered mental status (OR = 1.46; 95% CI = 1.01-2.60), and postoperative fever (OR = 4.31; 95% CI = 1.14-16.23). There were no differences in hemorrhagic complications, ophthalmological complications, or bacterial meningitis. Postoperative complications resulted in longer hospitalization and increased healthcare costs.

CONCLUSION: Endoscopic approaches are increasingly being utilized to manage sellar pathologies relative to microsurgery. Postoperative complications occur in both techniques with higher incidences observed following endoscopic procedures.

KEY WORDS: Endonasal, Endoscopic, Microscopic, Pituitary adenoma, Skull base surgery, Transsphenoidal

Neurosurgery 81:458–472, 2017 DOI:10.1093/neuros/nyx350 www.neurosurgery-online.com

Surgical approaches to the sella turcica have evolved over the past century and this rich history has been excellently reviewed.[1,2] In the 1960s, with the introduction of the surgical microscope, microsurgical approaches were developed and these became the standard

ABBREVIATIONS: CI, confidence interval; **CPT-4,** Current Procedural Terminology, Fourth Edition; **CSF,** cerebrospinal fluid; **DI,** diabetes insipidus; **DVT,** deep vein thrombosis; **ICD-9-CM,** International Classification of Diseases, Ninth Revision, Clinical Modification; **OR,** odds ratio; **PE,** pulmonary embolism; **SIADH,** syndrome of inappropriate antidiuretic hormone

Supplemental digital content is available for this article at www.neurosurgery-online.com.

surgical procedure to sellar lesions and pituitary tumors in the latter half of the 20th century. In the 1990s, purely endoscopic transsphenoidal procedures were reported for sellar and pituitary lesions.[3-8] Currently, both microscopic and endoscopic techniques are utilized in the surgical management of sellar/pituitary masses, and endoscopic pituitary surgery is increasing in frequency.[9]

There is significant interest in comparing these 2 techniques and numerous studies have reported outcomes for both microsurgical and endoscopic pituitary surgery.[10-17] These studies are often limited to single centers and a single or few numbers of surgeons.[10-17] In an attempt to address some of the biases in single center/surgeon experiences, several groups have performed systematic reviews and meta-analyses to synthesize the current literature on these 2 surgical techniques.[18-23] In our study, we sought to estimate surgical complications, trends, and costs associated with both microscopic and endoscopic approaches for the entire specialty not just the aggregated data in the literature and employed a sampled large population approach to obtain these estimates.

METHODS

Data Source

Data for the study was obtained from the Truven Analytics Health MarketScan database.[24] The database contains information on more than 225 million unique patients available from claims records from large employers and health plans across various geographical regions.[25] It contains fully integrated patient level data, including inpatient, outpatient, as well as drug and laboratory information. Individual patients are identified with a unique identifier number within the database that is used to link deidentified patient information between inpatient and outpatient charts in order to access patient's personal health information.[25] The data are compliant with the Health Insurance Portability and Accountability Act and undergoes a rigorous validation process in order to ensure completeness, accuracy, and reliability.[25] In this study, we accessed all relevant patient healthcare information, as well as data on utilization and costs from the 2010 to 2014 MarketScan database.[24]

Study Sample

The study was carried out as a retrospective study. All inpatient records were reviewed and patients who had transsphenoidal surgery were identified using Current Procedural Terminology, Fourth Edition (CPT-4) procedure codes and included for analysis in the study. Identified patients were categorized as having had either microscopic (CPT-61548) or endoscopic (CPT-62165) surgery, while those patients who had both microscopic and endoscopic procedure codes within the same hospitalization record were excluded from our analysis. Only patients less than 65 yr of age were included in the study. Since our study sample included only deidentified data from a publicly available database and did not involve direct patient contact, Institutional Review Board committee approval and patient informed consent were not required for this study.

Variables Included

We examined patient characteristics including age, sex, and health plan information using variables contained within the MarketScan database. The presence of medical comorbidities was identified using the Charlson Comorbidity Index, a validated scale/instrument for categorizing patient comorbidities and for stratifying surgical risk for patients undergoing surgery based on the International Classification of Diseases diagnoses codes in administrative data.[26-28]

Main Outcome Measures

The main endpoints and outcome measures in the study were the development of specified inpatient postoperative complications identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. The specific complications identified were disorders of the pituitary (including diabetes insipidus [DI], syndrome of inappropriate antidiuretic hormone [SIADH], and iatrogenic pituitary disorders [postoperative hypopituitarism]), fluid and electrolyte disorders (including hypoosmolality/hyponatraemia, hyperosmolality/hypernatraemia), cerebrospinal fluid (CSF) leaks (including CSF rhinorrhoea, other CSF leaks, and dural tears), hemorrhagic complications (including hematoma, intracranial hemorrhage, iatrogenic cerebrovascular injury, internal carotid artery injury, and epistaxis), and ophthalmological complications (including visual field defects, paralytic strabismus [including third, fourth, sixth nerve palsies and ophthalmoplegia], and diplopia). Additional complications examined included altered mental status, postoperative nausea, central nervous system disorders, bacterial meningitis, and postoperative fever. Medical complications (including acute respiratory failure, deep vein thrombosis [DVT], and pulmonary embolism [PE]) were also examined. **Table**, **Supplemental Digital Content 1** lists the complications and corresponding ICD-9 codes used. Some patients contributed multiple events and were counted in multiple categories as appropriate. Incidence rates and predictors of complications in patients that underwent transsphenoidal surgery were also examined. We also identified specific principal admitting diagnoses (used as surrogates of indications for surgery) among patients that underwent transsphenoidal pituitary surgery. Unique variables contained within the database allow the identification of individual patient admitting diagnoses using ICD-9-CM diagnoses codes. Other end points examined were total length of hospitalization, hospitalization costs (including total gross payments made to the providers for covered services rendered during an admission and total net payments made to providers excluding out of pocket payments) associated with both microscopic and endoscopic transsphenoidal pituitary surgery, as well as incremental hospitalization costs associated with the development of postoperative complications. Additionally, national and regional estimates, as well as trends in utilization of microscopic and endoscopic transsphenoidal surgery were examined.

Statistical Analysis

We analyzed descriptive statistics, including means, rates, medians, standard deviations for continuous variables and calculated 95% confidence intervals (CI). Standard 2-tailed *t*-tests were used in comparing means between the 2 groups. Categorical variables were compared using Pearson's chi-squared analysis. Where appropriate, Fischer's exact test was also used to determine differences between subgroups of patients. Adjusted proportional-odds multivariate logistic regression was employed in examining the odds of complications comparing outcomes in microscopic vs endoscopic surgeries. Multiple models were constructed to determine the odds of occurrence for individual complications, in each case comparing endoscopic to microscopic (reference group) techniques. Variables adjusted for in our multivariate models included age, sex of patient, type of health plan, region of hospital, as well as patient comorbidities. The effect of case-mix was adjusted for in all of our regression models.

For more robust estimates in evaluating outcomes, we performed a matched propensity score analysis and subsequent regression based on the output from the propensity matching. This method allows for adjustment and a reduction of potential bias in estimating differential outcomes that arise as a result of apparent differences in outcome between 2 individual groups, and which may be dependent on measures and characteristics that affect the likelihood of receiving a particular treatment rather than that due to the effect of the treatment received.[29] It reduces bias due to confounding variables in estimating the effect of treatment outcome compared among groups that received a particular treatment vs those that did not.[30] Patients were matched on individual patient characteristics, comorbid conditions, and surgery indications and the propensity scores obtained were employed in separate regression analysis. Probability values for statistical significance were set at $P < .05$ in all of our analyses. All analyses were performed using Stata 14.0 statistical software (Stata, College Station, Texas).

Sensitivity Analysis

We also performed a sensitivity analysis restricting the entire analysis to a subset of patients with codes for specific pituitary disorders using the following ICD-9-CM codes: 227.3, 237.0, 253.0, 253.8, 255.0, and 194.3.

RESULTS

Study Population and Demographics

We identified 6044 records of transsphenoidal surgery in our initial search. Among these records, 158 contained both microscopic and endoscopic codes and thus were not included in our analysis. Thus, a total of 5886 transsphenoidal surgeries were studied, out of which 3207 (54.49%) were microscopic and 2679 (45.51%) were endoscopic procedures. Patient characteristics are outlined in Table 1. Majority of the patients that underwent transsphenoidal surgery were female (55.03%); the gender distribution was similar for both microscopic and endoscopic cohorts ($P = .57$). The mean age of all patients that underwent transsphenoidal surgery was 45.18 yr; mean age was similar in patients that underwent microscopic or endoscopic procedures [45.21 vs 45.14 yr, $P = .83$]. The overall age distribution of patients that underwent transsphenoidal surgery was as follows—less than 18 yr (2.92%), 18 to 34 yr (19.13%), 35 to 44 yr (21.25%), 45 to 54 yr (26.76%), and 55 to 64 yr (29.94%). There were no significant differences in age distribution of patients that underwent either type of transsphenoidal surgery ($P = .79$). There were, however, significant differences in utilization of the different transsphenoidal approaches (microscopic vs endoscopic) employed across different geographical regions. Most transsphenoidal surgeries were performed in the South (38.87%), followed by the West (20.46%), North-central (19.38%), and North-east (19.23%) regions. Over the interval of analysis, a greater proportion of endoscopic compared to microscopic procedures were performed in the North-east region (646/1132 $\approx$ 57.07% vs 486/1132 $\approx$ 42.93%, $P \leq .001$). In the North-central region, there were nearly equivalent proportions of microscopic and endoscopic cases. In the South and West, microscopic procedures predominated with approximately 59% of the procedures in each region (1358/2288 $\approx$ 59.35% and 714/1204 $\approx$ 59.30%, respectively). Although a significantly higher proportion of patients that underwent endoscopic transsphenoidal surgery had cerebrovascular comorbidities compared to patients that underwent microscopic surgery (6.42% vs 4.77%, $P = .01$), there was no difference in the Charlson Comorbidity Index between these 2 groups. Overall surgical mortality was low, and rates were similar across patients that underwent microscopic (0.22%) or endoscopic (0.11%) surgery. Majority (91.42%) of the patients that underwent either microscopic or endoscopic transsphenoidal pituitary surgery were routinely discharged home postoperatively.

Admitting Diagnoses and Indications for Surgery

The most common principal diagnosis among patients that underwent transsphenoidal pituitary surgery was benign neoplasm of the pituitary gland and craniopharyngeal duct (ICD-9-CM 227.3) which accounted for 81.86% of all surgeries, and this was true for patients that underwent either microscopic (82.20%) or endoscopic (81.45%) procedures. Other diagnoses included neoplasms of uncertain behavior of pituitary gland and craniopharyngeal duct (237.0), other disorders of the pituitary (253.8), neoplasms of unspecified nature of endocrine glands and other parts of nervous system (239.7), and Cushing's syndrome (255.0). See Table 2 for a list of common principal diagnoses/indications for surgery for both microscopic and endoscopic procedure groups.

Complications

On the whole, the most common complications associated with transsphenoidal pituitary surgery were disorders of the pituitary [19.05%] (including DI [16.90%], SIADH [2.02%], and iatrogenic pituitary disorders/hypopituitarism [1.36%]), fluid and electrolyte disorders [11.18%] (including hypoosmolality/hyponatraemia [5.03%], hyperosmolality/hypernatraemia [2.48%]), and postoperative CSF leak [10.35%] (including CSF rhinorrhoea [4.42%], other CSF leak [6.52%], and dural tear [1.38%]). Hemorrhagic complications occurred in 3.64% of patients including intracranial hemorrhage and epistaxis in 1.66% and 0.92% of patients, respectively. Ophthalmological complications occurred in 7.83% of patients including visual field defects, paralytic strabismus, and diplopia in 4.72%, 2.24%, and 1.60% of cases, respectively. Other less common complications were altered mental status [0.87%], bacterial meningitis [0.25%], and postoperative fever [0.22%]. The proportions of patients that developed postoperative complications of DI, SIADH, hypoosmolality/hyponatraemia, CSF rhinorrhoea, other CSF leak, altered mental status, and postoperative fever differed

TABLE 1. Population Characteristics

	Microscopic		Endoscopic		Total		
	n = 3207	(100.00)	n = 2679	(100.00)	n = 5886	(100.00)	*P*-value
Mean age in years (±standard error)	45.21	(13.19)	45.14	(13.23)	45.18	(13.20)	
Age							
≤18 yr	92	(2.87)	80	(2.99)	172	(2.92)	.79
18-34 yr	609	(18.99)	517	(19.30)	1126	(19.13)	
35-44 yr	697	(21.73)	554	(20.68)	1251	(21.25)	
45-54 yr	842	(26.26)	733	(27.36)	1575	(26.76)	
55-64 yr	967	(30.15)	795	(29.68)	1762	(29.94)	
Gender							
Male	1453	(45.31)	1194	(44.57)	2647	(44.97)	.57
Female	1754	(54.69)	1485	(55.43)	3239	(55.03)	
Health plan indicator							
Employer-based	1434	(44.71)	1199	(44.76)	2633	(44.73)	.98
Other health plan	1773	(55.29)	1480	(55.24)	3253	(55.27)	
Region							
North-east	486	(15.15)	646	(24.11)	1132	(19.23)	<.001
North-central	579	(18.05)	562	(20.98)	1141	(19.38)	
South	1358	(42.34)	930	(34.71)	2288	(38.87)	
West	714	(22.26)	490	(18.29)	1204	(20.46)	
Unknown	70	(2.18)	51	(1.90)	121	(2.06)	
Discharge status							
Discharged to home	2947	(91.89)	2434	(90.85)	5381	(91.42)	.11
Died	7	(0.22)	3	(0.11)	10	(0.17)	
Discharged to another facility	253	(7.88)	242	(9.03)	495	(8.41)	
Year							
2010	807	(25.16)	460	(17.17)	1267	(21.53)	<.001
2011	758	(23.64)	524	(19.56)	1282	(21.78)	
2012	707	(22.05)	573	(21.39)	1280	(21.75)	
2013	493	(15.37)	502	(18.74)	995	(16.90)	
2014	442	(13.78)	620	(23.14)	1062	(18.04)	
Preoperative medical comorbidities							
Acute myocardial infarction	32	(1.00)	26	(0.97)	58	(0.99)	.92
Congestive heart failure	17	(0.53)	15	(0.56)	32	(0.54)	.88
Peripheral vascular disease	7	(0.22)	6	(0.22)	13	(0.22)	.96
Cerebrovascular disease	153	(4.77)	172	(6.42)	325	(5.52)	.01
Chronic obstructive pulmonary disease	210	(6.55)	144	(5.38)	354	(6.01)	.06
Rheumatoid disease	29	(0.90)	22	(0.82)	51	(0.87)	.73
Peptic ulcer disease	4	(0.12)	3	(0.11)	7	(0.12)	.89
Mild liver disease	4	(0.12)	3	(0.11)	7	(0.12)	.89
Diabetes	412	(12.85)	346	(12.92)	758	(12.88)	.94
Complicated diabetes	12	(0.37)	16	(0.60)	28	(0.48)	.22
Hemiplegia/paraplegia	12	(0.37)	7	(0.26)	19	(0.32)	.45
Renal disease	22	(0.69)	24	(0.90)	46	(0.78)	.36
Cancer	287	(8.95)	239	(8.92)	526	(8.94)	.97
Metastatic cancer	30	(0.94)	28	(1.05)	58	(0.99)	.67
Charlson index							
None	2187	(68.19)	1809	(67.53)	3996	(67.89)	.78
Single comorbid condition	575	(17.93)	499	(18.63)	1074	(18.25)	
≥2 comorbid conditions	445	(13.88)	371	(13.85)	816	(13.86)	

significantly among patients that underwent microsurgery vs endoscopic surgery and were all higher in the endoscopic group. See Table 3 for the distribution of complications among patients that underwent microscopic and endoscopic surgery.

Results of multivariable logistic regression analysis adjusted for potential confounders revealed that compared to patients that underwent microsurgery, patients that underwent endoscopic surgery were more likely to have DI (odds ratio [OR] 1.54;

TABLE 2. Principal Diagnoses/Indications for Surgery

	ICD-9-CM code	Principal diagnoses	Frequency [n]	Percent [%]	Cumulative frequency [%]
All transsphenoidal pituitary surgery					
1	227.3	Benign neoplasm of pituitary	4818	81.86	81.86
2	237.0	Uncertain behavior neoplasm of pituitary	258	4.38	86.24
3	253.8	Other disorders of the pituitary	258	4.38	90.62
4	239.7	Endocrine/nervous system neoplasm unspecified	104	1.77	92.39
5	255.0	Cushing's syndrome	66	1.12	93.51
6	225.2	Benign neoplasm of cerebral meninges	28	0.48	93.99
7	194.3	Malignant neoplasm of pituitary	23	0.39	94.38
8	348.0	Cerebral cysts	19	0.32	94.70
9	198.89	Secondary malignant neoplasm	18	0.31	95.01
10	253.0	Acromegaly and gigantism	17	0.29	95.30
Microscopic transsphenoidal surgery					
1	227.3	Benign neoplasm of pituitary	2636	82.20	82.20
2	253.8	Other disorders of the pituitary	142	4.43	86.63
3	237.0	Uncertain behavior neoplasm of pituitary	126	3.93	90.56
4	239.7	Endocrine/nervous system neoplasm unspecified	66	2.06	92.62
5	255.0	Cushing's syndrome	42	1.31	93.93
6	194.3	Malignant neoplasm of pituitary	12	0.37	94.30
7	198.89	Secondary malignant neoplasm	11	0.34	94.64
8	348.0	Cerebral cysts	11	0.34	94.98
9	225.2	Benign neoplasm of cerebral meninges	10	0.31	95.29
10	253.0	Acromegaly and gigantism	6	0.19	95.48
Endoscopic transsphenoidal surgery					
1	227.3	Benign neoplasm of pituitary	2182	81.45	81.45
2	237.0	Uncertain behavior neoplasm of pituitary	132	4.93	86.38
3	253.8	Other disorders of the pituitary	116	4.33	90.71
4	239.7	Endocrine/nervous neoplasm system unspecified	38	1.42	92.13
5	255.0	Cushing's syndrome	24	0.90	93.03
6	225.2	Benign neoplasm of cerebral meninges	18	0.67	93.70
7	194.3	Malignant neoplasm of pituitary	11	0.41	94.11
8	253.0	Acromegaly and gigantism	11	0.41	94.52
9	348.0	Cerebral cysts	8	0.30	94.82
10	198.89	Secondary malignant neoplasm	7	0.26	95.08

95%CI: 1.34-1.77), hypoosmolality/hyponatraemia (OR 1.28; 95%CI: 1.01-1.62), CSF rhinorrhoea (OR 2.67; 95%CI: 2.03-3.51), other CSF leak (OR 1.63; 95%CI: 1.31-2.02), altered mental status (OR 1.64; 95%CI: 1.01-2.92), and postoperative fever (OR 5.06; 95%CI: 1.32-19.38). Results of the multivariate regression analysis are shown in Table 4. After propensity score matching and subsequent analysis, the results showed that patients that underwent endoscopic surgery were significantly more likely to develop DI (OR 1.48; 95%CI: 1.28-1.72), SIADH (OR 1.53; 95%CI: 1.04-2.24), hypoosmolality/hyponatraemia (OR 1.17; 95%CI: 1.01-1.34), CSF rhinorrhoea (OR 2.48; 95%CI: 1.88-3.28), other CSF leak (OR 1.59; 95%CI: 1.28-1.98), altered mental status (OR 1.46; 95%CI: 1.01-2.60), and postoperative fever (OR 4.31; 95%CI: 1.14-16.23) than their matched counterparts that underwent microscopic surgery. Results of the propensity score matching are shown in Table 4. Medical complications including acute respiratory failure [1.53%], DVT [0.53%], and PE [0.27%] did not show significant differences in rates and/or likelihood of occurrence among patients that underwent either microscopic or endoscopic transsphenoidal pituitary surgery (Table 5).

Trends

On the whole, the rates of transsphenoidal pituitary surgeries remained stable across time. An overall shift in the utility of the different approaches, however, was evident with an increase in the utility of endoscopic surgery and a corresponding decrease in the utility of microscopic surgery. Rates of endoscopic surgery increased overall in the United States from 36.31% in 2010 to 58.38% in 2014, an increase of approximately 60.78%, $P < .001$ (Figure 1). Further analysis of year to year changes in microscopic vs endoscopic utilization rates demonstrated the following changes associated with the transition from microscopic to endoscopic surgery: 2010 to 2011 (–7.22% vs +12.67%, $P = .02$), 2011 to 2012 (–6.60% vs +9.54%, $P = .04$), 2012 to 2013 (–10.14% vs +12.72%, $P = .01$), and 2013 to 2014 (–16.13% vs +15.64%, $P < .001$). The average annual rate of

TABLE 3. Postoperative Complications

	Microscopic		Endoscopic		Total		
	n = 3207	(100.00)	n = 2679	(100.00)	n = 5886	(100.00)	*P*-value
All disorders of the pituitary	513	(16.00)	608	(22.70)	1121	(19.05)	<.001
Diabetes insipidus	455	(14.19)	540	(20.16)	995	(16.90)	<.001
SIADH	50	(1.56)	69	(2.58)	119	(2.02)	.01
Iatrogenic pituitary disorder (hypopituitarism)	38	(1.18)	42	(1.57)	80	(1.36)	.21
All fluid and electrolyte disorders	319	(9.95)	339	(12.65)	658	(11.18)	<.001
Hypoosmolality/hyponatraemia	146	(4.55)	150	(5.60)	296	(5.03)	.02
Hyperosmolality/hypernatraemia	66	(2.06)	80	(2.99)	146	(2.48)	.07
All postop CSF leak/dura tear	244	(7.61)	365	(13.62)	609	(10.35)	<.001
CSF rhinorrhoea	84	(2.62)	176	(6.57)	260	(4.42)	<.001
Other CSF leak	165	(5.14)	219	(8.17)	384	(6.52)	<.001
Dura tear	35	(1.09)	46	(1.72)	81	(1.38)	.05
All hemorrhagic complications	105	(3.27)	109	(4.07)	214	(3.64)	.11
Hemorrhagic complication	22	(0.69)	30	(1.12)	52	(0.88)	.08
Hematoma	6	(0.19)	12	(0.45)	18	(0.31)	.07
Intracranial hemorrhage	49	(1.53)	49	(1.83)	98	(1.66)	.37
Iatrogenic cerebrovascular/ICA injury	16	(0.50)	9	(0.34)	25	(0.42)	.34
Epistaxis	25	(0.78)	29	(1.08)	54	(0.92)	.23
All ophthalmological complications	233	(7.27)	228	(8.51)	461	(7.83)	.08
Visual field defects	136	(4.24)	142	(5.30)	278	(4.72)	.06
Paralytic strabismus	70	(2.18)	62	(2.31)	132	(2.24)	.73
Diplopia	49	(1.53)	45	(1.68)	94	(1.60)	.64
Altered mental status	21	(0.65)	30	(1.12)	51	(0.87)	.04
Postoperative nausea	24	(0.75)	14	(0.52)	38	(0.65)	.28
Central nervous system disorder	20	(0.62)	17	(0.63)	37	(0.63)	.96
Bacterial meningitis	5	(0.16)	10	(0.37)	15	(0.25)	.10
Postoperative fever	3	(0.09)	10	(0.37)	13	(0.22)	.02

SIADH—syndrome of inappropriate antidiuretic hormone secretion; CSF—cerebrospinal fluid; ICA—internal carotid artery.

change associated with the microscopic to endoscopic transition over the entire time period (2010-2014) was ≈11.33%, $P < .001$.

Significant differences in regional utilization of microscopic and endoscopic approaches to transsphenoidal pituitary surgery were also evident with increasing rates of endoscopic procedures in each defined region. Specifically, rates in the utilization of endoscopic surgery increased significantly in the North-east region by approximately 31.80% from 49.78% in 2010 to 65.61% in 2014 ($P < .001$), in the North-central region from 40.32% in 2010 to 64.92% in 2014 representing a change of approximately 61.01% ($P < .001$), and in the West region from 30.51% in 2010 to 52.38% in 2014 representing a significant change of approximately 71.68% ($P < .001$). The highest increase in the rates of utilization of endoscopic surgery was observed in the South region by approximately 74.97% from 31.40% in 2010 to 54.94% in 2014 ($P < .001$).

Overall, microsurgical procedures were performed more commonly than endoscopic approaches nationally prior to 2013. These approaches were roughly equivalent in frequency in 2013. In 2014, there were statistically more endoscopic procedures performed nationally when compared to microsurgery. Endoscopic procedures first exceeded microsurgery in the North-east region in 2012. Subsequent to this time, similar trends were seen in the North-central (2013), South (2014), and West (2014) regions. Further analysis of regional trends revealed that the shifts from microsurgery to endoscopic surgery were significant in the North-east ($P < .001$), South ($P < .001$), West ($P < .001$), and North-central ($P < .001$) regions. Regional trends in the utilization of the different procedures are depicted in Figure 1.

The overall complication rate associated with transsphenoidal pituitary surgery was 40.04%, and increased by approximately 18.54% from 36.78% in 2010 to 43.60% in 2014 ($P = .01$) [Figure 2]. Overall complication rates associated with microscopic and endoscopic surgery were 35.27% and 45.76%, respectively, and increased by approximately 11.89% ($P = .28$) and 11.29% ($P = .26$), respectively across the period under study (ie, 2010 to 2014). In other words, the complication rates of endoscopic and microscopic surgeries did not significantly change over this time period; however, the overall complication rate did significantly increase due to the weighted average of transitioning from microsurgery with a lower complication rate to endoscopic surgery with a higher rate.

Yearly changes in complication rates associated with transsphenoidal surgery showed the following changes: 2010 to 2011 (+3.70%, $P = .28$), 2011 to 2012 (+8.97%, $P = .12$), 2012 to 2013 (–1.59%, $P = .81$), and 2013 to 2014 (+6.60%,

TABLE 4. **Adjusted Regression Analyses for Risk of Complications Comparing Endoscopic vs Microscopic (Reference Group) Pituitary Surgery**

	Multivariate logistic regression				Propensity score model (matched)			
	Odds ratio	[95% confidence interval]		P-value	Odds ratio	[95% confidence interval]		P-value
All disorders of the pituitary	1.54	1.35	1.76	<.001	1.51	1.31	1.73	<.001
Diabetes insipidus	1.54	1.34	1.77	<.001	1.48	1.28	1.72	<.001
SIADH	1.63	1.00	2.37	.05	1.53	1.04	2.24	.03
Iatrogenic pituitary disorder (hypopituitarism)	1.29	0.82	2.04	0.27	1.40	0.87	2.24	.17
All fluid and electrolyte disorders	1.30	1.10	1.54	<.001	1.25	1.05	1.48	.01
Hypoosmolality/hyponatraemia	1.28	1.01	1.62	.04	1.17	1.01	1.34	.03
Hyperosmolality/hypernatraemia	1.43	1.00	2.00	.05	1.35	0.96	1.90	.08
All postop CSF leak/dura tear	1.93	1.62	2.31	<.001	1.86	1.56	2.23	<.001
CSF rhinorrhoea	2.67	2.03	3.51	<.001	2.48	1.88	3.28	<.001
Other CSF leak	1.63	1.31	2.02	<.001	1.59	1.28	1.98	<.001
Dura tear	1.53	0.95	2.47	.08	1.55	0.94	2.56	.08
All hemorrhagic complications	1.26	0.95	1.68	.11	1.09	0.79	1.49	.60
Hemorrhagic complication	1.66	0.94	2.93	.08	1.50	0.84	2.68	.17
Hematoma	2.43	0.89	6.64	.08	2.50	0.86	7.27	.09
Intracranial hemorrhage	1.19	0.78	1.82	.42	0.90	0.53	1.53	.71
Iatrogenic cerebrovascular/ICA injury	0.63	0.27	1.50	.30	0.42	0.17	1.05	.07
Epistaxis	1.48	0.85	2.57	.16	1.49	0.84	2.62	.17
All ophthalmological complications	1.15	0.94	1.40	.17	1.11	0.90	1.35	.33
Visual field defects	1.23	0.96	1.57	.11	1.17	0.91	1.50	.23
Paralytic strabismus	1.02	0.71	1.45	.93	0.98	0.68	1.41	.91
Diplopia	1.05	0.69	1.60	.81	1.04	0.68	1.60	.85
Altered mental status	1.64	1.01	2.92	.04	1.46	1.01	2.60	.03
Postoperative nausea	0.69	0.35	1.36	.29	0.67	0.34	1.34	.26
Central nervous system disorder	1.01	0.52	1.97	.97	1.04	0.53	2.06	.90
Bacterial meningitis	2.82	0.91	8.69	.07	3.13	0.94	10.37	.06
Postoperative fever	5.06	1.32	19.38	.02	4.31	1.14	16.23	.03

SIADH—syndrome of inappropriate antidiuretic hormone secretion; CSF—cerebrospinal fluid; ICA—internal carotid artery.

TABLE 5. **Other Medical Complications and Mortality**

	Microscopic		Endoscopic		Total		
	n = 3207	(100.00)	n = 2679	(100.00)	n = 5886	(100.00)	P-value
Acute respiratory failure	45	(1.40)	45	(1.68)	90	(1.53)	.40
Deep vein thrombosis	11	(0.34)	20	(0.75)	31	(0.53)	.05
Pulmonary embolism	10	(0.31)	6	(0.22)	16	(0.27)	.62
Mortality	7	(0.22)	3	(0.11)	10	(0.17)	.32

$P = .35$), resulting in an overall annual rate of change of +4.42%, $P = .07$. Further analysis revealed yearly changes in rates of complications associated with microscopic surgery as follows: 2010 to 2011 (+6.07%, $P = .29$), 2011 to 2012 (+8.84%, $P = .32$), 2012 to 2013 (–10.43%, $P = .43$), and 2013 to 2014 (+8.22%, $P = .55$) resulting in an average annual change of (+3.17%, $P = .12$) over the period 2010 to 2014. Similarly, yearly changes in complications associated with endoscopic surgery showed: 2010 to 2011 (–1.68%, $P = .90$), 2011 to 2012 (+7.37%, $P = .42$), 2012 to 2013 (+3.73%, $P = .43$), and 2013 to 2014 (+1.64%, $P = .86$) resulting in an average change of +2.76% across the entire period, $P = .06$. Although complication rates remained higher among endoscopically performed surgeries compared to microscopic procedures during the period ($P < .001$), the change in year to year rates of complications associated with endoscopic surgery trended towards a decrease over time (2011-2014).

Whereas the overall complication rates in most regions revealed a positive change (increasing rates) across time, complication rates in the North-east region revealed a negative change (ie, decreasing rates) by a factor of approximately 0.19% for all transsphenoidal surgeries, with a decrease of approximately 2.93% observed for endoscopic procedures ($P = .59$). See Table 6 for trends in the complications across the different regions.

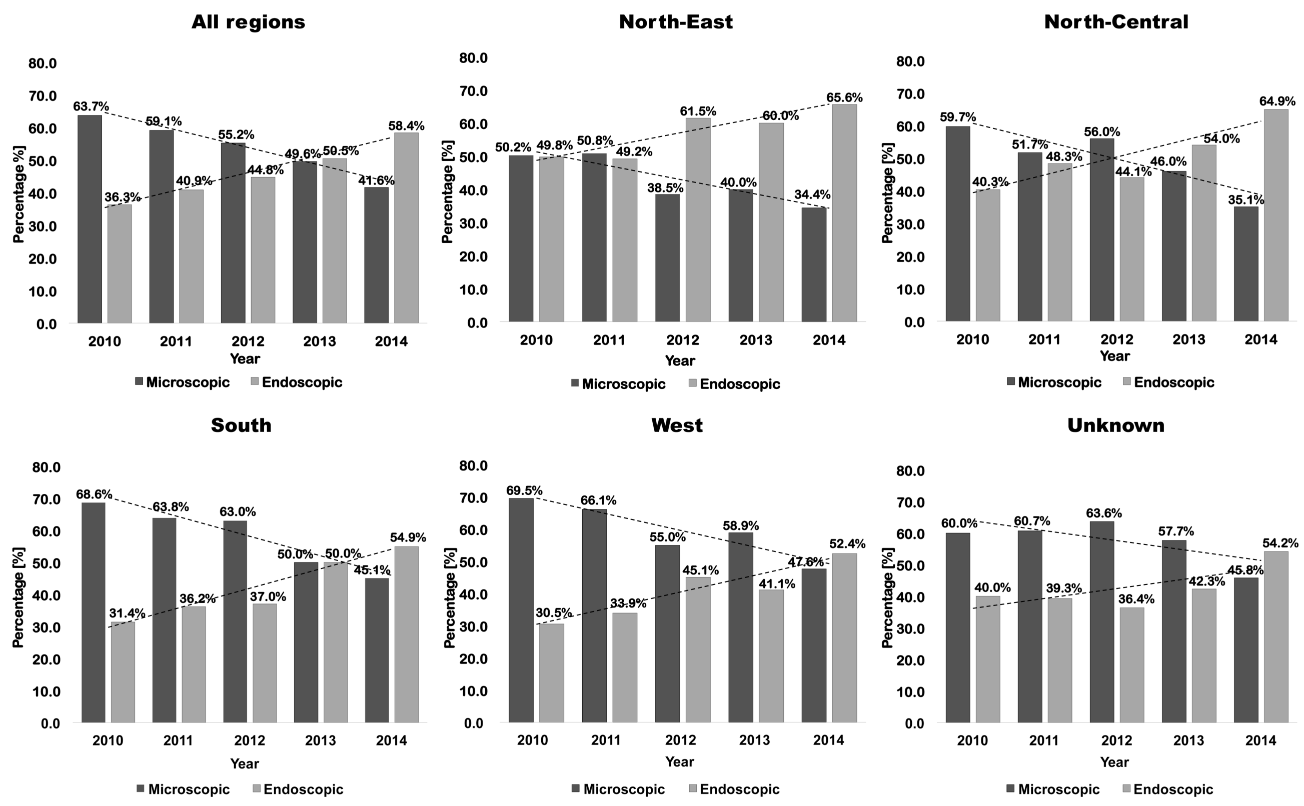

FIGURE 1. *Annual trends in the rates of utilization of transsphenoidal pituitary surgery (microscopic vs endoscopic).*

Costs and Length of Stay

Overall, the average individual total hospitalization costs associated with transsphenoidal pituitary surgery was \$35 432.04. Hospitalization costs were significantly higher among patients that underwent endoscopic surgery compared to microscopic surgery [\$38 447.27 (95%CI: \$36 833.01-\$40 061.53) vs \$32 913.23 (95%CI: \$31 835.95-\$33 990.51), $P < .001$]. Average total costs were also significantly higher among patients who developed complications compared to patients who did not develop complications [\$44 302.24 (95%CI: \$42 176.93-\$46 427.55) vs \$29 507.67 (95%CI: \$28 904.42-\$30 110.93), $P < .001$]; additional incremental costs represented an increase in average total hospitalization costs of approximately 50.14% among patients who developed complications ($P < .001$). Furthermore, among patients who did not develop complications, costs associated with endoscopic surgery were significantly higher than that of microscopic surgery ($P < .001$). There were no significant differences in the costs between microscopic and endoscopic cohorts among the subset of patients who developed one or more complications postoperatively ($P = .99$). Table 7 shows the results for total hospitalization costs and duration of hospital stay.

The total average length of hospitalization overall for patients that underwent transsphenoidal surgery was 3.75 d. There was no significant difference in the lengths of stay among patients that underwent microscopic vs endoscopic transsphenoidal surgery (3.68 vs 3.84 d, $P = .11$). Remarkably, the overall average duration of hospitalization increased significantly by approximately 100% in patients that developed complications compared to those who did not develop complications [5.36 vs 2.68d, $P \leq .001$].

Analysis of patient characteristics and presence of specific medical comorbid conditions as preoperative determinants of the likelihood of complications revealed that patients aged less than or equal to 18 yr old (OR 2.63; 95%CI: 1.93-3.63) were more likely to develop postoperative complications after undergoing transsphenoidal surgery. Also, the presence of medical comorbid conditions such as cerebrovascular disease and/or previous stroke (OR 4.85; 95%CI: 3.70-6.36), and disseminated/metastatic cancer (OR 1.46; 95%CI: 1.29-1.76) were significantly associated with an increased likelihood of developing complications after adjustment for possible confounders.

Sensitivity analysis. To best optimize the comparability of the 2 groups and minimize the possibility of capturing cases unrelated to pituitary/sellar pathology which were managed endoscopically and coded using CPT-62165, we also performed a sensitivity analysis. Results of this analysis conducted among a subset of

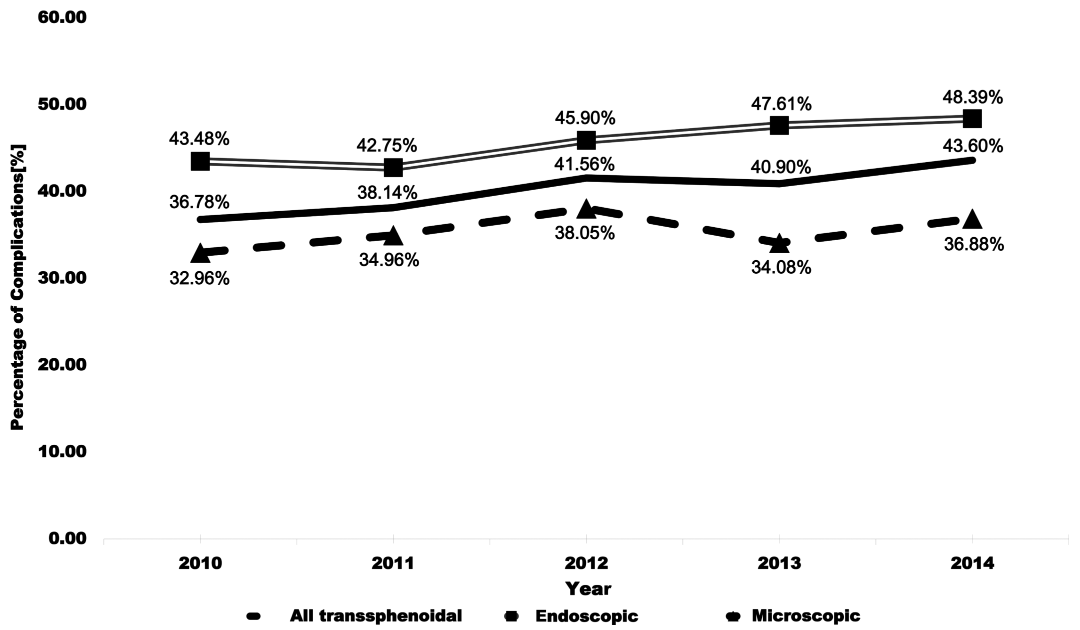

FIGURE 2. *Annual trends in the rates of complications associated with transsphenoidal pituitary surgery.*

patients with specific pituitary disorders [microscopic (n = 3024) and endoscopic (n = 2503)] representing approximately 93.90% of our overall sample confirmed higher rates of DI, SIADH, hypoosmolality/hyponatraemia, CSF rhinorrhoea, other CSF leak, and postoperative fever in patients undergoing endoscopic pituitary surgery. These results are shown in the **Table**, **Supplemental Digital Content 2**.

DISCUSSION

Postoperative Complications

We studied 5886 transsphenoidal pituitary surgery cases that occurred in the United States from 2010 to 2014. Most cases involved microscopic procedures. The leading indication among patients undergoing transsphenoidal pituitary surgery was a diagnosis of benign neoplasm of the pituitary and craniopharyngeal duct (ICD-9-CM 227.3). This finding is consistent with other studies that have examined the spectrum of surgical indications in transsphenoidal pituitary surgery.[31] Findings from our study show that one or more postoperative complications occurred in 40% of all cases that underwent transsphenoidal pituitary surgery. This is comparable with complication rates reported in other national studies ranging from 27% to 42% among patients that underwent transsphenoidal pituitary surgery.[32,33] A higher incidence of complications occurred among patients that underwent surgery via the endoscopic technique during this period. In the propensity-adjusted analysis, which is our dominant model, we found that patients who underwent endoscopic surgery were more likely to develop DI, SIADH, hypoosmolality/hyponatraemia, CSF rhinorrhoea and other CSF leak, altered mental status, and postoperative fever compared to patients that underwent microscopic surgery. There were no differences in hemorrhagic complications, ophthalmological complications, or bacterial meningitis between these techniques. Similar findings were obtained in our sensitivity analyses, robust in all inclusion domains, except for altered mental status. Importantly, the observed differences in outcome and complications noted in our study were obtained after casemix adjustment.

The most common complication noted in our analysis of patients that underwent transsphenoidal pituitary surgery was DI, with a higher incidence and likelihood among patients that underwent surgery via an endoscopic approach compared to microscopic procedure. This finding is in contrast to the meta-analyses by Deklotz et al, Ammirati et al, and Gao et al in which no significant difference was noted in postoperative DI between these 2 surgical groups and the meta-analysis by Goudakos et al in which DI was found to be less frequent in patients undergoing endoscopic surgery.[19,21-23] In our study, we also found higher rates of CSF rhinorrhoea and other CSF leak among patients that underwent endoscopic surgery. This too is in contrast to several of the reported meta-analyses in which there was no significant difference in the leak rates between these procedures.[19,22,23] In addition, the meta-analysis by DeKlotz et al found a decreased incidence of CSF leak rate in patients that underwent an endoscopic procedure.[21]

In our study, the overall rate of bacterial meningitis was less than 1%, consistent with existing literature.[21,33,34] We did not find any differences in the rates of meningitis associated with the use of the microscope vs the endoscope, this despite the increase

TABLE 6. Annual Rate of Complications by Region

	2010	2011	2012	2013	2014	Total	% change 2010-2014	*P*-value
North-east								
Microscopic	32.14	33.06	34.04	25.00	26.32	30.66	−18.11	.59
Endoscopic	50.45	45.83	43.33	52.50	48.97	47.99	−2.93	.59
All transsphenoidal	41.26	39.34	39.75	41.50	41.18	40.55	−0.19	.99
North-central								
Microscopic	41.06	32.86	40.43	41.25	37.31	38.51	−9.13	.59
Endoscopic	37.25	32.06	45.95	46.81	49.19	41.99	32.05	.03
All transsphenoidal	39.53	32.47	42.86	44.25	45.03	40.23	13.91	.03
South								
Microscopic	29.68	36.22	38.87	37.36	42.70	36.01	43.87	.03
Endoscopic	46.78	45.90	48.02	50.00	48.85	47.96	4.42	.94
All transsphenoidal	35.05	39.72	42.26	43.68	46.08	40.87	31.47	.01
West								
Microscopic	34.15	37.01	36.00	33.82	34.55	35.15	1.17	.98
Endoscopic	33.33	48.10	45.53	40.00	47.93	43.67	43.80	.25
All transsphenoidal	33.90	40.77	40.29	36.36	41.56	38.62	22.60	.36
Unknown								
Microscopic	16.67	23.53	42.86	6.67	36.36	27.14	118.12	.15
Endoscopic	50.00	45.45	50.00	27.27	30.77	39.22	−38.46	.73
All transsphenoidal	30.00	32.14	45.45	15.38	33.33	32.23	11.10	.20
All regions								
Microscopic	32.96	34.96	38.05	34.08	36.88	35.27	11.89	.28
Endoscopic	43.48	42.75	45.9	47.61	48.39	45.76	11.29	.26
All transsphenoidal	36.78	38.14	41.56	40.9	43.6	40.04	18.54	.01

in rates of CSF leak associated with endoscopy. The finding in our study of similar rates of meningitis in patients undergoing microscopic and endoscopic transsphenoidal surgery is consistent with findings from multiple meta-analyses.[19,21-23]

From a vascular standpoint, we found no differences in the rates of hemorrhagic complications including intracranial hemorrhage, epistaxis, and iatrogenic cerebrovascular/ICA injury between patients that underwent microscopic vs endoscopic transsphenoidal surgery. Although a potentially devastating intraoperative and postoperative complication, the incidence of intracranial hemorrhage in patients undergoing transsphenoidal surgery is rare.[35-37] In our study, we found an inclination towards a reduced risk of iatrogenic vascular injury among patients that underwent endoscopic surgery, although this was not statistically significant. This is in contrast to a study by Ammirati et al who reported increased vascular complications with endoscopic techniques.[23]

From the foregoing, it is evident that there are similarities and discrepancies between our study findings and findings from meta-analyses that have also examined outcomes in microscopic vs endoscopic pituitary surgery. There are several important aspects to consider here in trying to understand the disparate findings. Although the statistical power of meta-analyses is enhanced by aggregate pooling of effects from smaller clinical studies and trials, it must be mentioned that the findings obtainable from meta-analysis studies are only as good as the individual studies from which the data were drawn.[38,39] Moreover, the more similar the study protocols are from which the meta-analysis was done, the more likely the validity of the findings of the meta-analysis. For this reason, meta-analyses are inherently subject to potential bias which may include biases contained within the individual studies from which the meta-analyses were conducted.[39] In addition, endoscopic pituitary surgeon–researchers likely to publish their findings may be more likely those whose practices are at high-volume centers and who may have had considerable experience and expertise with endoscopic techniques. Researchers are also more likely to publish their findings when those findings are in line with previously published material as the generally accepted views or notions on the topic.[40,41] Additionally, in our population-based study, we provide a snapshot of complications during a transition phase—from microscopic to endoscopic pituitary surgery—and although neurosurgeons currently in training will be more increasingly exposed to endoscopic pituitary and skull base techniques, there is a learning curve for neurosurgeons experienced in microsurgery adopting endoscopic procedures.[42-45] Thus, it is probable that the differences observed in our study findings and those from previous meta-analyses may in fact reflect inherent differences in the patient populations studied. Taking the above into consideration, the value of our study and its relevance in understanding the true incidence and scope of specific postoperative complications in transsphenoidal pituitary surgery resides in the fact our findings do not represent a select group of patients or practice settings, but rather generalize more broadly across the entire spectrum of patients undergoing transsphenoidal pituitary surgery.

TABLE 7. Costs and Length of Stay

	Observations	Mean	95% confidence interval LL	95% confidence interval UL	*P*-value
All transsphenoidal surgery					
Total payment (in US dollars)					
Microscopic	3207	32 913.23	31 835.95	33 990.51	
Endoscopic	2679	38 447.27	36 833.01	40 061.53	<.001
Total	5886	35 432.04	34 489.29	36 374.78	
Total net payment (in US dollars)					
Microscopic	3207	31 026.00	29 960.78	32 091.22	
Endoscopic	2679	36 258.08	35 013.89	37 502.26	<.001
Total	5886	33 407.37	32 593.99	34 220.74	
Total length of stay (d)					
Microscopic	3207	3.68	3.54	3.82	
Endoscopic	2679	3.84	3.70	3.98	.11
Total	5886	3.75	3.65	3.85	
Transsphenoidal surgery without complications					
Total payment (in US dollars)					
Microscopic	2076	28 135.17	27 421.88	28 848.46	
Endoscopic	1453	31 468.66	30 423.19	32 514.14	<.001
Total	3529	29 507.67	28 904.42	30 110.93	
Total net payment (in US dollars)					
Microscopic	2076	26 437.12	25 726.22	27 148.02	
Endoscopic	1453	29 720.07	28 711.61	30 728.53	<.001
Total	3529	27 788.81	27 197.39	28 380.24	
Total length of stay (d)					
Microscopic	2076	2.68	2.60	2.75	
Endoscopic	1453	2.68	2.57	2.79	.97
Total	3529	2.68	2.61	2.74	
Transsphenoidal surgery with complications					
Total payment (in US dollars)					
Microscopic	1131	41 683.56	38 995.08	44 372.05	
Endoscopic	1226	46 718.01	43 473.12	49 962.89	.99
Total	2357	44 302.24	42 176.93	46 427.55	
Total net payment (in US dollars)					
Microscopic	1131	39 449.09	36 791.51	42 106.66	
Endoscopic	1226	44 006.63	41 634.74	46 378.52	.99
Total	2357	41 819.70	40 044.26	43 595.15	
Total length of stay (d)					
Microscopic	1131	5.52	5.18	5.86	
Endoscopic	1226	5.22	4.96	5.48	.17
Total	2357	5.36	5.15	5.57	

Trends and Utilization

From our study, there is ample evidence indicating a transition in the utilization of the different approaches to transsphenoidal pituitary surgery, from microscopic to endoscopic nationally, and across different geographical regions of the United States. A similar finding was also observed in a study analyzing Medicare and Medicaid data.[9] In our study, the average annual rate of change associated with the microscopic–endoscopic transition in the US was approximately 11 percent/yr. The greatest rates in adoption of endoscopic techniques (≈+16%) and a parallel decline in microscopic techniques (≈−16%) occurred between 2013 and 2014 and notably in 2014, endoscopic procedures were more commonly performed than microsurgical pituitary procedures. On the other hand, the rate of change in complications between 2011 and 2012 represented the highest increase observed with endoscopic techniques (+7.37%) during the time period of our study and this rate of change appeared to have slowed down between 2012 to 2013 (+3.73%) and 2013 to 2014 (+1.64%). Taken together, these trends of increasing adoption of endoscopic techniques coupled with the progressive slowing of complications may suggest an overall evolution in utilization and complications during this transition phase, a trend likely to improve as more surgeons adopt endoscopic approaches.

In our analysis, the North-east region demonstrated the earliest transition to endoscopic transsphenoidal surgery (2012) and the highest volume in the utility of endoscopic techniques. Concordant with the increase in and current major utilization of endoscopic pituitary surgery in the North-east, our study also revealed a reduction, albeit nonsignificant, in the rates of complications associated with endoscopic surgery in this region. We are not able to determine causality; however, this finding is interesting given the relationship between surgical volume and outcome which has been confirmed in several surgical specialties and has also been reported in studies relating to pituitary surgery.[32,46,47] Of particular interest however was the fact that in spite of the somewhat higher overall complication rates associated with endoscopic techniques, there remained a significant shift towards increased utilization and adoption of endoscopic techniques. Predictably, the rising trend and shift towards increased utilization of endoscopic surgery may provide some explanation for the observed higher incidence of complications associated with endoscopy that occurred during the period across different geographical regions in the United States. Interestingly however, there were no statistically significant changes in the overall yearly rates of complications associated with endoscopic transsphenoidal pituitary surgery that occurred across the time frame of our study.

Our analysis of costs associated with uncomplicated transsphenoidal surgery and incremental costs due to complications was particularly revealing given the paucity of data on costs associated with transsphenoidal surgery in the United States. Generally, the average total costs associated with endoscopic surgery were significantly elevated compared to microscopic surgery. However, similar lengths of hospitalization were observed for uncomplicated microscopic and endoscopic transsphenoidal pituitary surgery. Our analysis further demonstrated that postoperative complications resulted in overall higher total costs and longer hospital stays. On the whole, for both sets of patients that underwent microscopic or endoscopic transsphenoidal pituitary surgery, those that developed one or more postoperative complications had twice the average duration of hospital stays, and had significantly higher hospitalization costs by a factor of approximately 50% increase overall compared to those without any complications. Given the multiple and complex factors that contribute to the cost differential between these groups, further studies are necessary to fully understand drivers of costs in pituitary surgery.

Limitations of the Study

A major strength of this study is the large population-based sample of patients analyzed that underwent transsphenoidal pituitary surgery, which increases the generalizability of our findings. This study also contributes valuable updated population-based data on postoperative complication burden and associated costs in transsphenoidal pituitary surgery in the United States. It should be noted, however, that our study has numerous limitations. One limitation is that since our study focused on patients under 65 yr of age, the findings from this study must be cautiously applied to older patients.

As is common with research conducted using insurance claims data, this study has some unique challenges. Generally, healthcare claims data are primarily collected for the purposes of billing rather than for research and as such, there is the possibility of unintended miscoding errors within our database, a situation that might inadvertently lead to an underestimation or exaggeration of some of our findings. However, the impact of this limitation is offset by the large sample size of our studied population. Another limitation is a lack of clinical information relating to disease severity and duration, a situation that could possibly affect patient outcome and the likelihood of developing postoperative complications. In addition, the unavailability of biochemical laboratory information and neuro-ophthalmological evaluation make us unable to identify patients with preoperative biochemical and visual abnormalities, respectively and adjust for the same in our analyses. Additionally, the indication for surgery may be another limiting factor that might influence the interpretation of the study findings. In our study, however, we take into account the variability due to case-mix and adjust accordingly in our regression and matched propensity analyses. In order to further minimize confounding arising from nonspecificity in coding and utilization of endoscopic codes for broader indications which might have higher complication rates compared with pituitary surgery, we performed sensitivity analyses limited to patients with identified pituitary pathologies. In this sensitivity analysis, we confirmed the major findings from our matched propensity model. Our analyses, however, are not robust to account for confounding from expanded endonasal endoscopic approaches coded with CPT-62165.

Other limitations of the MarketScan database may have to do with the sampling methodology, and with the nature of the sample population. Notably, the MarketScan data are based on a large convenience nonrandom sample mostly obtained from contributors to the database including more than 300 employers and over 40 different health plans.[24] It is thus mostly representative of a population of mid- to large-size employer-sponsored insured individuals. Because the sample is not random, there may be concerns regarding its generalizability to specific patient populations. The database also provides information on patient's state of residence, metropolitan statistical area, and geographical region. The approximately 50 million patients in the main databases each year are located in all 50 states, with good representation from each state.[24] The sampling methodology employed in data collection is fairly uniform across states within different geographical regions, thereby minimizing bias and ensuring a balanced representation of individual patient populations from the different regions. However, due to the nonrandomness of the sample, there still exists a possibility for introducing bias when comparing outcomes likely due to sampling techniques and/or due to regional variability within and across different geographical regions (ie, within-region variability and between-region variability). Taking this limitation into consideration, our analyses not only compared complications between endoscopic and microsurgical transsphenoidal procedures, we also compared outcomes within individual regions in order to minimize the potential for bias and over- or underestimation in the effect of our studied outcomes.

Notably, the primary outcome examined in this study was postoperative complications arising in patients that underwent microscopic and endoscopic transsphenoidal pituitary surgery. There is no metric contained within this database for extent of resection, remission rates for secreting adenomas, need for additional treatment, etc. Consequently, a value analysis could not be performed evaluating these 2 surgical procedures. Caution is therefore needed in interpretation of the implication of complications as evaluated in our study as these do not necessarily equate to the overall outcome or success of surgery. For example, would one accept a higher complication rate for a higher gross total resection rate? Expanded databases or registries which collect comprehensive data including such outcome metrics would greatly enhance the analysis during this transition from microscopic to endoscopic transsphenoidal surgery.

It should also be mentioned that no unique identifier exists within the database that specifically identifies postoperative complications separately from those occurring preoperatively. As a result, it is possible that estimates for postoperative complications may in some instances reflect conditions that may have been present preoperatively potentially resulting in skewed estimates. While this limitation may be less likely to affect estimates for more common complications with a higher degree of probability such as DI and/or fluid and electrolyte disorders, there may be some unintended overestimation for less commonly encountered postoperative complications with a lesser degree of probability such as diplopia and/or visual field defects which may have been present prior to surgery. In addition, this dataset is unable to differentiate between transient and permanent complications.

Also important to the discussion and comparative evaluation of microscopic and endoscopic approaches and/or factors implicated in the development of postoperative complications after transsphenoidal pituitary surgery is the degree of proficiency of the surgeon with either technique. Regardless of whichever technique is employed, patient outcome and the likelihood of postoperative complications are largely dependent on the surgeon's experience and expertise. Since the early days of transsphenoidal surgery, the impact of surgeon experience in influencing patient outcome of surgery has continually been recognized. Consistently in the literature, surgeons with high operative volumes and primary subspecialization in pituitary surgery have reported better surgical outcome in their patients which is thought to be largely attributable to significant gain in experience that occurs over time.[11,46] The role of specialization and thus of provider volume in improving patient outcome and obtaining better results from surgery, and in minimizing complications and untoward postoperative outcomes was also acknowledged by Harvey Cushing, and was a subject to which he placed much emphasis during his career.[48] This is applicable to the current microsurgical–endoscopic transition as surgeons progress from novice to master endoscopic pituitary surgeons. As further advancements are made in endoscopic instrumentation and techniques in transsphenoidal pituitary surgery and as more surgeons continue to embrace this technique, the overall complication rates at the national level may remain higher for a while, however, over time these rates may decline when more pituitary surgeons gain substantial experience with the technique. In our database study, individual provider identifier variables were unfortunately unavailable in more than 75% of cases and, as a consequence, we were unable to account for the effect of provider volume in the development of postoperative complications in our analyses. Regardless of the above limitations, our analysis is unique in that it is the first major nationwide appraisal of transsphenoidal surgery in the United States that evaluates national and regional volume in the incidence, trends, and the likelihood of complications associated with both microscopic and endoscopic techniques, while examining the cost implications associated with the development of complications.

CONCLUSION

Pituitary surgery is undergoing a transition with increased utilization of endoscopic techniques. In this large population-based study examining postoperative complications and costs associated with the development of complications in patients undergoing transsphenoidal pituitary surgery in the United States, complications occurred in a significant number of patients overall and endoscopic procedures were associated with an increased incidence of postoperative complications including DI, SIADH, hypoosmolality/hyponatremia, CSF rhinorrhoea, other CSF leak, altered mental status, and postoperative fever. Notably, the presence of complications after transsphenoidal pituitary surgery resulted in increased hospitalization and substantial additional costs of care. Our findings of increased rates of complications in patients undergoing endoscopic pituitary surgery, which are in contrast to several published meta-analyses, may reflect early experience during the adoption phase of endoscopic pituitary and skull base techniques. Continued analysis and serial critical review of surgical outcomes are important during this transition.

Disclosure

This work has not been previously presented at any previous scientific meeting. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Doglietto F, Prevedello DM, Jane JA, Han J, Laws ER. Brief history of endoscopic transsphenoidal surgery–from philipp bozzini to the first world congress of endoscopic skull base surgery. *Neurosurg Focus*. 2005;19(6):E3.
2. Liu JK, Das K, Weiss MH, Laws ER, Couldwell WT. The history and evolution of transsphenoidal surgery. *J Neurosurg*. 2001;95(6):1083-1096.
3. Jankowski R, Auque J, Simon C, Marchal JC, Hepner H, Wayoff M. How I do it: head and neck and plastic surgery: endoscopic pituitary tumor surgery. *Laryngoscope*. 1992;102(2):198-202.

4. Sethi DS, Pillay PK. Endoscopic management of lesions of the sella turcica. *J Laryngol Otol*. 1995;109(10):956-962.
5. Rodziewicz GS, Kelley RT, Kellman RM, Smith MV. Transnasal endoscopic surgery of the pituitary gland: technical note. *Neurosurgery*. 1996;39(1):189-192.
6. Jho HD, Carrau RL. Endoscopic endonasal transsphenoidal surgery: experience with 50 patients. *J Neurosurg*. 1997;87(1):44-51.
7. Cappabianca P, Alfieri A, de Divitiis E. Endoscopic endonasal transsphenoidal approach to the sella: towards functional endoscopic pituitary surgery (FEPS). *Minim Invasive Neurosurg*. 1998;41(2):66-73.
8. Shikani AH, Kelly JH. Endoscopic debulking of a pituitary tumor. *Am J Otolaryngol*. 1993;14(4):254-256.
9. Rolston JD, Han SJ, Aghi MK. Nationwide shift from microscopic to endoscopic transsphenoidal pituitary surgery. *Pituitary*. 2016;19(3):248-250.
10. Dallapiazza R, Bond AE, Grober Y, et al. Retrospective analysis of a concurrent series of microscopic versus endoscopic transsphenoidal surgeries for Knosp Grades 0–2 nonfunctioning pituitary macroadenomas at a single institution. *J Neurosurg*. 2014;121(3):511-517.
11. O'Malley BW, Grady MS, Gabel BC, et al. Comparison of endoscopic and microscopic removal of pituitary adenomas: single-surgeon experience and the learning curve. *Neurosurg Focus*. 2008;25(6):E10. doi:10.3171/FOC.2008.25.12.E10.
12. D'Haens J, Van Rompaey K, Stadnik T, Haentjens P, Poppe K, Velkeniers B. Fully endoscopic transsphenoidal surgery for functioning pituitary adenomas: a retrospective comparison with traditional transsphenoidal microsurgery in the same institution. *Surg Neurol*. 2009;72(4):336-340.
13. Little AS, Kelly DF, Milligan J, et al. Comparison of sinonasal quality of life and health status in patients undergoing microscopic and endoscopic transsphenoidal surgery for pituitary lesions: a prospective cohort study. *J Neurosurg*. 2015;123(3):799-807.
14. Zaidi HA, Awad A-W, Bohl MA, et al. Comparison of outcomes between a less experienced surgeon using a fully endoscopic technique and a very experienced surgeon using a microscopic transsphenoidal technique for pituitary adenoma. *J Neurosurg*. 2016;124(3):596-604.
15. Gaillard S. The transition from microscopic to endoscopic transsphenoidal surgery in high-caseload neurosurgical centers: the experience of Foch Hospital. *World Neurosurg*. 2014;82(6 suppl):S116-S120.
16. Razak AA, Horridge M, Connolly DJ, et al. Comparison of endoscopic and microscopic trans-sphenoidal pituitary surgery: early results in a single centre. *Br J Neurosurg*. 2013;27(1):40-43.
17. Cappabianca P, Alfieri A, Colao A, Ferone D, Lombardi G, de Divitiis E. Endoscopic endonasal transsphenoidal approach: an additional reason in support of surgery in the management of pituitary lesions. *Skull Base Surg*. 1999;9(2):109-117.
18. Rotenberg B, Tam S, Ryu WHA, Duggal N. Microscopic versus endoscopic pituitary surgery: a systematic review. *Laryngoscope*. 2010;120(7):1292-1297.
19. Goudakos JK, Markou KD, Georgalas C. Endoscopic versus microscopic trans-sphenoidal pituitary surgery: a systematic review and meta-analysis. *Clin Otolaryngol*. 2011;36(3):212-220.
20. Strychowsky J, Nayan S, Reddy K, Farrokhyar F, Sommer D. Purely endoscopic transsphenoidal surgery versus traditional microsurgery for resection of pituitary adenomas: systematic review. *J Otolaryngol*. 2011;40(2):175-185.
21. DeKlotz TR, Chia SH, Lu W, Makambi KH, Aulisi E, Deeb Z. Meta-analysis of endoscopic versus sublabial pituitary surgery. *Laryngoscope*. 2012;122(3):511-518.
22. Gao Y, Zhong C, Wang Y, et al. Endoscopic versus microscopic transsphenoidal pituitary adenoma surgery: a meta-analysis. *World J Surg Oncol*. 2014;12:94.
23. Ammirati M, Wei L, Ciric I. Short-term outcome of endoscopic versus microscopic pituitary adenoma surgery: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2013;84(8):843-849.
24. MarketScan Databases | Life Sciences. Available at: http://truvenhealth.com/markets/life-sciences/products/data-tools/marketscan-databases. Accessed November 20, 2016.
25. Hansen L. The marketscan databases for life sciences researchers. *Truven Health Analytics*. 2016. Life Sciences Research Data and Analytic Tools. Available at: http://truvenhealth.com/markets/life-sciences/products/data-tools. Accessed November 25, 2016.
26. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.
27. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619.
28. Moonesinghe SR, Mythen MG, Das P, Rowan KM, Grocott MPW. Risk stratification tools for predicting morbidity and mortality in adult patients undergoing major surgery: qualitative systematic review. *Anesthesiology*. 2013;119(4):959-981.
29. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivar Behav Res*. 2011;46(3):399-424.
30. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70(1):41-55.
31. Cote DJ, Wiemann R, Smith TR, Dunn IF, Al-Mefty O, Laws ER. The expanding spectrum of disease treated by the transnasal, transsphenoidal microscopic and endoscopic anterior skull base approach: a single-center experience 2008–2015. *World Neurosurg*. 2015;84(4):899-905.
32. Barker FG, Klibanski A, Swearingen B. Transsphenoidal surgery for pituitary tumors in the United States, 1996–2000: mortality, morbidity, and the effects of hospital and surgeon volume. *J Clin Endocrinol Metab*. 2003;88(10):4709-4719.
33. Patil CG, Lad SP, Harsh GR, Laws ER, Boakye M. National trends, complications, and outcomes following transsphenoidal surgery for Cushing's disease from 1993 to 2002. *Neurosurg Focus*. 2007;23(3):E7. doi:10.3171/foc.2007.23.3.9.
34. Karppinen A, Kivipelto L, Vehkavaara S, et al. Transition from microscopic to endoscopic transsphenoidal surgery for nonfunctional pituitary adenomas. *World Neurosurg*. 2015;84(1):48-57.
35. Laws ER. Vascular complications of transsphenoidal surgery. *Pituitary*. 1999;2(2):163-170.
36. Brinjikji W, Lanzino G, Cloft HJ. Cerebrovascular complications and utilization of endovascular techniques following transsphenoidal resection of pituitary adenomas: a study of the nationwide inpatient sample 2001–2010. *Pituitary*. 2014;17(5):430-435.
37. Krings JG, Kallogjeri D, Wineland A, Nepple KG, Piccirillo JF, Getz AE. Complications following primary and revision transsphenoidal surgeries for pituitary tumors. *Laryngoscope*. 2015;125(2):311-317.
38. Panesar SS, Bhandari M, Darzi A, Athanasiou T. Meta-analysis: A practical decision making tool for surgeons. *Int J Surg*. 2009;7(4):291-296.
39. Ioannidis JP, Lau J. Pooling research results: benefits and limitations of meta-analysis. *Jt Comm J Qual Improv*. 1999;25(9):462-469.
40. Sutton AJ, Song F, Gilbody SM, Abrams KR. Modelling publication bias in meta-analysis: a review. *Stat Methods Med Res*. 2000;9(5):421-445.
41. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J Clin Epidemiol*. 2000;53(11):1119-1129.
42. Snyderman C, Kassam A, Carrau R, Mintz A, Gardner P, Prevedello DM. Acquisition of surgical skills for endonasal skull base surgery: a training program. *Laryngoscope*. 2007;117(4):699-705.
43. Smith SJ, Eralil G, Woon K, Sama A, Dow G, Robertson I. Light at the end of the tunnel: the learning curve associated with endoscopic transsphenoidal skull base surgery. *Skull Base*. 2010;20(2):69-74.
44. Snyderman CH, Fernandez-Miranda J, Gardner PA. Training in neurorhinology: the impact of case volume on the learning curve. *Otolaryngol Clin North Am*. 2011;44(5):1223-1228.
45. Qureshi T, Chaus F, Fogg L, Dasgupta M, Straus D, Byrne RW. Learning curve for the transsphenoidal endoscopic endonasal approach to pituitary tumors. *Br J Neurosurg*. 2016:1-6. doi:10.1080/02688697.2016.1199786.
46. Ahmed S, Elsheikh M, Stratton IM, Page RC, Adams CB, Wass JA. Outcome of transphenoidal surgery for acromegaly and its relationship to surgical experience. *Clin Endocrinol (Oxf)*. 1999;50(5):561-567.
47. Shahlaie K, McLaughlin N, Kassam AB, Kelly DF. The role of outcomes data for assessing the expertise of a pituitary surgeon. *Curr Opin Endocrinol Diabetes Obes*. 2010;17(4):369-376.
48. Greenblatt SH. Harvey Cushing's paradigmatic contribution to neurosurgery and the evolution of his thoughts about specialization. *Bull Hist Med*. 2003;77(4):789-822.

Supplemental digital content *is available for this article at www.neurosurgery-online.com.*

Acknowledgment

We would like to acknowledge Joseph K. Canner, MHS, for his assistance with data acquisition in the preparation of this manuscript.

COMMENT

I think this is an interesting though limited report. It looks at historical data and appears to make the assumption that over time the increased risks and cost of the endoscopic procedure will somehow match or improve upon those of the microscopic procedure. The authors call this a "transition" period even though the final result of this transition remains unknown.

Unfortunately, this study does not address outcome in any way. To justify increased risk and cost, there must be an improvement in outcome. I do not think it is appropriate at this point to simply write off the increased complication rates and cost to a "learning curve." It is entirely possible that these differences will remain and the surgical community will have to decide if these increases in risk and cost are justified by the outcomes.

William F. Chandler
Ann Arbor, Michigan