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Microsurgical versus Endoscopic Transsphenoidal Resection for Acromegaly: A Systematic Review of Outcomes and Complications

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Abstract

Purpose: The aim of this systematic review is to evaluate the long-term endocrine outcomes and postoperative complications following endoscopic vs. microscopic transsphenoidal resection (TSR) for the treatment of acromegaly.

Methods: A literature review was performed, and studies with at least five patients who underwent TSR for acromegaly, reporting biochemical remission criteria and long-term remission outcomes were included. Data extracted from each study included surgical technique, perioperative complications, biochemical remission criteria and long-term remission outcomes.

Results: Fifty-two case series from 1976 to 2016 met the inclusion criteria, comprising 4,375 patients. Thirty-six reports were microsurgical (n=3,144) and thirteen were endoscopic (n=940). Three studies compared microsurgical (n=111) to endoscopic TSR outcomes (n=180). The overall initial and long-term remission rates were 58.2% vs. 57.4% and 69.2% vs. 70.2% for the microsurgical and endoscopic groups, respectively. For microadenomas, the initial and long-term remission rates were 77.6% vs. 82.2% and 76.9% vs. 73.5% for microsurgical and endoscopic approaches, respectively. For macroadenomas, the initial and long-term remission rates were

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46.9% vs. 60.0% 40.2% vs. 61.5% for microsurgical and endoscopic approaches, respectively. The rates of postoperative CSF leak were 3.0% vs. 2.3% for the microscopic and endoscopic groups, respectively. The rates of hypopituitarism and transient diabetes insipidus were 6.7% vs. 6.4% and 9.0% vs. 7.8% for the microscopic and endoscopic groups, respectively.

Conclusions: Both endoscopic and microsurgical approaches for TSR of growth hormone-secreting adenomas are viable treatment options for patients with acromegaly, and yield similarly high rates of remission under the most current consensus criteria.

Keywords

acromegaly; growth hormone; pituitary adenoma; transsphenoidal; endoscopic; microscopic; review

Introduction

Acromegaly, arising from a growth hormone (GH)-secreting pituitary adenoma, is an uncommon disorder that causes significant morbidity and mortality. [1–4] Transsphenoidal resection (TSR), the preferred first-line treatment for acromegaly, has the ability to achieve biochemical and clinical remission upon complete adenoma extirpation, with modest complication rates. [5–9] Significant improvements in life expectancy have been associated with successful adenoma resection. [10]

Microscopic TSR, which has been the mainstay of surgical management over the past fifty years, has since been partially supplanted by the innovation and refinement of the endoscopic technique. [11–20] Although endoscopic TSR has grown in popularity among neurosurgeons, recent series have been generally remiss of large patient cohorts, reporting of operative complications, and comparison of long-term endocrine outcomes to those achieved by microscopic TSR. As such, the optimal surgical approach for the resection of GH-secreting adenomas remains unclear. The aim of this systematic review is to compare the endocrine outcomes and postoperative complication rates of microscopic vs. endoscopic TSR for the treatment of acromegaly.

Methods

Inclusion criteria

Studies qualified for inclusion in the final analysis based on the following criteria: (1) patients with clinical stigmata and biochemical features consistent with a diagnosis of acromegaly; (2) at least five patients who underwent initial or revision TSR; (3) reporting of biochemical remission criteria, and immediate and long-term remission outcomes; and (4) English language. Studies published before the pioneering case series on the endoscopic approach for pituitary adenomas in 1997 were considered microsurgical series by default. [21] Studies published after this date were excluded if the approach was not specified, or if an endoscope was used to augment the microsurgical approach.

Literature Search

No registered review protocol was utilized in this study. This review follows the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. A systematic literature search of the PubMed, Cochrane Library and Embase databases was conducted on June 10, 2017 using the search term: “transsphenoidal AND acromegaly AND adenoma.” Following the search, the articles were then screened by title and abstract. The remaining articles underwent full text review for eligibility, as set forth in the inclusion criteria.

Literature Review and Data Extraction

Included studies were stratified based on their use of a microsurgical or endoscopic technique. Study-specific criteria for biochemical remission were noted and used as the definition of remission. When reported, the following clinical outcomes were extracted: achievement of initial postoperative biochemical remission, perioperative complications, relapse rates, and biochemical remission rates at last follow-up. Perioperative complications included intra- and postoperative cerebrospinal fluid (CSF) leaks, vascular injuries, visual deficits, endocrine abnormalities, meningitis, epistaxis, and transient or permanent diabetes insipidus (DI). In patients who did not achieve initial remission, adjuvant therapy included medical therapy, radiotherapy, stereotactic radiosurgery (SRS), and/or repeat TSR. When information on tumor size was available, patients were further classified into four subgroups: (1) microsurgery-microadenoma, (2) microsurgery-macroadenoma, (3) endoscopy-microadenoma, and (4) endoscopy-macroadenoma. The definition of micro- and macroadenoma was study-specific. Giant adenomas (≥3cm) were classified as macroadenomas.

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0.0 (Armonk, NY: IBM Corp., 2014). Descriptive statistics of pooled data from microsurgical and endoscopic series were obtained for the following outcomes: initial biochemical remission, relapse, biochemical remission at last follow-up, perioperative complications, and adjuvant therapy. Unclear risks of bias were assumed for retrospective studies.

Results

Study selection and characteristics of included studies

The initial screening process resulted in 95 articles, which were further reviewed for data relevance and usability. After application of the inclusion criteria, 43 studies were excluded for the following reasons: use of the endoscope as an adjunct; lack of clear specification of surgical approach used; insufficient reporting of remission criteria, perioperative or long-term outcomes of TSR; overlapping data from the same institution and reporting of data only from patients who achieved initial remission. For the final quantitative analysis, 52 case series, comprising a total of 4,375 patients, were included. Of these series, 36 were microsurgical [12, 22–57] and 13 were endoscopic, [11, 13–18, 58–63], comprising 3,144 and 940 patients, respectively (Figure 1). Three studies compared microsurgical and

endoscopic approaches, comprising 111 and 180 patients, respectively.[12, 64, 65] The mean follow-up duration was 61.3 months (Table 1).

Clinical Outcomes

Of the 3,255 patients who underwent microscopic TSR, initial endocrine remission was achieved in 1,894 (58.2%). Follow-up data was available for 2,761 patients, with a mean follow-up interval of 59.8 months. Relapse during the follow-up period occurred in 53 of 1,608 patients (3.3%). At last follow-up, endocrine remission was achieved in 1,842 of 2,661 patients (69.2%). Of the 1,120 patients included in the endoscopic series, initial remission was achieved in 643 (57.4%). Follow-up information was available for 1,096 patients, with a mean follow-up interval of 62.7 months. Relapse occurred in 34 of 546 patients (6.2%), and at last follow-up, remission was achieved in in 620 of 883 patients (70.2%).

Of the microsurgical series that stratified remission and relapse data by tumor size (Table 2), initial remission was achieved in 326 of 420 microadenomas (77.6%) and in 453 of 970 macroadenomas (46.7%). There were no reported relapses in the microadenoma group. However, 10 of 160 macroadenoma patients (1.9%) relapsed. Endocrine remission at last follow-up (Figure 2) was observed in 173 of 225 microadenomas (76.9%) and in 164 of 408 macroadenomas (40.2%).

Of the endoscopic series that stratified remission and relapse data by tumor size (Table 2), initial remission was achieved in 67 of 83 microadenomas (82.2%) and in 201 of 335 macroadenomas (60.0%). There were no reported relapses in the microadenoma group. Relapse occurred in 2 of 242 macroadenoma patients (0.6%). Remission at last follow-up (Figure 2) was observed in 75 of 102 microadenomas (73.5%) and in 220 of 358 macroadenomas (61.5%).

Surgical Complications

For studies that reported intraoperative complications, CSF leak was the most common complication, which occurred in 39 of 1, 373 (2.8%) and 86 of 603 (17.4%) patients who underwent microscopic and endoscopic TSR, respectively (Table 3). The rates of persistent postoperative CSF leak were comparable between the groups, occurring in 3.0% and 2.3% of patients in microscopic and endoscopic groups, respectively. Hypopituitarism and transient DI were the most frequently reported postoperative complications. Hypopituitarism, defined as one or more new endocrine abnormalities, was observed in 191 of 2,542 (6.7%) and 52 of 817 (6.4%) patients in the microscopic and endoscopic groups, respectively. Transient DI was observed in 208 of 2, 492 (9.0%) and in 69 of 889 (7.8%) patients in the microscopic and endoscopic groups, respectively. Permanent DI occurred infrequently, and was reported in 2.0% of microsurgical and 1.7% of endoscopic TSR patients, respectively.

Adjuvant Therapy

For patients in whom initial remission was not achieved with microscopic TSR (Table 3), 209 of 780 (36.8%) patients received medical therapy, 68 of 867 (7.8%) patients underwent repeat TSR, 263 of 809 (32.5%) patients underwent radiotherapy, and 35 of 867 (4.0%)

patients underwent SRS. For patients in whom initial remission was not achieved with endoscopic TSR, 221 of 625 (35.4%) patients received medical therapy, 68 of 611 (11.1%) patients underwent repeat TSR, 26 of 331 (7.9%) patients underwent radiotherapy, and 58 of 492 (11.8%) patients underwent SRS.

Consensus Remission Criteria

Of the microsurgical case series that used the 2000 or 2010 consensus remission criteria, 740 of 1311 (56.4%) patients achieved initial endocrine remission (Figure 3). Relapse occurred in 12 of 841 (1.4%) patients, and long-term remission was achieved in 733 of 1,117 (65.6%) patients. Of the endoscopic case series that used the 2000 or 2010 remission criteria, 608 of 1,053 (57.7%) patients achieved initial remission. Relapse occurred in 32 of 512 (0.6%) patients, and long-term remission was achieved in 576 of 789 (73.0%) patients.

Of the microsurgical series which stratified outcomes by tumor size and using the 2000 or 2010 criteria (Figure 3), 173 of 222 microadenomas (77.9%) and in 301 of 636 macroadenomas (47.4%) achieved initial remission. No relapses were observed in either group. Long-term remission was reported in 37 of 48 microadenomas (77.1%) and in 100 of 191 macroadenomas (52.4%). Of the endoscopic series which stratified outcomes by tumor size and using the 2000 or 2010 criteria, initial remission was achieved in 64 of 79 microadenomas (81.0%) and in 210 of 273 macroadenomas (76.9%). No relapses occurred in either group. Long-term remission was reported in 40 of 47 microadenomas (85.1%) and in 87 of 133 macroadenomas (65.4%).

Discussion

Systemic elevation of GH and IGF-1 levels in patients with acromegaly is associated with significant morbidity and mortality. With the advent of novel therapies, the potential to increase life expectancy and achieve therapeutic remission in patients with a wide spectrum of clinical and radiographic disease burden has grown.[10] TSR, which can rapidly normalize hormone levels and provide relief from mass effect, is currently favored over medical therapy. [7, 12, 66, 67] The earliest transsphenoidal approaches to the pituitary made use of the microscope to effectively visualize the operative field. [68, 69] The endoscopic-assisted transsphenoidal approach, introduced in 1963 by Guiot et al, refers to the use of the endoscope as an adjunct to the microscopic removal of a tumor. [70] Although this approach was succeeded, in the 1990’s, by the pure endoscopic transsphenoidal approach, a recent series has highlighted the utility of the endoscopic-assisted technique for its ability to achieve additional adenoma removal following maximal microscopic resection of large and invasive tumors. [71, 72]

Further refinement of the pure endoscopic approach has led to its popularization, in some institutions, over the microscopic approach. However, optimal treatment protocols for patients with acromegaly remain unclear, due to a lack of long-term follow-up and comparison of remission outcomes between surgical modalities, in recent series. [12] Previous reports of endoscopic TSR for acromegaly have been limited by small cohort sizes, short durations of clinical and/or radiographic follow-up, and lack of a uniform definition of remission.[12]

Recent series have advocated for surgical decisions regarding approach to be based upon tumor size and position, preferring microscopic TSR for small, and endoscopic for large tumors.[73] The relative advantages afforded by the endoscope are that it offers a wider, more panoramic view, enabling better visualization and control of the lateral aspects of the tumor and operative field, including views into the suprasellar compartment and lateral aspect of cavernous sinus. However, the disadvantages of the endoscope are that it does not offer three-dimensional stereotactic images like those obtained with the operative microscope, and its surgical instruments have limited maneuverability. [12] The recent development and uptake of three-dimensional endoscopes into clinical practice may, in the imminent future, offset these current disadvantages [74]. Intra-operative MRI, which has been used as an adjunct to both microsurgical and endoscopic techniques, provides an early objective assessment of the radicality of tumor resection [75]. With its use, an improvement in surgical outcomes and consequent remission rates has been reported in two microsurgical and two endoscopic case series [62, 76–78]. Greater accessibility to this technology may, therefore, lead to increased application in the resection of GH-secreting pituitary adenomas.

This review found overall initial and long-term remission rates to be comparable between the endoscopic and microscopic approaches. Better outcomes were achieved for microadenomas, irrespective of surgical modality. Highlighting the relevance of tumor size to the appropriateness of surgical approach, use of the endoscopic technique may achieve higher initial and long-term remission rates in patients with macroadenomas, providing emphasis to the potential benefit of this approach for large tumors. Our findings are consistent with recent analyses suggesting that remission rates achieved by TSR are generally higher for GH-secreting microadenomas, but that endoscopic TSR may achieve improved rates of complete tumor resection and biochemical remission for macroadenomas. [79–81]

Adjuvant therapy, which includes hormone-suppressant medication, repeat surgery, SRS or radiotherapy, plays an important role in the long-term management of patients who do not attain immediate remission following TSR. [82, 83] Although the rates of adjuvant medical therapy were comparable between the two groups, radiotherapy was more frequently employed following microsurgical (32.5%) than endoscopic (7.9%) TSR. This may be due to the fact that the more recently published case series reporting the endoscopic approach correspond with an increasing popularization of adjuvant SRS over radiotherapy. [84] Although there was a high rate of intra-operative CSF leak observed in the endoscopic group (17.4%), rates of persistent CSF leak and postoperative endocrine complications were comparable between the two groups.

Based on updated 2010 consensus guidelines for remission from acromegaly, high rates of biochemical remission, ranging from 77–87% in patients with microadenomas and 63–66% in patients with macroadenomas, have been achieved with the use of endoscopic TSR. [12, 14] That the majority of patients do achieve remission holds promise, relative to prior series reporting a wider variety of outcomes. Under the less strict biochemical criteria of the 2000 consensus report, remission rates ranged from 42%–72% with microsurgery and 56%–83% with endoscopy. [16–18, 23, 26, 28, 67, 85–98] Although the results from this review are

largely consistent with the most recent reports, we have observed higher long-term remission rates for macroadenoma resection with the use of the endoscopic technique.

Different surgical approaches offer unique balances of advantages and limitations, but none are immune to the challenges of complete resection of large and laterally localized tumors. For any surgical approach, the utility of the Knosp grade as a preoperative predictor of outcome has been emphasized.[12, 25, 26, 66, 99–102] It is well established that Knosp grade 3 or 4 tumors are associated with significantly lower rates of complete resection and biochemical remission.[7, 12, 26, 99] In some series, the Knosp grade has been shown to be even more predictive of postoperative remission than size for acromegaly patients.[13, 17, 18, 88, 103–105] The potential for the endoscopic technique to achieve a better visualization of the operative field and a more complete resection, in cases of cavernous sinus invasion, should, therefore, be further investigated. It should also be noted that patients treated in higher volume centers have better overall outcomes, lending credence to the benefit of surgeon experience, regardless of surgical approach.[12, 14, 28, 106, 107]

The present study's strengths include the large number of patients and longitudinal nature of follow-up of the included case series. However, there are several important limitations of the study which should be noted. The comparison of results between endoscopic and microsurgical series was based on a summation of data from a heterogeneous cohort of patients, with differences in the number of cases and duration of follow-up between each group. Definitions for the diagnosis of acromegaly and biochemical remission were not consistent between studies. Older studies may be limited by early imaging techniques. Furthermore, operator expertise in either technique can dramatically influence patient outcomes and studies intending to compare the two approaches may have strong inherent biases. Hence, a true objective comparison may never be achieved, and the limited number of studies directly comparing approaches has precluded a meta-analysis from being performed.

Conclusions

Both endoscopic and microsurgical approaches for TSR provide viable treatment options for patients with acromegaly, yielding similarly high rates of endocrine remission under the most current consensus criteria without observed differences in postoperative complications. Higher rates of remission were achieved for microadenomas, irrespective of surgical modality. The endoscopic approach may offer a benefit in the resection of macroadenomas, where the greater field of view affords a greater potential for complete extirpation. However, surgeon expertise and familiarity with each of the techniques are likely to concurrently affect outcomes. Due to limitations in the literature, a direct comparison between the approaches cannot be carried out, and therefore, further studies directly comparing endoscopic and microsurgical approaches are warranted, in order to further clarify their respective advantages in the surgical management of acromegaly.

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Abbreviations:

TSR	transsphenoidal resection
GH	growth hormone
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
CSF	cerebral spinal fluid
DI	diabetes insipidus
SRS	stereotactic radiosurgery

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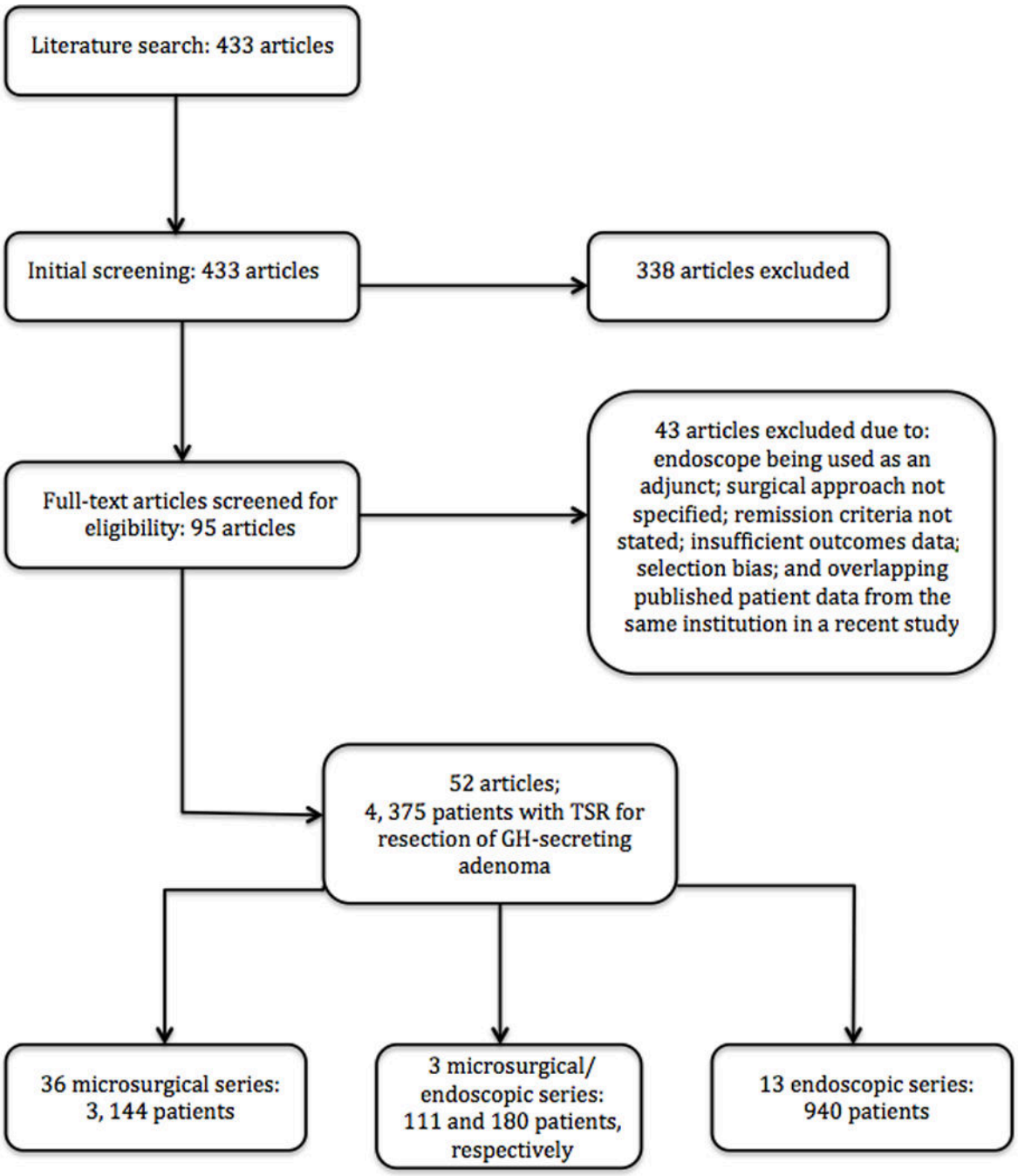

Figure 1.
Flow chart demonstrating the literature review process and selection of case series.

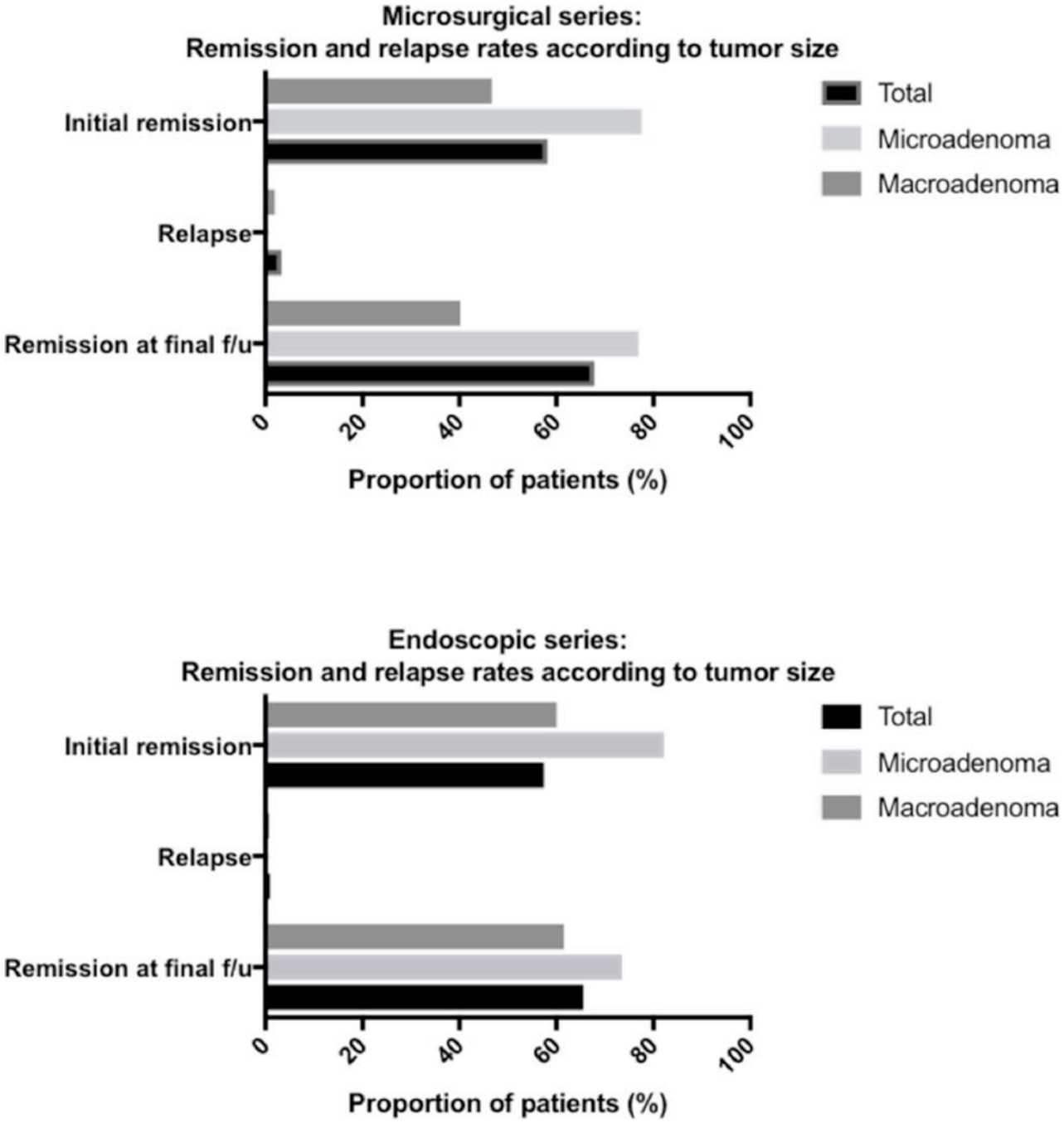

Figure 2:

Summary of remission and relapse rates according to surgical approach and tumor size.

Abbreviations: f/u = follow-up.

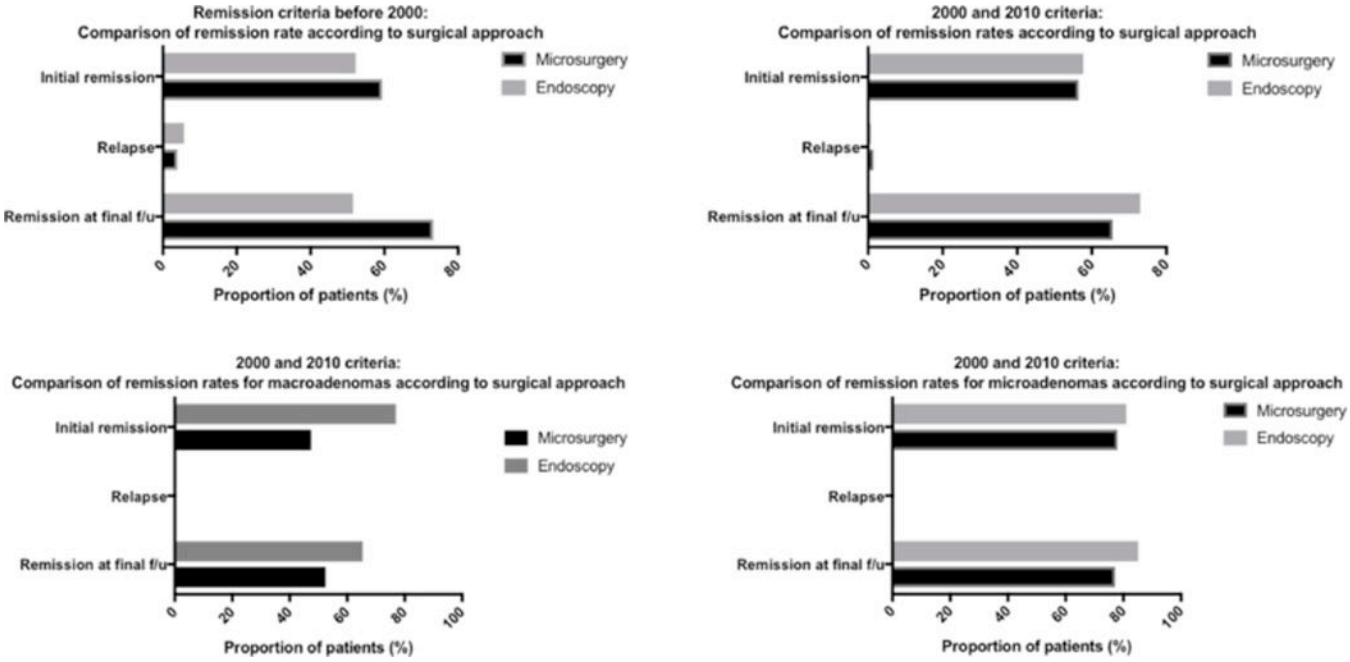

Figure 3:

Summary of remission and relapse rates according to surgical approach and tumor size.

Abbreviations: f/u = follow-up.

Table 1:

Summary of surgical outcomes for microsurgical and endoscopic case series.

Microsurgical Case Series								
Author	**Year**	**Patients, n**	**Initial Remission, n**	**Patients with f/u, n**	**f/u, mo**	**Relapse, n**	**Remission at last f/u, n**	**Remission Criteria**
Fathalla H et al	2015	23	8	23	56.6	0	-	2010
Sarkar S et al	2014	47	17	47	22.38	0	-	2010
Nishioka H et al	2014	150	127	150	22	0	149	2010
Sun H et al	2014	59	26	59	13.4	0	31	2010
Starke RM et al	2013	41	28	41	18.4	0	28	2010
Li ZQ et al	2012	52	16	49	3	0	16	2000
Krzentowaka-Korek A et al	2011	85	32	-	-	0	-	2000
Shen M et al	2010	39	7	39	-	0	8	2000
Abassioun K et al	2006	151	101	108	-	2	99	Random GH ≤ 10 ng/mL
Ertruk E et al	2005	30	10	30	42	0	-	Basal or OGTT GH ≤ 2 ng/mL
Nomikos P et al	2005	506	290	506	146	2	288	2000
Kurosaki M et al	2003	22	13	22	-	0	13	Normalized IGF-1, OGTT GH < 1 ng/mL, basal GH < 2.5 ng/mL
Beauregard C et al	2003	103	56	95	-	4	57	2000
De P et al	2003	90	57	90	130.8	0	57	2000
Krieger MD et al	2003	205	116	181	60	1	116	Normalized IGF-1, basal GH < 2 ng/mL
Kreutzer J et al	2001	57	40	57	37.7	1	41	2000
Biermasz NR et al	2000	59	36	59	192	5	58	2000
Absoch A et al	1998	254	193	172	-	9	150	Basal GH ≤ 5 ng/mL
Freda PU et al	1998	115	70	99	64.8	6	82	Normalized IGF-1 or basal/suppressed GH of ≤ 2 ng/mL
Yamada S et al	1997	44	25	39	81.6	0	34	Normalized IGF-1, basal GH ≤ 3 ng/mL, OGTT GH ≤ 1ng/mL, TRH/GnRH GH < 10ng/mL
Sheaves R et al	1996	100	42	32	45.6	1	31	Basal GH ≤ 5 ng/mL
Osman IA et al	1994	79	32	66	85.5	-	35	Basal GH ≤ 5 mU/L and OGTT GH ≤ 2 mU/L
Tindall GT et al	1993	103	85	88	102	0	85	Basal GH ≤ 5 ng/mL, SM-C < 2.2 U/mL
Buchfelder M et al	1991	61	43	61	72	6	39	Basal GH ≤ 5ng/mL and OGTT GH ≤ 2 ng/mL
Losa M et al	1989	29	16	25	-	0	12	OGTT GH ≤ 1 ng/mL and normalized SM-C
Fahlbusch R et al	1988	42	24	-	-	-	-	Basal GH ≤ 5 ng/mL

Microsurgical Case Series								
Author	**Year**	**Patients, n**	**Initial Remission, n**	**Patients with f/u, n**	**f/u, mo**	**Relapse, n**	**Remission at last f/u, n**	**Remission Criteria**
van't Verlaat J. et al	1988	25	14	25	42	0	14	Basal GH ≤ 5 mU/L; OGTT GH ≤ 4 mU/L; disappearance of TRH responsiveness if present pre-op
Ross DA et al	1988	214	117	174	76	5	131	Basal GH ≤ 5 ng/mL
Arafah BM et al	1987	43	21	43	-	0	21	Basal GH ≤ 5 ng/mL and normal GH dynamics
Karashima T et al	1986	44	15	-	-	-	-	Fasting GH ≤ 5 ng/mL and no response to TRH, LHRH, and/or bromocriptine
Roelfesma F et al	1985	60	37	60	39.6	-	48	Basal GH ≤ 5 mU/L
Serri O et al	1985	25	21	25	82.8	3	18	Basal GH ≤ 5 ng/mL and OGTT GH ≤ 2.5 ng/mL
Grisoli F et al	1985	100	60	100	-	6	56	Basal GH ≤ 5 ng/mL
Bynke O et al	1983	14	10	14	27	1	11	Basal GH ≤ 5 ng/mL
Arafah BU et al	1980	25	11	25	-	0	11	Basal GH < 5ng/mL and normal GH dynamics
Tucker HS et al	1980	32	24	32	48	0	24	Basal GH ≤ 5 ng/mL
Laws ER Jr et al	1979	82	34	80	19	1	50	Basal GH ≤ 10 ng/mL
Leavens ME et al	1977	16	10	16	24	0	12	Basal HGH ≤ 10 ng/mL and normal HGH levels after TRH stimulation
Giovanelli MA et al	1976	29	10	29	-	0	17	Basal GH ≤ 10 ng/mL
Total		3255	1894	2761	59.8	53	1842	
Endoscopic Case series								
Netuka D et al	2016	105	64	105	35	1	-	2010
Halioglu O et al	2016	103	53	103	38	30	77	2000
Fathalla H et al	2015	42	19	42	56.6	0	-	2010
Sarkar S et al	2014	66	19	66	22.4	0	-	2010
Yildirum A et al	2014	56	37	56	18	0	53	2010
Paluzzi A et al	2014	49	25	49	37.3	0	34	2010
Zhou T et al	2014	133	88	114	-	0	107	2000
Hazer DB et al	2013	214	126	214	33.16	0	134	2010
Starke RM et al	2013	72	51	72	18.4	0	51	2010
van Bunderen CC	2013	30	9	28	13.2	1	-	2000
Wang YY et al	2012	43	29	41	34	0	29	2010
Dusek T et al	2011	49	29	49	57.12	0	36	2000

Microsurgical Case Series								
Author	**Year**	**Patients, n**	**Initial Remission, n**	**Patients with f/u, n**	**f/u, mo**	**Relapse, n**	**Remission at last f/u, n**	**Remission Criteria**
Wagenmakers MA et al	2011	40	20	40	56	2	19	IGF-1 normal for age and sex, OGTT GH < 2 mU/l
Gondim JA et al	2010	67	50	67	24	0	54	2000
Hofstetter CP et al	2010	24	9	24	23.2	0	11	2010
Campbell PG et al	2010	27	15	26	24.5	0	15	IGF-1 normal for age/sex, OGTT GH < 1ng/mL, random GH < 2.5 ng/mL
Total		1120	643	1096	62.7	34	620	

Abbreviations: GH = growth hormone; OGTT = oral glucose tolerance test; IGF-1 = insulin-like growth factor 1; GnRH = gondatropin releasing hormone; SM-C = somatomedin C, TRH = thyrotropin releasing hormone, LHRH = lutenizing hormone releasing hormone, n = number, mo = month, f/u = follow up.

Table 2:

Summary of microsurgical and endoscopic case series, comparing surgical outcomes for macroadenoma and microadenoma.

Author	Year	Microsurgery-Microadenoma						Microsurgery-Macroadenoma					
		Patients, n	Initial Remission, n	Patients with f/u, n	f/u, mo	Relapse, n	Remission at last f/u, n	Patients, n	Initial Remission, n	Patients with f/u, n	f/u, mo	Relapse, n	Remission at last f/u, n
Starke RM et al	2013	10	8	10	18.4	0	8	31	20	31	18.4	0	20
Krzentowaka-Korek A et al	2011	19	17	-	-	0	-	52	16	49	3	0	16
Li ZQ et al	2012	0	-	-	-	-	-	66	15	-	-	-	-
Ertruk E et al	2005	11	7	11	42	0	-	39	7	39	-	-	8
Shen M et al	2010	0	-	-	-	-	-	19	3	19	42	0	-
Nomikos P et al	2005	142	107	142	146	-	-	354	182	354	146	-	-
Beauregard C et al	2003	22	18	22	-	-	-	52	31	52	-	-	-
De P et al	2003	29	23	29	130.8	0	23	61	34	61	130.8	0	34
Krieger MD et al	2003	127	99	-	60	0	100	54	17	-	60	1	16
Biermasz NR et al	2000	9	-	9	192	-	6	50	-	50	192	-	30
Freda PU et al	1998	25	22	-	64.8	0	23	90	48	-	64.8	6	59
Fahlbusch R et al	1988	4	3	-	-	-	-	38	21	-	-	-	-
van't Verlaat J. et al	1988	8	5	8	42	0	5	17	9	17	42	0	9
Karashima T et al	1986	6	3	-	-	-	-	38	12	-	-	-	-
Roelfesma F et al	1985	9	6	9	39.6	-	-	42	25	42	39.6	-	-
Serri O et al	1985	8	8	8	82.8	0	8	17	13	17	82.8	3	10
Total		429	326	248	81.8	0	173	1020	453	731	74.7	10	164
		Endoscopy-Microadenoma						**Endoscopy-Macroadenoma**					
Netuka D et al	2016	16	12	16	35	0	13	89	-	-	-	-	-
Yildirum A et al	2014	5	4	5	18	0	-	51	33	51	18	0	-
Palluzzi A et al	2014	5	4	5	37.3	0	5	44	21	44	37.3	0	29
Hazer DB et al	2013	51	-	51	33.16	0	32	163	-	163	33.16	0	102
Starke RM et al	2013	13	12	13	18.4	0	12	59	39	59	18.4	0	39
Wang YY et al	2012	13	10	13	34	0	10	30	19	30	34	0	19

Author	Year	Microsurgery-Microadenoma						Microsurgery-Macroadenoma					
		Patients, n	Initial Remission, n	Patients with f/u, n	f/u, mo	Relapse, n	Remission at last f/u, n	Patients, n	Initial Remission, n	Patients with f/u, n	f/u, mo	Relapse, n	Remission at last f/u, n
Dusek T et al	2011	13	10	13	57.12	0	-	36	19	36	57.12	0	-
Wagenmakers MA et al	2011	0	-	-	-	-	-	40	20	40	56	2	19
Gondim JA et al	2010	14	12	14	24	0	-	53	38	53	24	0	-
Campbell PG et al	2010	4	3	4	24.5	0	3	22	12	22	24.5	0	12
Total		134	67	134	31.3	0	75	587	201	498	33.6	2	220

Abbreviations: n = number; mo = month; f/u = follow-up.

Table 3:

Summary table of intra-operative and post-operative complications between the microsurgical and endoscopic groups.

Microsurgical Case Series												
			Intra-operative complications (n)			Post-operative complications (n)						
Author	**Year**	**Patients**	**CSF Leak**	**Vascular injury**	**Visual deficit**	**CSF Leak**	**Hypopituitarism**	**Pan-hypopituitarism**	**Meningitis**	**Epistaxis**	**Transient DI**	**Permanent DI**
Fathalla H et al	2015	23	-	-	-	2	1	-	-	1	8	4
Sarkar S et al	2014	14	17	-	0	2	18	10	2	-	2	-
Nishioka H et al	2014	150	0	0	0	0	0	0	0	0	0	0
Sun H et al	2014	59	-	-	-	0	-	-	-	-	6	2
Starke RM et al	2013	41	12	0	0	1	-	0	0	1	2	0
Li ZQ et al	2012	52	-	0	2	-	0	0	0	0	3	1
Krzentowaka-Korek A et al	2011	85	0	0	0	0	-	-	0	0	0	-
Shen M et al	2010	39	-	-	-	-	-	-	-	-	-	-
Abassioun K et al	2006	151	0	0	0	12	28	0	1	0	17	2
Ertruk E et al	2005	30	-	0	0	-	3	-	-	0	-	-
Nomikos P et al	2005	506	-	1	0	-	15	0	-	0	0	6
Kurosaki M et al	2003	22	-	-	-	-	-	-	-	-	-	0
Beauregard C et al	2003	103	-	1	-	-	3	-	-	-	-	-
De P et al	2003	90	-	-	0	-	22	39	3	0	16	14
Krieger MD et al	2003	205	-	-	-	-	-	-	-	-	-	-
Kreutzer J et al	2001	57	0	0	0	1	3	0	0	-	2	1
Biermasz NR et al	2000	59	-	-	-	-	3	-	-	-	-	-
Absoch A et al	1998	254	0	0	0	5	4	0	6	0	54	4
Freda PU et al	1998	115	0	1	0	0	0	0	0	0	4	0
Yamada S et al	1997	44	-	0	0	-	3	1	0	0	21	0
Sheaves R et al	1996	100	-	1	0	-	21	0	8	0	29	8
Osman IA et al	1994	79	10	-	0	0	10	0	0	0	3	0
Tindall GT et al	1993	103	-	0	1	-	3	3	0	0	7	1
Buchfelder M et al	1991	61	-	-	-	-	-	-	-	-	-	-

Microsurgical Case Series												
			Intra-operative complications (n)			Post-operative complications (n)						
Author	**Year**	**Patients**	**CSF Leak**	**Vascular injury**	**Visual deficit**	**CSF Leak**	**Hypopituitarism**	**Pan-hypopituitarism**	**Meningitis**	**Epistaxis**	**Transient DI**	**Permanent DI**
Losa M et al	1989	29	0	0	0	0	0	1	0	1	9	0
Fahlbusch R et al	1988	42	-	-	-	-	-	-	-	-	-	-
van't Verlaat J. et al	1988	25	0	1	0	0	3	2	0	0	2	2
Ross DA et al	1988	214	0	5	0	11	10	4	4	1	1	0
Arafah BM et al	1987	43	0	0	0	0	-	-	-	-	10	1
Karashima T et al	1986	44	-	-	-	-	-	-	-	-	-	-
Roelfesma F et al	1985	60	-	-	2	-	17	2	1	0	2	0
Serri O et al	1985	25	-	-	-	-	-	-	-	-	-	-
Grisoli F et al	1985	100	-	2	-	-	0	0	-	-	-	-
Bynke O et al	1983	14	0	0	0	1	-	-	0	0	0	0
Arafah BU et al	1980	25	0	1	1	0	1	0	0	0	4	1
Tucker HS et al	1980	32	0	0	0	1	-	4	1	0	10	1
Laws ER Jr et al	1979	82	-	0	0	-	3	10	0	0	0	0
Leavens ME et al	1977	16	0	0	0	5	0	0	1	0	7	0
Giovanelli MA et al	1976	29	0	0	0	3	-	0	0	0	5	0
Total, n/n (%)[†]		3222	39/1373 (2.8)	13/2400 (0.5)	6/2440 (0.2)	44/ 1455 (3.0)	191/2542 (6.7)	76/2368 (3.2)	27/1861 (1.4)	4/2349 (0.1)	208/2492 (9.0)	48/2375 (2.0)
Endoscopic Series												
Netuka D et al	2016	105	-	-	-	2	10	-	-	-	1	-
Fathalla H et al	2015	42	-	-	-	2	1	-	`-	-	8	4
Sarkar S et al	2014	66	22	-	0	1	12	14	-	1	6	-
Yildirum A et al	2014	56	-	1	-	2	1	3	0	0	2	1
Zhou T et al	2014	133	19	0	1	0	5	3	1	2	12	0
Hazer DB et al	2013	214	29	0	0	5	8	1	1	1	0	2
Starke RM et al	2013	72	23	1	0	2	-	-	1	4	6	3
van Bunderen CC	2013	30	-	-	-	-	-	-	-	-	-	-

Microsurgical Case Series

			Intra-operative complications (n)			Post-operative complications (n)					
Author	**Year**	**Patients**	**CSF Leak**	**Vascular injury**	**Visual deficit**	**CSF Leak**	**Hypopituitarism**	**Pan-hypopituitarism**	**Meningitis**	**Epistaxis**	**Transient DI**	**Permanent DI**
Wang YY et al	2012	43	-	0	0	-	5	0	1	0	14	2
Dusek T et al	2011	49	-	1	0	-	-	-	1	0	-	-
Wagenmakers MA et al	2011	40	-	0	0	3	5	0	0	4	15	0
Gondim JA et al	2010	67	0	0	0	0	5	0	0	4	3	0
Hofstetter CP et al	2010	24	12	0	1	2	0	2	0	0	0	0
Campbell PG et al	2010	27	0	0	0	1	0	0	0	0	2	0
Total, n/n (%)[†]		968	86/ 603 (17.4)	3/725 (0.4)	2/ 735 (0.2)	20/ 855 (2.3)	52/ 817 (6.4)	23/ 670 (3.4)	5/ 725 (0.7)	16/791 (2.0)	69/ 889 (7.8)	12/ 718 (1.7)

[†]Total n/n = complication / total patients. Abbreviations: Intra-op = intra-operative; post-op = post-operative; CSF = cerebral spinal fluid; DI = diabetes insipidus; n = number.

Table 4:

Summary table comparing mode and rate of adjuvant therapy between microsurgical and endoscopic groups.

Microsurgical Series					
Author	**Year**	**Patients requiring medical therapy, n/n**	**Patients requiring repeat surgery, n/n**	**Patients requiring radiotherapy, n/n**	**Patients requiring radiosurgery, n/n**
Nishioka H et al	2014	15/150	0/150	4/150	0/150
Starke RM et al	2013	7/13	0/13	2/13	6/13
Krzentowaka-Korek A et al	2011	53/53	0/53	0/53	0/53
Shen M et al	2010	0/32	0/32	0/32	11/32
Abassioun K et al	2006	0/7	0/7	-	0/7
Ertruk E et al	2005	13/20	6/20	8/20	3/20
Kurosaki M et al	2003	8/9	0/9	0/9	3/9
Beauregard C et al	2003	5/47	10/47	12/47	0/47
De P et al	2003	33/33	0/33	31/33	0/33
Kreutzer J et al	2001	13/17	1/17	0/17	10/17
Biermasz NR et al	2000	6/23	0/23	19/23	0/23
Absoch A et al	1998	7/61	3/61	24/61	0/61
Freda PU et al	1998	15/45	12/45	30/45	2/45
Yamada S et al	1997	1/19	0/19	0/19	0/19
Sheaves R et al	1996	0/58	0/58	0/58	0/58
Osman IA et al	1994	0/47	9/47	-	0/47
Tindall GT et al	1993	13/18	0/18	12/18	0/18
Losa M et al	1989	9/9	3/9	2/9	0/9
van't Verlaat J. et al	1988	11/11	0/11	11/11	0/11
Ross DA et al	1988	-	7/87	38/87	0/87
Roelfesma F et al	1985	0/23	2/23	19/23	0/23
Bynke O et al	1983	0/4	2/4	-	0/4
Tucker HS et al	1980	0/8	3/8	5/8	0/8
Laws ER Jr et al	1979	0/48	3/48	27/48	0/48
Leavens ME et al	1977	0/6	4/6	2/6	0/6
Giovanelli MA et al	1976	0/19	3/19	17/19	0/19
Total, n/n (%[†])		209/780 (26.8 %)	68/867 (7.8 %)	263/809 (32.5 %)	35/867 (4.0 %)
Endoscopic Series					
Netuka D et al	2016	24/105	7/105	-	32/105
Halioglu O et al	2016	70/103	9/103	9/103	0/103
Yildirum A et al	2014	19/56	16/56	-	3/56
Zhou T et al	2014	23/133	4/133	-	-
Hazer DB et al	2013	0/88	22/88	0/88	0/88
Starke RM et al	2013	11/21	0/21	6/21	9/21

Microsurgical Series					
Author	**Year**	**Patients requiring medical therapy, n/n**	**Patients requiring repeat surgery, n/n**	**Patients requiring radiotherapy, n/n**	**Patients requiring radiosurgery, n/n**
van Bunderen CC	2013	16/21	4/21	1/21	0/21
Wang YY et al	2012	12/14	-	4/14	0/14
Dusek T et al	2011	14/20	0/20	0/20	5/20
Wagenmakers MA et al	2011	14/20	2/20	6/20	2/20
Gondim JA et al	2010	0/17	4/17	0/17	0/17
Hofstetter CP et al	2010	9/15	0/15	0/15	5/15
Campbell PG et al	2010	9/12	0/12	0/12	2/12
Total, n/n (%)[†]		221/625(35.4%)	68/611(11.1%)	26/331 (7.9 %)	58/492(11.8 %)

Abbreviations: n = number.

[†]Total n/n = patients receiving adjuvant therapy after surgery / patients not in remission after initial surgery