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REVIEW ARTICLE - PITUITARIES

Intra-operative MRI vs endoscopy in achieving gross total resection of pituitary adenomas: a systematic review

Christian P. Soneru[1,2] · Charles A. Riley[1] · Katherine Hoffman[3] · Abtin Tabaee[1] · Theodore H. Schwartz[4]

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Abstract

Background Intraoperative magnetic resonance imaging (iMRI) is a technology that may improve rates of gross total resection (GTR) for pituitary adenomas. The endoscope is another less expensive technology, which also may maximize resection rates. A direct comparison of these approaches and their additive benefit has never been performed.

Methods A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) standard. PubMed and Embase databases were searched for studies that examined GTR for pituitary adenoma resection with either endoscopic transsphenoidal surgery (eTSS), microscopic transsphenoidal surgery with iMRI (mTSS + iMRI), or endoscopic transsphenoidal surgery with iMRI (eTSS + iMRI).

Results Eighty-five studies that reported GTR rates in 7124 pituitary adenoma patients were identified. For all pituitary adenomas, eTSS had a pooled proportion of GTR of 68.9% (95% CI 64.7–73.0%) which was similar to that of mTSS + iMRI (GTR 68.3%; 95% CI = 59.4–76.5%) and eTSS + iMRI (GTR 70.7%; 95% CI = 56.9–89.6%). For the subgroup of pituitary macroadenomas, pooled proportions for GTR were similar between eTSS and mTSS + iMRI (eTSS: GTR 59.4%; 95% CI = 49.6–68.7% vs mTSS + iMRI: GTR 68.8%; 95% CI = 57.3–79.3%), and higher for eTSS + iMRI (81.1%; 95% CI = 75.5–86.2%). The post-operative CSF leak proportion for eTSS (4.7%; 95% CI = 3.6–5.9%) was similar to that for eTSS + iMRI (3.7%; 95% CI = 1.6–6.5%) and mTSS + iMRI (4.6%; 95% CI = 2.0–8.3%). No direct statistical comparisons could be performed.

Conclusion Final GTR proportions are similar whether the surgeon uses a microscope supplemented with iMRI or endoscope with or without iMRI. The benefit of the two technologies may be complementary for macroadenomas. These findings are important to consider when comparing the efficacy of different technical strategies in the management of pituitary adenomas.

Keywords Intra-operative MRI · Endoscopic · Pituitary adenoma · Gross total resection

Introduction

Since the advent of transsphenoidal surgery for sellar pathology in the early twentieth century, significant improvements in surgical outcomes have closely followed technological advances, often due to improved visualization. The operating microscope was first used for microscopic transsphenoidal surgery (mTSS) in the 1960s and led to higher rates of tumor resection as well as decreased surgical morbidity [59]. More recently, endoscopic endonasal transsphenoidal surgery (eTSS) has gained popularity as an alternative to mTSS [84]. The use of endoscopes allows for a wide panoramic view and the possibility to visualize far laterally with the use of angled scopes. Although a large-scale, randomized trial to compare these two modalities has not been performed, a recent meta-analysis found that eTSS resulted in a higher rate of gross total resection for pituitary adenoma as compared to mTSS [3].

This article is part of the Topical Collection on *Pituitaries*

✉ Christian P. Soneru
cpsoneru@gmail.com

[1] Department of Otolaryngology – Head and Neck Surgery, Weill Cornell Medicine, New York Presbyterian Hospital, New York, NY, USA

[2] Cambridge, USA

[3] Division of Biostatistics and Epidemiology, Department of Healthcare Policy and Research, Weill Cornell Medicine, New York Presbyterian Hospital, New York, NY, USA

[4] Department of Neurosurgery, Weill Cornell Medicine, New York Presbyterian Hospital, New York, NY, USA

A recent technology that has become increasingly more popular in transsphenoidal surgery is real-time intraoperative MRI (iMRI). First reported by Jolesz et al. in 1994 [48], there are now a number of systems available that vary in field strength as well as magnet and room configuration [8][17]. The major theoretical benefit provided by iMRI is the improved rate of gross total resection (GTR) provided by the detection of unexpected tumor remnants [17]. iMRI was initially, and is currently, used most often in conjunction with microscope-based surgeries where the narrow corridor provided by the Hardy retractor or the nasal passages limit the field of view. Several studies have demonstrated that iMRI is useful at detecting residual tumor that can subsequently be removed but study designs do not allow surgeons to be blinded which inherently introduces bias [10, 31, 32, 38, 58, 62, 72, 86].

However, the use of iMRI has not been widely adopted given the costs associated with installing such a system. A 2011 economic analysis of iMRI use demonstrated that a low-field system costs $3.8 million for implementation and operation, with an estimated economic life of 5 years and zero end-of-life salvage value [61]. Moreover, the use of iMRI increases operative time by approximately 2 h [85]. These high costs and increased operative time associated with iMRI must be balanced against the improved outcomes when considering whether to install and utilize such a system in a medical center. To date, no comparison has been done comparing rates of GTR using eTSS, eTSS with iMRI (eTSS + iMRI), and mTSS + iMRI to ascertain which technology is most effective achieving this goal. The purpose of this systematic review is to compare the estimated pooled rate of GTR after eTSS, eTSS + iMRI, and with mTSS + iMRI.

Methods

The manuscript was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) standard. The literature was systematically reviewed with PubMed and Embase databases. Search terms included the following: (((Pituitary neoplasm) OR (Pituitary tumor) OR (pituitary adenoma)) AND ((((microscopic) OR (microsurger*)) AND ((intraoperative magnetic resonance) OR (magnetic resonance) OR (intraoperative MRI))) OR (endoscopic))). Duplicates were removed. Exclusion criteria included case reports, commentaries, abstracts, reviews, animal studies, studies with an endoscopically assisted approach, studies with pediatric patients (< 18 years), cadaveric studies, lack of post-operative MRI, and non-English studies.

All databases were searched on May 23, 2018, and duplicates were removed. All articles were screened for title and abstract to identify articles reporting GTR for transsphenoidal pituitary adenoma resection with either an eTSS, eTSS + iMRI, or mTSS + IMRI. Selected articles underwent full-text screening. Only articles that reported GTR specifically for pituitary adenomas were included. We chose GTR as an outcome because not all studies were reported on endocrine outcomes or visual outcomes and this was the outcome that was most consistently analyzed. In addition, the goal of iMRI is to achieve increased rates of GTR, so we chose GTR as a measure of iMRI success. As another outcome metric, we also looked at rate of cerebrospinal fluid (CSF) leak. This metric was available for most studies and is also useful since it related to rates of GTR since the more aggressively the surgeon attempts a GTR, the higher the likely incidence of CSF leak. Study characteristics that were extracted from the full text of selected studies included authors, publication year, hospital or hospitals where procedure was performed, sample size, patient demographics, tumor type, rate of GTR, and rate of post-operative CSF leak. Operative time was not used as an endpoint as few studies analyzed this as an outcome. In order to eliminate the chance of including patients twice, studies from the same institution with overlapping inclusion criteria and study time periods were marked and only the study with the larger study group was included.

The proportions of GTR and post-operative CSF leak (stratified by type of procedure) were calculated with the use of StatsDirect statistical software (Version 3.1.20) (7/18/2018 StatsDirect Ltd., Cheshire, England). The presence of statistical heterogeneity in the GTR proportions of the individual studies to be pooled was tested through the chi-square test (i.e., Cochrane's Q test) and a p value ≤ 0.20 was used to indicate the presence of heterogeneity. Heterogeneity was also tested using an inconsistency measure (i.e., I^2 percentage) and a percentage $\geq 50\%$ was used to indicate the presence of heterogeneity. In the case of lack of heterogeneity, fixed-effects models were used for the meta-analyses. If heterogeneity was present ($p \leq 0.20$ or $I^2 \geq 50\%$), random-effects models were used. For the GTR proportions of interest, the results of each study were expressed as binary proportions with exact 95% confidence intervals. Each pooled (summary) GTR proportion was calculated using either a fixed-effects or random-effects (DerSimonian-Laird) model (based on heterogeneity criteria as defined above) and forest plots were generated to display the individual study GTR proportions and the pooled (summary) GTR proportions.

For each of the GTR proportions (i.e., stratified by type of procedure), the presence of publication bias was evaluated through a funnel plot, which is a scatter plot of the GTR proportions estimated from the individual studies vs a measure of study size or precision. In this graphical representation, larger and more precise studies are plotted at the top, near the combined (pooled) GTR proportion, whereas smaller and less precise studies will show a wider distribution below. If there is no publication bias, the studies would be expected to be symmetrically distributed on both sides of the pooled GTR proportion line. In the case of publication bias, the funnel plot

may be asymmetrical, since the absence of studies would distort the distribution on the scatter plot. Egger's test and the Begg-Mazumdar rank correlation test were used to statistically assess the presence of publication bias.

Results

The systematic search resulted in 2501 articles after duplicates were removed. After title and abstract screening, 2361 were excluded, resulting in 140 articles for full-text evaluation. After full-text screening, a total of 85 studies were included in the meta-analysis, with a total of 7124 patients who underwent surgery for pituitary adenomas (Fig. 1). For the studies involving eTSS, the median percentage of males was 50.7% (range 36.4–69.2%) while the median percentage of males was 60.5% in the mTSS + iMRI studies (range 40.0–83.3%) and 52.1% in the eTSS + iMRI studies (range 43.0–68.0%) (Tables 1, 2, and 3**)**. Mean age per study ranged from 26.2 to 60.1 years, with a median of means of 49.6 years for the eTSS studies, 48.9 years for the mTSS + iMRI studies, and 51.2 for the eTSS + iMRI studies. The median percentage of macroadenomas was 89.8%, 100%, and 100% for eTSS, mTSS + iMRI, and eTSS + iMRI, respectively. The median percentage of functional pituitary adenomas was 42.03% for the eTSS group of studies, 28.1% for the mTSS + iMRI group, and 38.8% for the eTSS + iMRI group.

We found 62 studies in which GTR was studied for eTSS, for a total of 5990 patients (Table 4). Using a random-effects model, the pooled proportion of GTR among these studies was 68.9% (95% CI = 64.7–73.0%, I^2 = 91.3% Fig. 2). For mTSS + iMRI, GTR was demonstrated in 15 studies for a total of 634 patients (Table 5). Similarly, a random-effects model was used to calculate a pooled proportion of 68.3% (95% CI = 59.4–76.5%, I^2 = 80.3%; Fig. 3). For eTSS + iMRI, GTR was demonstrated in 8 studies for 500 total patients (Table 6). Given the small number of studies, a random-effects model was used to calculate a pooled GTR proportion of 70.7% (95% CI = 56.9–82.9%, I^2 = 89.6%; Fig. 4). The pooled proportions could not be directly compared.

To stratify outcomes based on adenoma size, we searched for studies in which GTR was calculated for macroadenomas. We identified 26 studies in which eTSS was performed that calculated GTR for a total of 1546 macroadenomas and a pooled proportion of GTR of 59.4% (95% CI = 49.6–68.7%). The GTR proportion for macroadenomas was demonstrated in 10 studies of mTSS + iMRI for a total of 371 macroadenomas. The pooled proportion of GTR in this group was 68.8% (95% CI = 57.3–79.3%). There were 4 studies in which eTSS + iMRI was performed that determined GTR for a total of 202 macroadenomas and a pooled proportion of GTR of 81.1% (95% CI = 75.5–86.2%). GTR could not be evaluated for microadenomas or by functional status given limited data.

There were 47 studies that included a post-operative CSF leak rate among the studies evaluating eTSS (Table 4). The pooled proportion among these studies was 4.7% (95% CI = 3.6–5.9%. Among the studies evaluating mTSS + iMRI, we identified 11 studies that calculated a post-operative CSF leak rate (Table 5). The pooled proportion among these studies was

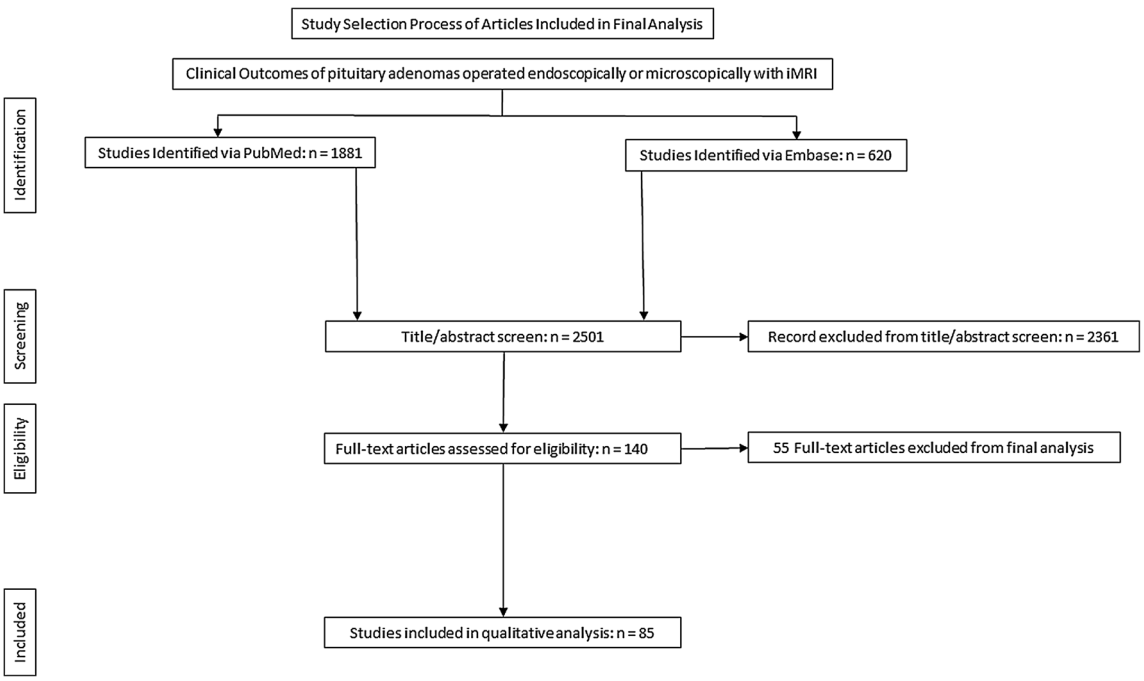

Fig. 1 Flowchart: study selection process of the identified studies

Table 1 Characteristics of the studies evaluating GTR with eTSS

Study	Year of publication	Surgical intervention	No. of PA	Age	Gender		According to size		According to function	
				Mean ± SD	M (%)	F (%)	% macroadenoma	% microadenoma	% NFPA	% FPA
Ajlan et al. [1]	2017	eTSS	176	50	45.5	54.5	76.7	23.3	60.2	39.8
Akbari et al. [2]	2018	eTSS	16	39.43 ± 15.21	56	44	n/a	n/a	n/a	n/a
Arbolay et al. [4]	2009	eTSS	7	40.6	57.1	42.9	n/a	n/a	49.4	50.6
Bokhari et al. [11]	2013	eTSS	79	56.7 ± 16.3	44	56	91.1	8.9	49.4	50.6
Campbell et al. [12]	2010	eTSS	26	45.7	37.5	62.5	84.6	15.4	0	100
Cappabianca et al. [13]	2002	eTSS	146	46.06	46.6	53.4	85.6	14.4	54.8	45.2
Chabot et al. [14]	2015	eTSS	39	56.3 ± 15.6	64.1	35.9	100	0	92.3	7.7
Charalampaki et al. [15]	2009	eTSS	134	57	46.7	53.3	44.8	11.2	56	44
Chi et al. [16]	2013	eTSS	80	50.84 ± 13.62	56	44	80.0	20.0	42.5	57.5
Choe et al. [18]	2008	eTSS	12	47 ± 12	41.7	58.3	75.0	25.0	0	100
Chone et al. [19]	2014	eTSS	47	54	n/a	n/a	89.4	10.6	63.8	36.2
Conrad et al. [21]	2016	eTSS	40	56.5	50	50	90.0	10.0	72.5	27.5
Constantino et al. [22]	2016	eTSS	28	46	60	40	100	0	7.1	92.9
Cusimano et al. [23]	2012	eTSS	29	50.3 ± 15.4	55	45	100	0	86.2	13.8
Dallapiazza et al. [24]	2014	eTSS	43	56.7 ± 16.9	55.8	44.2	100	0	100	0
Dallapiazza et al. [25]	2015	eTSS	80	56.6 ± 13	47.5	52.5	100	0	100	0
De Witte et al. [26]	2011	eTSS	83	50.07 ± 13.81	53	47	88	12	53.0	47.0
Dehdashti et al. [27]	2008	eTSS	200	49.9	54.5	45.5	21	79	55.5	43.0
Di Maio et al. [29]	2011	eTSS	20	49.4	35	65	n/a	n/a	75	25
Duz et al. [30]	2008	eTSS	28	n/a	n/a	n/a	n/a	n/a	42.9	57.1
Frank et al. [34]	2006	eTSS	173	54	52.6	47.4	99.4	0.6	100	0
Gao et al. [36]	2016	eTSS	60	44.6	43.3	56.7	78.3	21.7	45	55
Gondim et al. [39]	2011	eTSS	301	42.44 ± 15.31	44.5	55.5	17.6	82.4	44.9	55.1
Guo-Dong et al. [40]	2016	eTSS	100	43.4 ± 14	59	41	n/a	n/a	52	48
Guvenc et al. [41]	2016	eTSS	45	48.3 ± 14.1	42.2	57.8	68.9	31.1	48.9	51.1
Han et al. [42]	2013	eTSS	250	43.8	39.6	60.4	82.8	17.2	58.8	41.2
Hofstetter et al. [44]	2012	eTSS	71	49.9 ± 16.7	46.5	53.5	100	0	63.4	36.6
Jain et al. [45]	2007	eTSS	10	40.1	n/a	n/a	90	10	n/a	n/a
Jang et al. [46]	2016	eTSS	331	48.4	43.8	56.2	70.4	29.6	47.4	52.6
Jho et al. [47]	2001	eTSS	68	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Juraschka et al. [49]	2014	eTSS	66	54.58 ± 14.8	68.5	31.5	100	0	89.4	10.6
Kalinin et al. [50]	2016	eTSS	97	n/a	39.2	60.8	n/a	n/a	n/a	n/a
Karppinen et al. [51]	2015	eTSS	41	54.58 ± 14.8	68.5	31.5	100	0	100	0
Kenan et al. [52]	2006	eTSS	59	44.7	n/a	n/a	100	0	32.2	67.8
Kim et al. [53]	2018	eTSS	331	53	46.8	53.2	99.4	0.6	100	0
Kumar et al. [55]	2012	eTSS	151	53.1	48.7	51.3	78.8	21.2	53.6	46.4
Kuo et al. [56]	2016	eTSS	38	50.8 ± 13.1	63.2	36.8	100	0	n/a	n/a
Lee et al. [57]	2016	eTSS	208	50.7 ± 14.1	41.7	58.3	83.6	16.4	70.2	29.8
Lopez-Garcia [60]	2018	eTSS	86	54	53	47	89.5	10.5	n/a	n/a
Messerer et al. [63]	2011	eTSS	82	57	57.3	42.7	n/a	n/a	100	0
Nakao et al. [64]	2011	eTSS	43	55	53.4	46.6	100	0	100	0
Nie et al. [66]	2015	eTSS	52	46.8	46.2	53.8	86.5	13.5	32.7	67.3
O'Malley et al. [67]	2008	eTSS	21	47.9	60	40	n/a	n/a	n/a	n/a
Pinar et al. [69]	2015	eTSS	32	48.6	43.8	56.2	62.5	37.5	31.3	68.8
Prajapati et al. [70]	2018	eTSS	17	41.06 ± 11.76	n/a	n/a	n/a	n/a	n/a	n/a
Qureshi et al. [71]	2016	eTSS	78	52.2 ± 18.1	55.1	44.9	96.2	3.8	n/a	n/a
Sankhla et al. [74]	2013	eTSS	13	45.8	38.5	61.5	100	0	69.2	30.8
Sanmillan et al. [75]	2017	eTSS	146	n/a	n/a	n/a	n/a	n/a	68.5	29.5
Sheehan et al. [78]	1999	eTSS	16	59.2 ± 15.1	69.2	30.8	100	0	100	0
Shou et al. [79]	2016	eTSS	178	46.1	43.8	56.2	n/a	n/a	51.7	48.3
Song et al. [81]	2014	eTSS	22	n/a	40	60	100	0	0	100
Sun G et al. [83]	2018	eTSS	42	47.6	42.9	57.1	90.5	9.5	31	69
Taniguchi et al. [87]	2015	eTSS	25	n/a	n/a	n/a	n/a	n/a	84	16
Tao et al. [88]	2010	eTSS	22	45.2	36.4	63.6	100	0	68.2	31.8
Thomas et al. [89]	2014	eTSS	50	50 ± 13	42	58	82	18	76.0	24.0

Table 1 (continued)

Study	Year of publication	Surgical intervention	No. of PA	Age	Gender		According to size		According to function	
				Mean ± SD	M (%)	F (%)	% macroadenoma	% microadenoma	% NFPA	% FPA
Tosaka et al. [90]	2015	eTSS	30	52.5 ± 19	46.7	53.3	100	0	n/a	n/a
Wongsirisuwan et al. [91]	2014	eTSS	38	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Yildirim et al. [92]	2016	eTSS	160	48.5	55	45	100	0	100.0	0.0
Zaidi et al. [93]	2016	eTSS	55	55.9 ± 13.8	63.6	36.4	n/a	n/a	100.0	0.0
Zhan et al. [94]	2015	eTSS	313	60.1	60	40	83.1	16.9	100.0	0.0
Zhang X et al. [95]	2008	eTSS	78	45.1	46.2	53.8	85.9	14.1	55.1	44.9
Zhang Y et al. [96]	2008	eTSS	678	36.5	44	56	72.3	27.7	13.1	86.9

GTR gross total resection, *eTSS* endoscopic transsphenoidal surgery, *PA* pituitary adenomas, *NFPA* non-functioning pituitary adenomas, *PFA* functioning pituitary adenomas, *n/a* not available

4.6% (95% CI = 2.0–8.3%). For studies evaluating eTSS + iMRI, we identified 6 studies that calculated a pooled proportion of post-operative CSF leak rates of 3.7% (95% CI = 1.6–6.5%; Table 6). These pooled proportions could not be directly compared.

To assess for publication bias, inverted funnel plots were created for the GTR analysis of pituitary adenomas (Figs. 5, 6, and 7). For the eTSS group of studies, bias indicators were suggestive of publication bias (Begg-Mazumdar $p = 0.0077$; Egger $p < 0.0001$). For the mTSS + iMRI and eTSS + iMRI groups of studies, the bias indicators were not suggestive of publication bias (mTSS + iMRI: Begg-Mazumdar $p = 0.2816$, Egger $p = 0.078$; eTSS + iMRI: Begg-Mazumdar $p > 0.9049$; Egger $p = 0.8074$), although the small number of studies limits the power of these tests.

Discussion

This systematic review demonstrates that eTSS with or without iMRI results in a similar rate of GTR and post-operative CSF leak when compared to patients undergoing mTSS +

Table 2 Characteristics of the studies evaluating GTR with mTSS + iMRI

Study	Year of publication	Surgical intervention	No. of PA	Age	Gender		According to size		According to function	
				Mean ± SD	M (%)	F (%)	% macroadenoma	% microadenoma	% NFPA	% FPA
Baumann et al. [5]	2010	mTSS + iMRI	6	46	83.3	16.7	100	0	83.3	16.7
Bellut et al. [6]	2010	mTSS + iMRI	39	47 ± 14	64.9	35.1	25.6	69.2	0	100
Berkmann et al. [7]	2012	mTSS + iMRI	60	59 ± 15	70	30	n/a	n/a	100	0
Boellis et al. [9]	2014	mTSS + iMRI	21	49.0 ± 14.2	71.4	28.6	100	0	33.3	66.7
Bohinski et al. [10]	2001	mTSS + iMRI	29	51	60	40	100	0	72.4	27.6
Coburger et al. [20]	2014	mTSS + iMRI	74	55	62	38	n/a	n/a	70.3	29.7
Fahlbusch et al. [31]	2001	mTSS + iMRI	44	53 ± 14.9	65.9	34.1	100	0	88.6	11.4
Fomekong et al. [32]	2014	mTSS + iMRI	73	50 ± 17	63	37	100	0	n/a	n/a
Gerlach et al. [38]	2008	mTSS + iMRI	40	55.5 ± 13.5	55	45	100	0	70	30
Hlavica et al. [43]	2013	mTSS + iMRI	103	59	54.8	45.2	100	0	100	0
Li et al. [58]	2015	mTSS + iMRI	30	36	43.3	56.7	100	0	30	70
Martin et al. [62]	1999	mTSS + iMRI	5	26.2 ± 5.5	40	60	100	0	40	60
Ramm-Pettersen et al. [72]	2011	mTSS + iMRI	20	48.6 ± 9.5	65	35	100	0	80	20
Sylvester et al. [85]	2015	mTSS + iMRI	41	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Szerlip et al. [86]	2011	mTSS + iMRI	49	49	48	52	81.6	2.0	71.4	28.6

mTSS + iMRI microscopic transsphenoidal surgery with intraoperative MRI, *PA* pituitary adenomas, *NFPA* non-functioning pituitary adenomas, *PFA* functioning pituitary adenomas, *n/a* not available

Table 3 Characteristics of the studies evaluating GTR with eTSS + iMRI

Study	Year of publication	Surgical intervention	No. of PA	Age	Gender		According to size		According to function	
				Mean ± SD	M (%)	F (%)	% macroadenoma	% microadenoma	% NFPA	% FPA
Garcia et al. [37]	2017	eTSS + iMRI	30	55	43	57	100	0	50	50
Netuka et al. [65]	2011	eTSS + iMRI	105	48.3	48.6	51.4	84.8	15.2	0	100
Pal'a et al. [68]	2017	eTSS + iMRI	28	55	68	32	n/a	n/a	60.7	39.3
Schwartz et al. [76]	2006	eTSS + iMRI	15	49.1 ± 12.8	60	40	100	0	46.7	53.3
Serra et al. [77]	2016	eTSS + iMRI	50	52	51.9	48.1	n/a	n/a	66	44
Sylvester et al. [85]	2015	eTSS + iMRI	115	49 ± 13.7	47	53	n/a	n/a	61.7	38.3
Zaidi et al. [93]	2016	eTSS + iMRI	20	51.6	45	55	100	0	55	45
Zhang H et al. [85][97]	2017	eTSS + iMRI	137	n/a	53.2	46.8	100	0	75.2	24.8

eTSS + iMRI endoscopic transsphenoidal surgery with intraoperative MRI, *PA* pituitary adenomas, *NFPA* non-functioning pituitary adenomas, *PFA* functioning pituitary adenomas, *n/a* not available

iMRI for all pituitary adenomas. For the subset of patients with pituitary macroadenomas, the pooled rate of GTR for mTSS + iMRI was slightly higher than that for eTSS alone but lower than that for eTSS + iMRI, although no direct comparison could be performed. These results indicate that the effective use of endoscopy is as useful an adjunct as the addition of iMRI to the more traditional microscope-based approach for achieving GTR for adenomas. However, the combined use of both techniques may offer an additive benefit. Nevertheless, there is great heterogeneity among studies that report eTSS, eTSS + iMRI, and mTSS + iMRI. This is not surprising considering the relatively low quality of evidence in the included studies, most of which is retrospective in study design. As such, our data suggest that these results should be interpreted with some caution.

IMRI was first used as an adjunct to neurosurgical practice by Jolesz et al. in 1994 [48] and has since been used in a number of neurosurgical procedures, including mTSS. The major theoretical benefit is that iMRI allows for the detection of tumor remnant that the surgeon is unable to visualize during surgery. Whether this technology leads to an increased extent of resection is unclear. Three of the studies that we identified were single-arm retrospective studies that summarized the corresponding institution's initial experience with mTSS + iMRI [6, 9, 43]. However, the majority of the studies were single-arm studies that compared a surgeon's perception of the extent of resection and the findings on the initial intraoperative scan to the final postoperative rates of GTR [10, 31, 32, 38, 58, 62, 71, 86]. These studies found that iMRI led to increased rates of resection in 6.2–58% of cases. Although these findings are positive, the surgeons were not blinded and may not have been as aggressive as possible during their first attempt knowing that the iMRI would be used. A better study design would be to compare the final extent of resection achieved after iMRI-guided additional resection with a series of cases in which iMRI was not available. Only two such studies were identified. Berkmann et al. performed a retrospective, controlled, non-randomized study comparing patients undergoing pituitary adenoma resection with mTSS + iMRI as opposed to mTSS alone. The use of iMRI was found to increase the rate of GTR (85% vs 69%) [7]. Another study performed a similar comparison and found no significant difference in GTR whether or not iMRI was used with mTSS, although mTSS + iMRI led to a higher rate of complete resection in the subgroup of patients in which gross resection was the intent [20].

The endoscope was also introduced more recently into surgical practice and advocates claim that the increased field of view and more aggressive bone openings allows greater extent of resection compared with mTSS. The addition of angled endoscopes also significantly improves the visualization of remnant tumor. While several meta-analyses have shown better rates of GTR with eTSS [28, 54], others have found no difference [72, 73, 80, 82]. In a meta-analysis examining outcomes and complication rates between endoscopic or sublabial transseptal transsphenoidal surgery, DeKlotz et al. compared 2335 patients in 21 endoscopic studies to 2565 patients in 17 sublabial studies and found superior GTR rates (79% vs 65%, $p < 0.0001$) and lower CSF leak rates (5% vs 7%, $p < 0.01$) in the endoscopic cohort [28]. Similarly, Gao et al. found that in 15 studies involving 1014 patients that underwent eTSS, the rate of GTR was higher compared to the mTSS group, while there was no difference in postoperative CSF leak rates between the two groups [35]. Conversely, Rotenberg found no difference in extent of resection between the eTSS and mTSS approaches [73]. Likewise, Strychowsky et al. observed in a recent

Table 4 Results of GTR and post-operative CSF leak rate in pituitary adenoma resection for studies evaluating eTSS

Study	Surgical intervention	No. of PA	Total cases of GTR								
			Pituitary adenoma (%)	Macroadenoma (%)	Microadenoma (%)	NFPA (%)	FPA (%)	GH (%)	ACTH (%)	PRL (%)	% post-operative CSF leak
Ajlan et al. [1]	eTSS	176	78	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Akbari et al. [2]	eTSS	16	81.3	n/a	n/a	n/a	n/a	n/a	n/a	n/a	18.8
Arbolay et al. [4]	eTSS	7	71.4	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0
Bokhari et al. [11]	eTSS	79	63.2	59.7	100	48.7	77.5	73.7	100	75	3
Campbell et al. [12]	eTSS	26	73.1	n/a	n/a	n/a	73.1	73.1	n/a	n/a	3.8
Cappabianca et al. [13]	eTSS	146	62.3	58.4	85.7	56.2	69.7	63.9	76.9	76.9	2.1
Chabot et al. [14]	eTSS	39	56.4	56.4	n/a	n/a	n/a	n/a	n/a	n/a	10.3
Charalampaki et al. [15]	eTSS	134	94	n/a	n/a	98.7	88.1	88.4	87.5	93.8	n/a
Chi et al. [16]	eTSS	80	63.8	n/a	n/a	n/a	n/a	n/a	n/a	n/a	5
Choe et al. [18]	eTSS	12	83.3	77.8	100	n/a	83.3	88.8	66.6	n/a	16.67
Chone et al. [19]	eTSS	47	95.7	n/a	n/a	93.3	100	n/a	n/a	n/a	4
Conrad et al. [21]	eTSS	40	85	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Constantino et al. [22]	eTSS	28	14.3	14.3	n/a	n/a	n/a	n/a	n/a	n/a	17.80
Cusimano et al. [23]	eTSS	29	79.3	79.3	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Dallapiazza et al. [24]	eTSS	43	96.4	96.4	n/a	96.4	n/a	n/a	n/a	n/a	7
Dallapiazza et al. [25]	eTSS	80	71	71.0	n/a	71	n/a	n/a	n/a	n/a	2.5
De Witte et al. [26]	eTSS	83	29.6	22.5	80	n/a	n/a	n/a	n/a	n/a	6.2
Dehdashti et al. [27]	eTSS	200	88	n/a	n/a	88.0	87.2	85	85	92.	n/a
Di Maio et al. [29]	eTSS	20	60	n/a	n/a	73.3	20	n/a	n/a	n/a	5
Duz et al. [30]	eTSS	28	53.5	n/a	n/a	n/a	n/a	n/a	n/a	n/a	28.6
Frank et al. [34]	eTSS	173	76.9	61.1	100	n/a	n/a	n/a	n/a	n/a	n/a
Gao et al. [36]	eTSS	60	81.7	78.7	92.3	n/a	n/a	n/a	n/a	n/a	n/a
Gondim et al. [39]	eTSS	301	77.4	n/a	n/a	71.1	82.5	85.3	72.9	85.4	2.6
Guo-Dong et al. [40]	eTSS	100	60	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Guvenc et al. [41]	eTSS	45	46.7	n/a	n/a	n/a	n/a	n/a	n/a	n/a	6.7
Han et al. [42]	eTSS	250	86.4	n/a	n/a	n/a	n/a	n/a	n/a	n/a	3.6
Hofstetter et al. [44]	eTSS	71	76.1	76.1	n/a	n/a	n/a	n/a	n/a	n/a	1.4
Jain et al. [45]	eTSS	10	50	44.4	100	n/a	n/a	n/a	n/a	n/a	10
Jang et al. [46]	eTSS	331	69.2	n/a	n/a	62.4	n/a	90	86.2	68.3	1.8
Jho et al. [47]	eTSS	68	77.9	n/a	n/a	77.9	n/a	n/a	n/a	n/a	n/a
Juraschka et al. [49]	eTSS	66	24.2	24.2	n/a	n/a	n/a	n/a	n/a	n/a	9.6
Kalinin et al. [50]	eTSS	97	50.5	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0

Table 4 (continued)

Study	Surgical intervention	No. of PA	Total cases of GTR								
			Pituitary adenoma (%)	Macroadenoma (%)	Microadenoma (%)	NFPA (%)	FPA (%)	GH (%)	ACTH (%)	PRL (%)	% post-operative CSF leak
Karppinen et al. [51]	eTSS	41	56	56	n/a	n/a	n/a	n/a	n/a	n/a	2.4
Kenan et al. [52]	eTSS	59	64.4	64.4	n/a	68.4	62.5	58.8	n/a	60.9	2.4
Kim et al. [53]	eTSS	331	74.9	n/a	n/a	n/a	n/a	n/a	n/a	n/a	2.4
Kumar et al. [55]	eTSS	151	87.4	87.4	87.5	85.2	90	n/a	n/a	n/a	12.6
Kuo et al. [56]	eTSS	38	20.5	20.5	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Lee et al. [57]	eTSS	208	49.5	n/a	n/a	n/a	n/a	n/a	n/a	n/a	2.4
Lopez-Garcia [60]	eTSS	86	77	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0
Messerer et al. [63]	eTSS	82	74	n/a	n/a	74.0	n/a	n/a	n/a	n/a	12.1
Nakao et al. [64]	eTSS	43	47	47	n/a	n/a	n/a	n/a	n/a	n/a	0
Nie et al. [66]	eTSS	52	88.5	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0
O'Malley et al. [67]	eTSS	21	66	n/a	n/a	n/a	n/a	n/a	n/a	n/a	12
Pinar et al. [69]	eTSS	32	56.2	45	75	n/a	n/a	n/a	n/a	n/a	9.3
Prajapati et al. [70]	eTSS	17	64.7	n/a	n/a	n/a	n/a	n/a	n/a	n/a	11.76
Qureshi et al. [71]	eTSS	78	93.6	n/a	n/a	n/a	n/a	n/a	n/a	n/a	10.23
Sankhla et al. [74]	eTSS	13	61.5	61.5	n/a	n/a	n/a	n/a	n/a	n/a	30.7
Sanmillan et al. [75]	eTSS	146	51.4	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Sheehan et al. [78]	eTSS	16	43.8	43.8	n/a	43.8	n/a	n/a	n/a	n/a	n/a
Shou et al. [79]	eTSS	178	72.5	n/a	n/a	71.7	73.3	72.1	75	78.1	n/a
Song et al. [81]	eTSS	22	72.7	72.7	n/a	n/a	72.7	n/a	n/a	n/a	n/a
Sun G et al. [83]	eTSS	42	73.8	n/a	n/a	n/a	n/a	n/a	n/a	n/a	9.8
Taniguchi et al. [87]	eTSS	14	56	n/a	n/a	n/a	n/a	n/a	n/a	n/a	4
Tao et al. [88]	eTSS	22	64	64	n/a	73.3	42.9	n/a	n/a	n/a	4.6
Thomas et al. [89]	eTSS	50	74	n/a	n/a	n/a	n/a	n/a	n/a	n/a	4
Tosaka et al. [90]	eTSS	30	40	40	n/a	n/a	n/a	n/a	n/a	n/a	0
Wongsirisuwan et al. [91]	eTSS	38	73.3	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Yildirim et al. [92]	eTSS	160	90	90	n/a	90	n/a	n/a	n/a	n/a	1.88
Zaidi et al. [93]	eTSS	55	78.2	n/a	n/a	78.2	n/a	n/a	n/a	n/a	0
Zhan et al. [94]	eTSS	313	76.4	n/a	n/a	76.4	n/a	n/a	n/a	n/a	3.8
Zhang X et al. [95]	eTSS	78	79.5	n/a	n/a	n/a	n/a	n/a	n/a	n/a	5.1
Zhang Y et al. [96]	eTSS	678	80.1	n/a	n/a	n/a	n/a	n/a	n/a	n/a	2.1

n/a not available

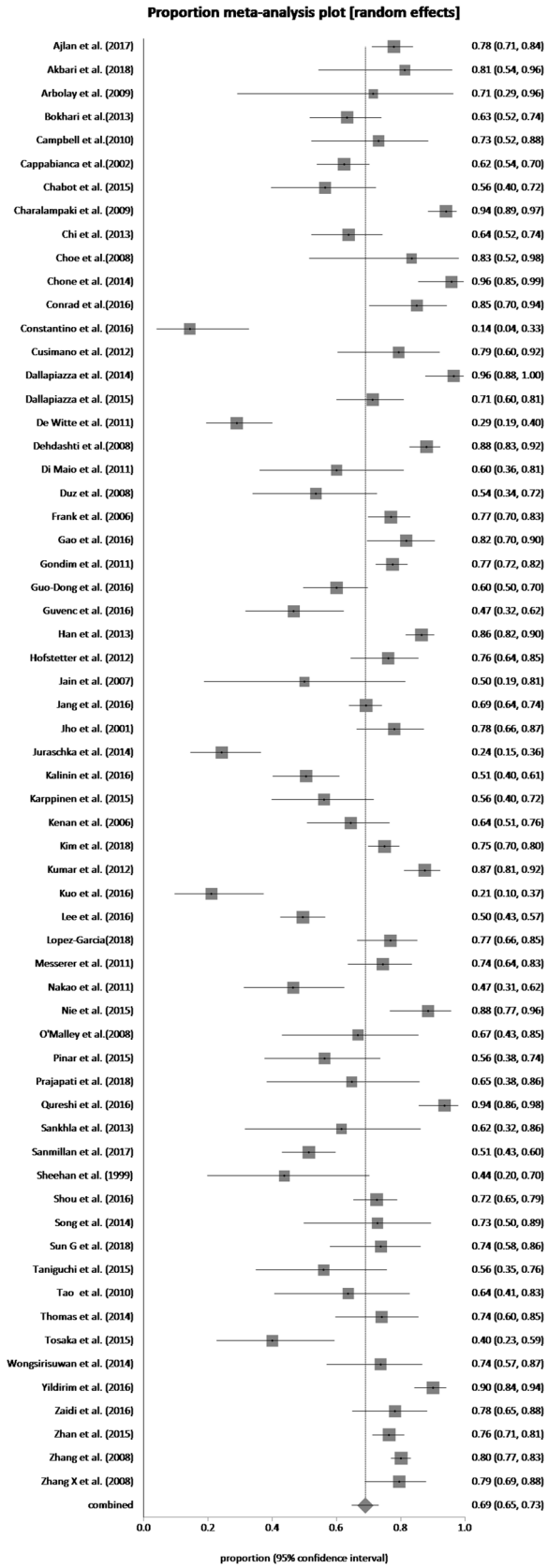

Fig. 2 Forest plot of all studies for GTR in patients undergoing eTSS. Pooled proportion = 68.9% (95% CI = 64.7–73.0%). Cochran $Q = 697.4$ ($p < 0.0001$). $I^2 = 91.3\%$ (95% CI = 89.8–92.4%)

systematic review that while the endoscopic approach for resection of pituitary adenomas resulted in lower mean blood loss, shorter hospital stays and operative times, and fewer nasal complications, no statistical differences were noted in GTR rates or post-operative diabetes insipidus [82]. In a recent study by Almutairi et al., however, eTSS resulted in a higher rate of GTR as compared to mTSS for all patients with pituitary adenoma in a fixed-effects model, but found no significant difference with a random-effects model [3]. Finally, in a meta-analysis limited only to giant adenomas, Komotar et al. showed that eTSS had higher rates of gross total resection (47.2% vs 30.9%; $p = 0.008$) and improved visual outcome (91.1% vs 34.8%; $p = 0.003$) compared with mTSS [54].

Cost is another critical consideration when determining whether to utilize iMRI for pituitary pathology. The iMRI system has significant installation and operation costs, which have been estimated to approach $4 million. Furthermore, this system has a shelf-life of about 5 years, resulting in periodic upgrades and maintenance. A high volume of mTSS and higher complexity of macroadenoma pituitary tumors might justify the use of iMRI in lieu of eTSS. However, the use of an iMRI during a mTSS case increases the average operative time by nearly two additional hours to a procedure that is already several hours in duration. With an extrapolated cost of $600 per minute in the operating room, surgeons, anesthesiologists, and administrators must consider these variables when pondering whether or not to adopt iMRI, as it seems that there is little reason to acquire an iMRI system for this purpose. A possible area of future study would be a direct comparison of operating room time and costs between these techniques.

There are several limitations to this study. First, the strength of a systematic review is dependent on the studies included within the review. As nearly all studies in this review were retrospective single-cohort case series and no study included a direct comparison between eTSS and mTSS + iMRI, a meta-analysis of an effect measure (i.e., odds ratio, relative risk, or risk difference) was not possible. Additionally, there was significant heterogeneity between studies in terms of pre-operative tumor grading and for documenting outcomes based on tumor characteristics. Due to these limitations, we were only able to determine pooled proportions of GTR for pituitary adenomas overall and for macroadenomas. Given the relatively small number of studies evaluating iMRI, we were not able to distinguish the outcomes of low and high magnetic field resonance systems, which is an important distinction as blood and other hemostatic materials may affect image definition when using low-field resonance [17]. Another limitation is that we were

Table 5 Results of GTR and post-operative CSF leak rate in pituitary adenoma resection for studies evaluating mTSS + iMRI

Study	Surgical intervention	No. of PA	Total cases of GTR								
			Pituitary adenoma (%)	Macroadenoma (%)	Microadenoma	NFPA (%)	FPA (%)	GH (%)	ACTH (%)	PRL (%)	% post-operative CSF leak
Baumann et al. [5]	mTSS + iMRI	6	66.6	66.6	n/a	80	0	0	n/a	n/a	16.6
Bellut et al. [6]	mTSS + iMRI	39	79.5	n/a	n/a	n/a	79.5	79.5	n/a	n/a	2.6
Berkmann et al. [7]	mTSS + iMRI	60	85.0	n/a	n/a	85	n/a	n/a	n/a	n/a	0
Boellis et al. [9]	mTSS + iMRI	21	100.0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Bohinski et al. [10]	mTSS + iMRI	29	55.2	55.2	n/a	52.4	62.5	50	100	n/a	3.4
Coburger et al. [20]	mTSS + iMRI	74	65.0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	8.1
Fahlbusch et al. [31]	mTSS + iMRI	44	75.0	75.0	n/a	n/a	n/a	n/a	n/a	n/a	0
Fomekong et al. [32]	mTSS + iMRI	73	65.0	65.0	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Gerlach et al. [38]	mTSS + iMRI	40	37.5	37.5	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Hlavica et al. [43]	mTSS + iMRI	103	68.0	68.0	n/a	n/a	n/a	n/a	n/a	n/a	5.8
Li et al. [58]	mTSS + iMRI	30	80.0	80.0	n/a	n/a	n/a	n/a	n/a	n/a	13.3
Martin et al. [62]	mTSS + iMRI	5	80.0	80.0	n/a	n/a	n/a	n/a	n/a	n/a	20
Ramm-Pettersen et al. [72]	mTSS + iMRI	20	60.0	60.0	n/a	n/a	n/a	n/a	n/a	n/a	5
Sylvester et al. [85]	mTSS + iMRI	41	36.6	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Szerlip et al. [86]	mTSS + iMRI	49	67.0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0

n/a not available

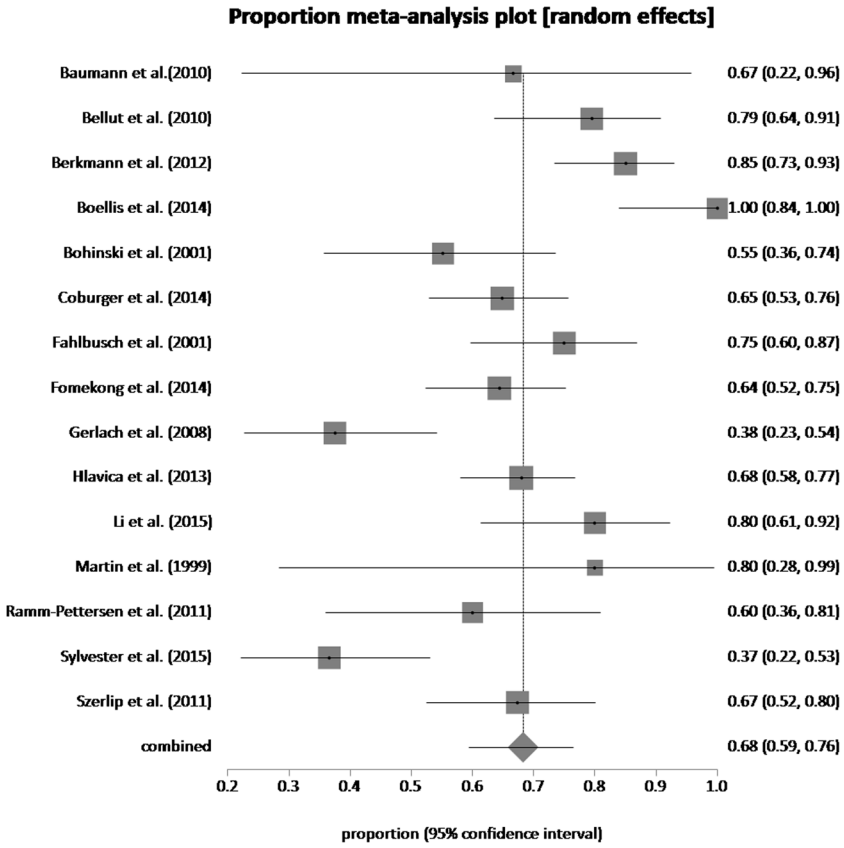

Fig. 3 Forest plot of all studies for GTR in patients undergoing mTSS + iMRI. Pooled proportion = 68.3% (95% CI = 67.1–86.7%). Cochran $Q = 71.2$ ($p < 0.0001$). $I^2 = 80.3\%$ (95% CI = 67.1–86.7%)

Table 6 Results of GTR and post-operative CSF leak rate in pituitary adenoma resection for studies evaluating eTSS + iMRI

Study	Surgical intervention	No. of PA	Total cases of GTR								% post-operative CSF leak
			Pituitary adenoma (%)	Macroadenoma (%)	Microadenoma (%)	NFPA	FPA (%)	GH (%)	ACTH (%)	PRL (%)	
Garcia et al. [37]	eTSS + iMRI	30	83.2	83.0	n/a	n/a	n/a	n/a	n/a	n/a	3.3
Netuka et al. [65]	eTSS + iMRI	105	71.4	n/a	n/a	n/a	71.4	71.4	n/a	n/a	5.0
Pal'a et al. [68]	eTSS + iMRI	28	71.4	n/a	n/a	n/a	n/a	n/a	n/a	n/a	10.7
Schwartz et al. [76]	eTSS + iMRI	15	86.7	86.7	n/a	n/a	n/a	n/a	n/a	n/a	0.0
Serra et al. [77]	eTSS + iMRI	50	61.0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Sylvester et al. [85]	eTSS + iMRI	115	36.5	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Zaidi et al. [93]	eTSS + iMRI	20	80.0	80.0	n/a	n/a	n/a	n/a	n/a	n/a	0.0
Zhang H et al. [85][97]	eTSS + iMRI	137	81.0	81.0	n/a	n/a	n/a	n/a	n/a	n/a	1.4

n/a not available

unable to incorporate surgeon experience, which likely affects outcomes [11]. Ideally, the comparison should be made where the surgeon stays the same throughout the study. However, we were unable to find any studies that allowed for this comparison. Lastly, given the heterogeneous outcome reporting, we were only able to determine pooled proportions for GTR. We were unable to determine pooled rates for other outcomes, such as likelihood of endocrinological success for patients with functional pituitary adenomas, which is likely more important as an outcome measure in the evaluation of surgery for functional tumors. Additionally, we were not able to take into account the histology of functional adenomas given the lack of more granular data. This is an important consideration as outcomes vary based on tumor histology [33]. Moreover, the lack of homogeneity of the number or patients for each study is a significant limitation.

When multiple technologies to improve management of one pathology are introduced simultaneously, early adopters of the different technologies document their

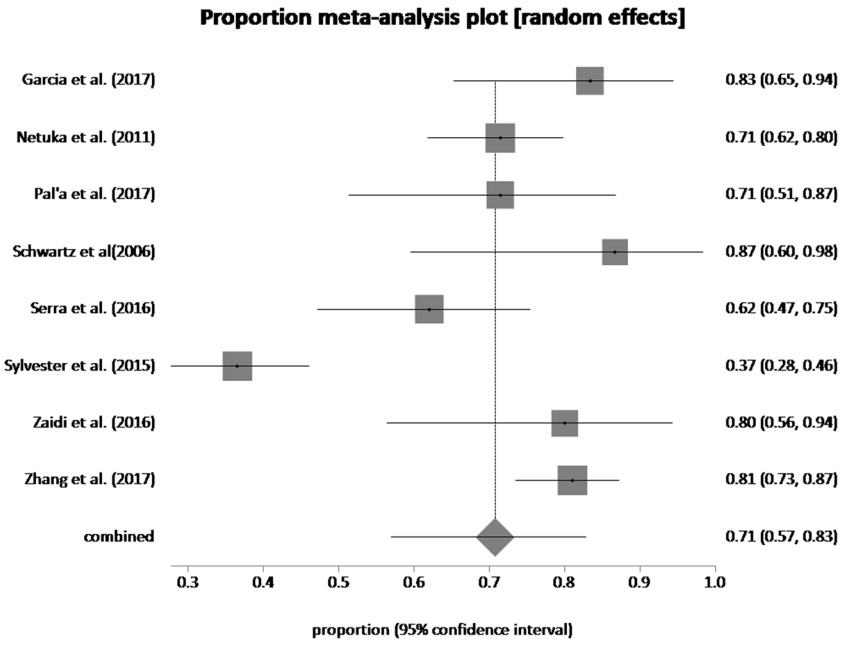

Fig. 4 Forest plot of all studies for GTR in patients undergoing eTSS + iMRI. Pooled proportion = 70.7% (95% CI = 56.9–82.9%). Cochran $Q = 67.4$ ($p < 0.0001$). $I^2 = 89.6\%$ (95% CI = 82–93.1)

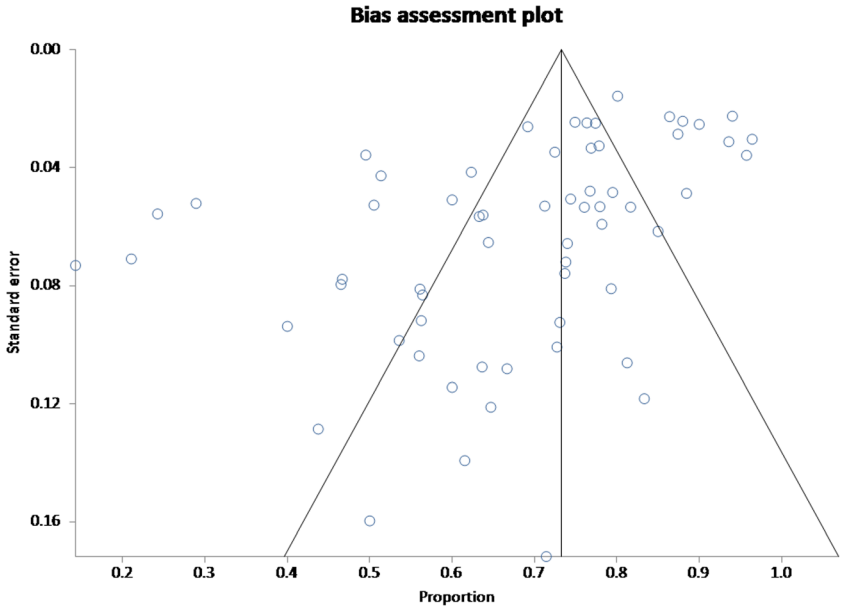

Fig. 5 Funnel plot of all studies for GTR in patients undergoing eTSS

experiences, often with retrospective case series. As the microscope, endoscope, and intraoperative MRI are all tools used to improve outcomes in the resection of pituitary adenomas, the use of one does not necessarily prohibit the other techniques. However, when hospital administrators are contemplating capital investments and surgical recruitments, comparisons of the various techniques may be useful. As no study has been performed that directly compares the two groups and a randomized prospective study is unlikely to occur due to practice patterns, a systematic review provides the best evidence to date.

Conclusion

Although a comparative meta-analysis could not be performed, this study demonstrates that iMRI added to mTSS or eTSS appears to provide a similar proportion of GTR as eTSS alone in the resection of pituitary adenomas. Although an additive benefit may exist for macroadenomas, further studies are required to substantiate this possibility. Given the high cost and additional operative time associated with iMRI, these results are important to consider when deciding between the various techniques available in the management of pituitary adenomas.

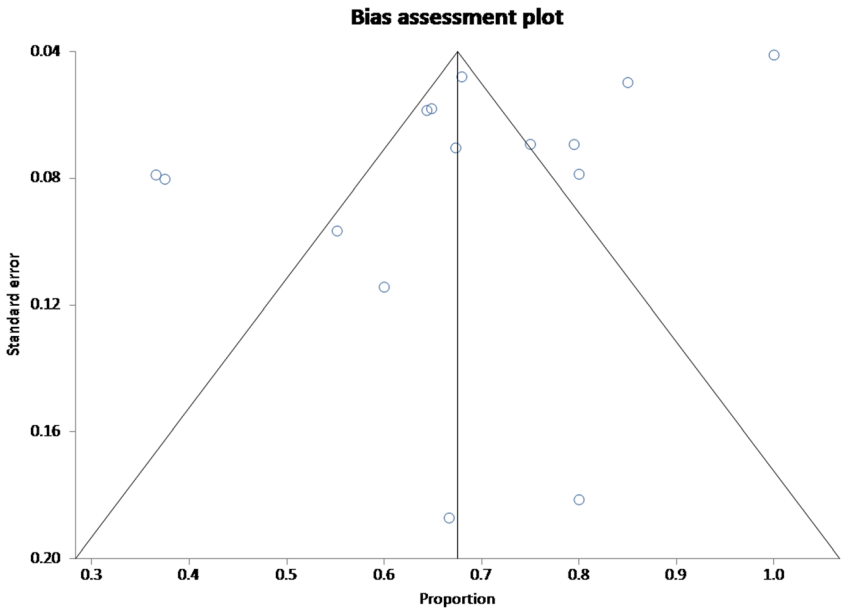

Fig. 6 Funnel plot of all studies for GTR in patients undergoing mTSS + iMRI

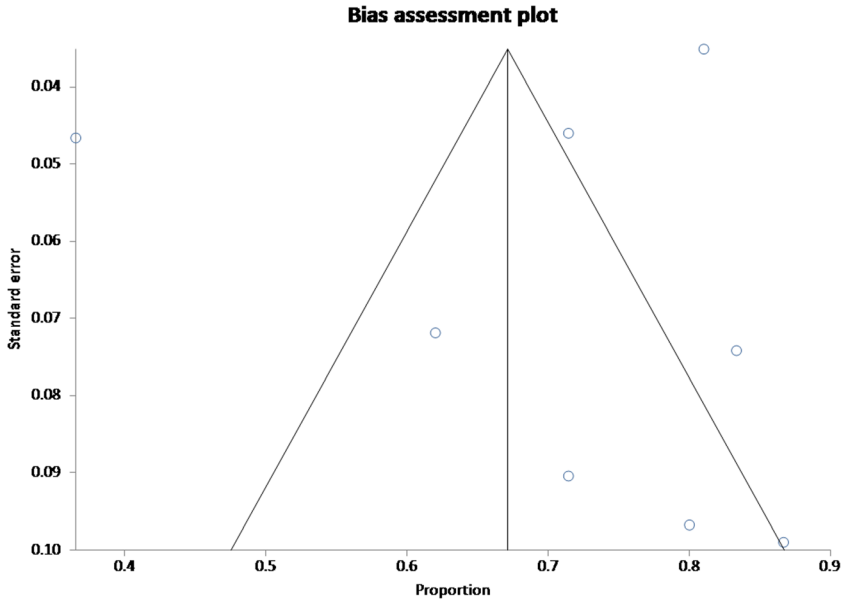

Fig. 7 Funnel plot of all studies for GTR in patients undergoing eTSS + iMRI

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval For this type of study, formal consent is not required.

Informed consent This article does not contain any studies with human participants performed by any of the authors.

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