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Review Article

Comparing redo surgery and stereotactic radiosurgery for recurrent, residual, and/or tumors showing progression in nonfunctioning pituitary adenomas: A systematic review and meta-analysis

Muhammad Yousuf Ul Islam[1], Saad Akhtar[2], Roua Nasir[1], Saad Bin Anis[3], Haissan Iftikhar[1], Farhan Raza Khan[4], Russell Seth Martins[1], Muhammad Ehsan Bari[1], Urooba Ahmed[5]

[1]Department of Neurosurgery, Aga Khan University, [2]Department of Neurosurgery, Liaquat National Hospital, [3]Department of Neurosurgery, Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, [4]Department of Surgery, Section of Dental Surgery, Aga Khan University, [5]Medical School, Liaquat National Hospital and Medical College (LNMC), Liaquat National University, Karachi, Pakistan.

E-mail: Muhammad Yousuf Ul Islam - yousuf3220@gmail.com; *Saad Akhtar - drsaadkhan84@gmail.com; Roua Nasir - rouanasir@gmail.com; Saad Bin Anis - saadanis@skm.org.pk; Haissan Iftikhar - haissaniftikhar@gmail.com; Farhan Raza Khan - farhan.raza@aku.edu; Russell Seth Martins - russell.martins@scholar.aku.edu; Muhammad Ehsan Bari - ehsan.bari@aku.edu; Urooba Ahmed - urubaahmed.27@gmail.com

***Corresponding author:**
Saad Akhtar,
Department of Neurosurgery,
Liaquat National Hospital,
Karachi, Pakistan.

drsaadkhan84@gmail.com

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ABSTRACT

Background: Non-functioning pituitary adenomas (NFPAs) are well-differentiated benign tumors originating from the adenohypophyseal cells of the pituitary gland. They present with headaches, visual disorders, or cranial nerve deficits. NFPAs can recur, progress, or present as residual tumors. We, therefore, conducted this review to compare the effects of both revision surgery and stereotactic surgery on tumor size, visual status, endocrine status, and complications.

Methods: A systematic review of published literature on recurrent, residual, or progressing NFPAs that underwent redo surgery or stereotactic radiosurgery from the inception till June 2020 was conducted as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Thirteen records (1209 patients) were included, and risk ratio (RR) and 95% confidence intervals (CIs) estimated from each study were pooled using a random-effects meta-analysis model.

Results: Redo surgery was the preferred intervention in patients presenting with larger tumor sizes and was more effective in reducing the tumor size as compared to stereotactic radiosurgery (SRS) (risk ratio [RR] 56.14; 95% CI, 16.45–191.58). There was more visual loss with revision surgery as compared to SRS (risk ratio [RR] 0.08; 95% CI, 0.03–0.20). However, SRS was associated with fewer complications, such as new diabetes insipidus, as compared to the redo surgery (risk ratio [RR] 0.01; 95% CI 0.01–0.03).

Conclusion: Redo surgery is the superior choice in the treatment of recurrent/residual or progressing NFPAs if the tumor size is large and an immediate reduction in tumor burden through debulking is warranted. However, redo surgery is associated with a higher risk of visual loss, new endocrinopathies, and other complications, in contrast to SRS.

Keywords: Endocrinopathy, NFPA, Nonfunctioning pituitary adenoma, Non-functioning pituitary tumors, PitNets, Stereotactic surgery, Transsphenoidal approach, Transsphenoidal surgery

INTRODUCTION

Non-functioning pituitary adenomas (NFPAs) are well-differentiated benign tumors that originate from the adenohypophyseal cells of the pituitary gland and do not present with symptoms of hormonal hypersecretion.[6] They represent a sizeable proportion, ranging from 22% to 54% of all pituitary adenomas.[9,19,28] The prevalence of clinically relevant NFPAs is estimated to be 7–41.3 cases/100,000 of the population by the data originating from Europe, North, and South America.[28] The clinical presentation of NFPAs is highly variable. As NFPAs do not present with hormonal hypersecretion, they are either diagnosed incidentally or when they become large enough to cause a mass effect on surrounding structures. Most frequently, they present with headaches due to stretching of the dura mater, mostly in occipital or frontal regions, visual disorders due to pressure on the optic chiasm, or very rarely as cranial nerve dysfunction due to expansion of the tumor laterally into the cavernous sinus.[1] Other rarer manifestations can be hypopituitarism, hyperprolactinemia due to pituitary stalk deviation, and, less frequently, pituitary apoplexy.[6]

The treatment options for NFPAs include observation with serial neuroimaging, repeat surgical intervention through either the transsphenoidal (microscopic or endoscopic) or transcranial route, stereotactic radiosurgery (SRS), fractionated or hypofractionated radiotherapy, and systemic medical therapy (cabergoline or temozolomide). However, NFPAs can recur, undergo progression, or present as residual tumors after incomplete resection and, thus, can be treated after primary surgery by either a redo surgery or SRS.

Surgical resection is the primary treatment for symptomatic patients with NFPAs [19], that is, those with ophthalmologic complaints and/or tumors affecting the optic pathway. Surgery is also urgently indicated for patients with apoplexy who develop neuro-ophthalmologic complaints. Surgical resection tends to have low mortality and morbidity rates; however, accomplishment of total or near-total resection can be difficult and varies in different series, ranging from 20% to 80%.[14,24] The alternative to redo surgical resection in the case of recurrent or residual tumors with progression is radiosurgery – a term coined in 1951 to delineate the procedure used to administer high doses of radiation in a single session to a small, critically located intracranial volume without opening the skull. The primary objective of radiosurgery is to eliminate or curtail the growth of cells, particularly within tumors. Over time, radiosurgery has evolved into a pivotal treatment option, with contemporary systems such as GammaKnife and CyberKnife offering viable alternatives to traditional surgical approaches for a range of intracranial conditions. There is a paucity of data in the literature on salvage treatment by either surgical resection or SRS in patients with recurrent/residual disease or tumors with progression in NFPAs.

Objective

The objective of this systematic review was to compare the effect of redo surgery and stereotactic surgery in terms of reduction of tumor size, deterioration of vision and existing hypopituitarism, and development of any new endocrinopathies or complications.

MATERIALS AND METHODS

Selection criteria

Inclusion criteria

We included studies published in the English language and with designs ranging from randomized controlled trials (RCTs) and quasi-experimental studies to cohort and cross-sectional studies that reported recurrent or residual disease and/or tumors with progression in NFPAs for which either transsphenoidal or transcranial surgical resection or SRS was performed. No restrictions on publication date were put. However, no RCTs were found on this topic.

Exclusion criteria

We excluded non-English publications, as well as qualitative studies like case reports or case series and reports that involved participants without a diagnosis of NFPAs.

Study selection

This review included observational cohort studies as well as cross-sectional studies.

Study participants

Our review included patients diagnosed with NFPAs.

Types of interventions

We included records that involved either endoscopic or microscopic transsphenoidal surgical resection or transcranial surgical resection or SRS for the treatment of NFPAs.

Outcomes measures

The primary outcomes were the proportion of patients with a reduction in tumor size, further deterioration in hypopituitarism, and worsening of vision after either redo surgery or SRS. Secondary outcomes were any new complications or endocrinopathies. Changes in the vision were defined as any subjective or objective improvement or deterioration in the visual fields after the intervention, as compared to the preintervention examination. Since there was massive heterogeneity in the way vision was tested, we included both subjective and objective measurements. Likewise, changes in the

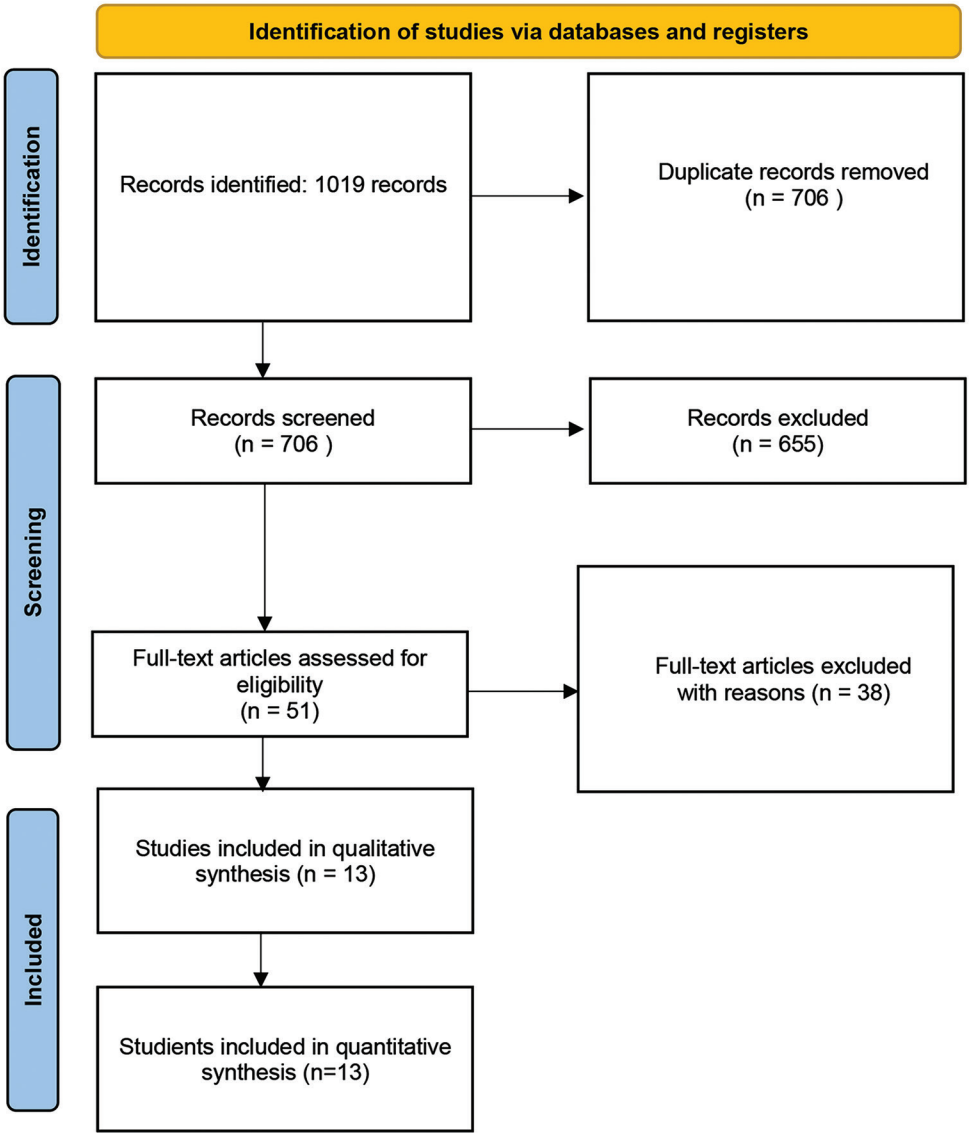

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses chart.

pituitary gland's function were defined as any improvement or deterioration in the pituitary gland's secretory function after the intervention, as compared to the preintervention status (based on hormone replacement requirement). Similarly, changes in the adenoma size were defined as at least a 15% increase or decrease in the size of the tumor as appreciated on a magnetic resonance imaging (MRI) scan conducted at least six months or more after the intervention.

Search strategy

The literature search was conducted systematically across multiple databases, including PubMed, Embase, Web of Science, and Wiley Cochrane Library, spanning from 1970 to June 2020. Various permutations of MESH terms "Stereotactic Radiosurgery" OR "GammaKnife Surgery" OR "CyberKnife Surgery" OR "Radiotherapy" OR "Stereotactic Radiotherapy" OR "Hypofractionated Radiotherapy" OR "Fractionated Radiotherapy" OR "Redo Surgery" OR "Repeat Surgery" OR "Revision Surgery" OR "Repeat Transsphenoidal Surgery" OR "Transcranial Surgery" OR "Endoscopic Endonasal Surgery" OR "Microscopic Transsphenoidal Surgery" OR "Endoscopic Transsphenoidal Surgery" AND "Residual Nonfunctioning Pituitary Adenomas" OR "Recurrent Nonfunctioning Pituitary Adenomas" OR "Silent Pituitary Adenomas" OR "NFPAs" were applied. After applying the rigorous Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology [Figure 1], we initially identified 1019 records. However, following careful screening, which involved eliminating duplicates and applying predefined inclusion and exclusion criteria, only 13 articles met the eligibility criteria for inclusion in our review.

Data collection and analysis

Selection of studies

Initial screening was done independently by two reviewers based on the inclusion criteria. Those records that did not align with the scope of our systematic review and meta-analysis were excluded. Full-text articles were selected as eligible studies and assessed for definitive inclusion as part of secondary screening by two independent reviewers as per the intervention arms and types of outcome measures. A third reviewer addressed any conflicts.

Data extraction and analysis

The data were extracted on a predefined template in Microsoft Excel with variables related to study design, patient demographics, tumor characteristics, and clinical outcomes. The data were subsequently analyzed utilizing both Microsoft Excel and R software to generate forest and funnel plots.

Assessment of methodological quality

The filtered articles were graded using a modified NIH risk of bias tool for observational cohort and cross-sectional studies to assess the methodological quality and possible bias within the study designs. Funnel plots are displayed according to the publishing bias.

RESULTS

Study selection process

The PRISMA flowchart is given in Figure 1. Only observational cohort studies (whether prospective or retrospective), as well as cross-sectional studies, were included since no RCTs were found. As collated in Table 1, we included 13 records with a total patient sample of 1209. A higher number of our records mentioned the usage of SRS as compared to redo surgery for nonfunctioning recurrent pituitary adenomas.

Critical appraisal

According to the assessment by the modified NIH risk of bias tool for observational cohort and cross-sectional studies, all of our studies were graded "fair quality," but one was of "poor quality." The assessment is given in Table 1.

Redo surgery

Not much information was available on the type of initial surgery in redo surgery, and when redo surgery was performed, it could not be ascertained from the records whether it was microscopic or endoscopic—however, studies by Hwang *et al*. and Nejm *et al*.[11,18] reported endoscopic revision surgeries after either microscopic or both microscopic and endoscopic approaches. Hwang *et al*. and Pollock and Carpenter[11,21] also mentioned transcranial approaches as part of most initial surgery for recurrent pituitary adenomas. Further details are shown in Table 2.

Benveniste *et al*.[2] reported redo surgery in 37 NFPA cases. Among those, 27% achieved gross total resection (GTR), with an average interval of 10.1 months between surgeries. Visual loss was reported in 62% of the patients, with 38% of them experiencing bitemporal field defects. Conversely, 27% of patients maintained stable vision, while 24% saw an improvement in vision, and 11% had a complete resolution of vision issues. Tumor size decreased in all cases except one, where it increased. Complications such as epistaxis, CSF leak, sinusitis, and diabetes insipidus (DI) were documented.

Table 1: Summary table.

Study	Study design	Risk of bias	Intervention	Sample size	GTR (%)	Mean interval (months)
Pomeraniec *et al*. 2018[22]	Retrospective cohort	Fair quality	Stereotactic radiosurgery	222	-	-
Negm *et al*. 2017[18]	Retrospective cohort	Fair quality	Redo surgery	24	50	73
Pomeraniec *et al*. 2016[23]	Retrospective cohort	Fair quality	Stereotactic radiosurgery	64	-	-
Hwang *et al*. 2013[11]	Retrospective cross-sectional	Fair quality	Redo surgery	27	55.5	70
Sheehan *et al*. 2013[25]	Retrospective cross-sectional	Fair quality	Stereotactic radiosurgery	512	-	-
Chang *et al*. 2010[4]	Retrospective cross-sectional	Fair quality	Redo surgery	81	39.5	49.2
Swords *et al*. 2009[27]	Retrospective cross-sectional	Poor quality	Stereotactic radiosurgery	8	-	-
Cho *et al*. 2009[5]	Retrospective cross-sectional	Fair quality	Stereotactic radiosurgery	17	-	-
Höybye and Rähn 2009[10]	Retrospective cross-sectional	Fair quality	Stereotactic radiosurgery	23	-	35
Liscák *et al*. 2007[13]	Prospective cross-sectional	Fair quality	Stereotactic radiosurgery	79	-	-
Mingione *et al*. 2006[17]	Retrospective cross-sectional	Fair quality	Stereotactic Radiosurgery	82	-	-
Benveniste *et al*. 2005[2]	Retrospective cohort	Fair quality	Redo surgery	37	27	10.1
Pollock and Carpenter 2003[21]	Retrospective cross-sectional	Fair quality	Stereotactic radiosurgery	33	-	-

GTR: Gross total resection

Table 2: Details about initial surgery and redo surgery.

Study	Intervention	Sample size	Tumor size (cm^3)	Initial endoscopic	Initial microscopic	Initial transcranial	Redo more than once	Redo twice	Redo thrice
Pomeraniec *et al.* 2018[22]	Stereotactic radiosurgery	222	12.9	-	-	-	31	22	9
Negm *et al.* 2017[18]	Redo surgery	24	11.75	19	22	0	36	4	2
Pomeraniec *et al.* 2016[23]	Stereotactic radiosurgery	64	9.85	-	-	-	32	-	8
Hwang *et al.* 2013[11]	Redo surgery	27	11.4	0	36	2	23	6	1
Sheehan *et al.* 2013[25]	Stereotactic radiosurgery	512	-	-	-	-	212	-	-
Swords *et al.* 2009[27]	Stereotactic radiosurgery	8	-	-	-	-	23	8	1
Cho *et al.* 2009[5]	Stereotactic radiosurgery	17	3.08	-	-	-	-	-	-
Höybye and Rähn 2009[10]	Stereotactic radiosurgery	23	1.1	-	-	-	-	2	-
Liscák *et al.* 2007[13]	Stereotactic radiosurgery	79	3.45	-	-	-	66	-	-
Mingione *et al.* 2006[17]	Stereotactic radiosurgery	82	4.8	-	-	-	47	37	9
Pollock and Carpenter 2003[21]	Stereotactic radiosurgery	33	-	-	-	2	23	7	-

Chang *et al.*[4] conducted a study involving 81 NFPA cases undergoing redo microscopic surgery with patients presenting at a mean interval of 49.2 months after the previous surgery. Among these patients, 33.3% presented with headaches, while 23.5% were incidentally diagnosed. Furthermore, 60.5% presented with visual loss, with vision remaining stable in most of the cases and worsening in four patients. Hypopituitarism was observed in 35.8% of patients, which improved in ten cases and remained constant in others. Tumor size decreased in all cases. The complication rate was 18%, with various complications including cerebrospinal fluid (CSF) leaks in two cases, meningitis in two cases, sinusitis in five cases, hematoma in two cases, DI in four cases, and one case of mortality.

Hwang *et al.*[11] conducted a study involving 27 NFPA patients who underwent initial microscopic transsphenoidal and transcranial surgery but subsequently required endoscopic redo surgery. Among these patients, 85.2% had previously undergone surgery more than once. The mean interval from the initial surgery to the redo procedure was approximately 70 months. Visual loss occurred in 88.9% of cases, while vision remained stable in about 14.8%, worsened in 3.7%, and improved in around 70.4% of cases. Tumor size decreased in all cases. Hypopituitarism occurred in 3.7% of cases, with panhypopituitarism in about 25.9% of cases and growth hormone deficiency (GH deficiency) in 7.4% of cases. New endocrine dysfunction developed in 18.5% of cases, including approximately 3.7% with new hypocortisolism. Complications included 14.8% of cases with DI and 3.7% of cases with one patient developing pulmonary embolism.

Negm *et al.*[18] conducted a study with 24 NFPA cases that underwent endoscopic redo surgery after initial both microscopic and endoscopic surgery were examined. The mean interval between the initial surgery and the redo surgery was 73 months. Among the cases, visual loss occurred in 70.8% of patients from the original sample, with around 45.8% demonstrating bitemporal effects. Vision remained stable in 33.3% of cases, worsened in roughly 4.2%, and improved in about 37.5% of cases. Out of the total cases, 70.8% developed hyperpituitarism, 37.5% developed hypopituitarism, and 20.8% had panhypopituitarism. At presentation, 8.3% had DI, and 4.2% presented with a headache, while 4.2% had a CSF leak. In addition, 25% of cases reported new-onset hypopituitarism. Tumor size decreased in 100% of cases.

SRS

From the records with complete information, the median maximum dose of SRS provided ranged from 29 Gy to 40 Gy, with the median tumor margin dose ranging from 16 Gy to 20 Gy, and the maximum dose to visual pathways staying in a close range of 7–7.4 Gy. The details of SRS are elucidated in Table 3.

Table 3: Details about SRS.

Study	Median maximum dose	Medial tumor margin	Maximum dose to visual pathways
Pomeraniec *et al*. 2018[22]	29	-	7.2
Pomeraniec *et al*. 2016[23]	32	16	4.2
Sheehan *et al*. 2013[25]	32	16	7.4
Liscák *et al*. 2007[13]	40	20	7
Pollock and Carpenter 2003[21]	-	16	-

SRS: Stereotactic radiosurgery

Pollock and Carpenter[21] reported 33 NFPA patients who underwent SRS where 70% had undergone transsphenoidal surgery (TSS) more than once before receiving SRS. Visual loss was observed in 24% of the patients, with 50% of them displaying bitemporal visual field defects. Vision remained stable in all cases. Hypopituitarism was initially present in 51% of the patients, while 15% developed new-onset hypopituitarism. In terms of tumor response, 48% experienced a decrease in tumor size, 48% had a constant tumor size, and only one patient demonstrated tumor growth and/or progression.

Mingione *et al*.[17] reported 82 patients who underwent SRS, with 47 having undergone redo surgery more than once. The visual loss occurred in 37 of these patients, but only one case experienced worsening, while the rest remained stable. Among the patients, 84.15% had hypopituitarism, including 6% with DI. In addition, 12 patients developed new hypopituitarism, consisting of four cases of hypocortisolism and nine cases of hypothyroidism. The mean tumor size at presentation was 4.8 cm^3 which decreased in 68.29% of cases, increased in 8.54%, and remained constant in 23.17% of cases.

Liscák *et al*.,[13] mentioned of 79 SRS patients, 83.54% had a history of redo surgery more than once, while 65.82% experienced visual loss, with four cases displaying improvement and no case displaying worsening vision. Furthermore, 82.28% of the patients had hypopituitarism (61.95% with panhypopituitarism), and there were two new cases of hypopituitarism (one of hypocortisolism and one of hypothyroidism each). Tumor size decreased in 88.61% of cases and remained constant in 11.39%, with no instances of progression. Höybye and Rähn[10] reported the use of SRS in 23 patients following initial surgery, with an average interval of 35 months between the previous surgery and SRS. The mean tumor size at presentation was 3.45 $cm^{3,}$ which decreased in 78.26% of cases, increased in 4.35%, and remained stable in 17.39%. In addition, the study reported two cases of patient mortality.

Cho *et al*.[5] investigated 17 cases undergoing SRS, all of whom exhibited visual impairment, which only deteriorated in two cases. Swords *et al*.[27] examined eight SRS patients, with seven experiencing panhypopituitarism and four reporting headaches. The mean tumor size at presentation was 3.08 cm^3, which was reduced in two cases, stayed consistent in four cases, and progressed in two cases.

Sheehan *et al*.[25] had a cohort of 512 cases that underwent SRS for NFPAs, with 41.4% of them requiring redo surgery more than once before undergoing SRS. Among these cases, roughly 57.8% presented with hypopituitarism, including about 15.0% with GH deficiency, 32.4% with hypogonadism, 40.4% with hypothyroidism, 30.9% with hypocortisolism, and 6.3% with DI. In addition, tumor size increased in around 6.1% of cases, and vision worsened in about 5.7% of cases. New-onset hypopituitarism developed in 18.0% of cases, comprising roughly 4.7% with hypogonadism, 5.7% with hypocortisolism, and 7.8% with hypothyroidism. Furthermore, around 1.2% of cases developed DI.

Pomeraniec *et al*.[22] conducted a study involving 222 cases of NFPAs that underwent SRS following TSS. Among these cases, 14.0% required surgeries more than once before SRS. Visual loss was observed in 62.6% of cases, while endocrinopathy was present in around 27.0% of cases, including panhypopituitarism in 8.1% of cases (comprising 9.9% with hypogonadism, 13.1% with hypothyroidism, and 4.9% with hypocortisolism). In addition, 54.9% of patients presented with headaches, 5.4% were diagnosed incidentally, 12.2% reported sexual dysfunction, and 18.5% experienced fatigue. The mean tumor size at presentation was 12.9 cm^3. There was the reduction in tumor size in 27.0% of cases, stability in 58.1% of cases, and an increase in 12.6% of cases, with a notable increase of 15% or more observed in approximately 8.1% of cases. New-onset hypopituitarism emerged in approximately 21.6% of cases, and it resolved in 9.9% of cases.

Pomeraniec *et al*.[23] conducted a study involving 64 patients who underwent SRS following TSS. Approximately half of these patients had previously undergone multiple surgeries before opting for SRS. The visual loss occurred in around 70.3% of the patients, while endocrinopathy was observed in 39.1% of cases, with roughly 20.3% categorized as panhypopituitarism (including 12.5% with hypothyroidism). Among the cases, 34.4% experienced headaches, 3.1% were diagnosed incidentally, roughly 32.8% reported sexual dysfunction, and 48.4% presented with fatigue. The mean tumor size at presentation was 9.85 cm^3. Tumor size

decreased in roughly 29.7% of cases, increased in about 6.3% of cases, and remained stable in the rest.

Tumor size

Revision surgery was more commonly done in the cohort of patients presenting with larger tumor sizes, as shown in Figure 2. As illustrated in Figure 3, every case within the redo surgery group exhibited a complete 100% reduction in tumor size, as opposed to tumors either remaining stable or progressing (risk ratio [RR] 56.14; 95% confidence interval [CI], 16.45–191.58) as compared to the SRS group which displayed a lower reduction rate in tumor size risk ratio [RR] 1.42 (95% CI, 0.53–3.83). There were concerns regarding heterogeneity and the potential for bias in the study (I^2 = 95%, $P < 0.01$) ([Figure 4].

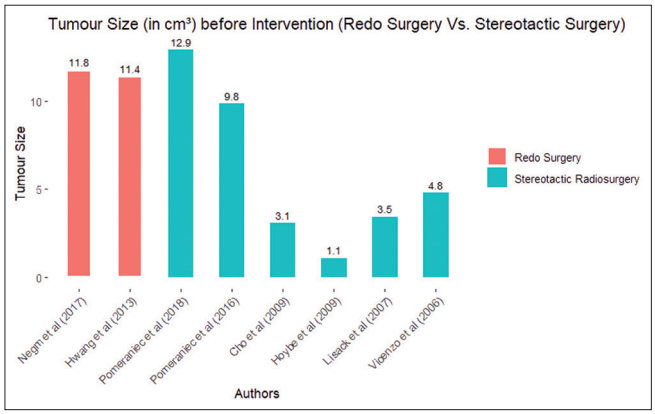

Figure 2: Bar chart for preintervention tumor size (Redo surgery vs. stereotactic radiosurgery).

Visual loss

Figure 5 highlights a similar prevalence of preexisting visual deficits in both the revision surgery and SRS arms. As displayed in Figure 6**,** approximately 5.6% of the cases in the redo surgery group experienced visual loss post-surgery (risk ratio [RR] 0.08; 95% CI, 0.03–0.20), which was higher compared to approximately 1% of cases in the stereotactic surgery (SRS) group (risk ratio [RR] 0.03; 95% CI, 0.01–0.1). No significant heterogeneity was present (I^2 = 0%, P = 0.58) [Figure 7].

Endocrinopathies

Our results indicate that hypopituitarism was more prevalent in the intervention arm of SRS as compared to revision surgery in Figure 8**,** which is contrary to what the inclusion criteria of revision surgery usually comprise. Further, details on preintervention and postintervention endocrine status are shown in Tables 4 and 5, respectively.

As Figure 9 illustrates, while both intervention groups had patients who presented with panhypopituitarism, it was observed that redo surgery was more strongly associated with panhypopituitarism compared to SRS (risk ratio [RR] 1.76, 95% CI of 0.99–3.12). Notably, there were noticeable variations within subgroups in this analysis, and concerns were raised regarding heterogeneity and potential bias of publication (I^2 = 93%, $P < 0.01$), as shown in Figure 10**.** As indicated in Figure 11, SRS was associated with fewer cases of new DI as compared to redo surgery postintervention (risk ratio [RR] 0.01; 95% CI 0.01–0.03). Significant heterogeneity

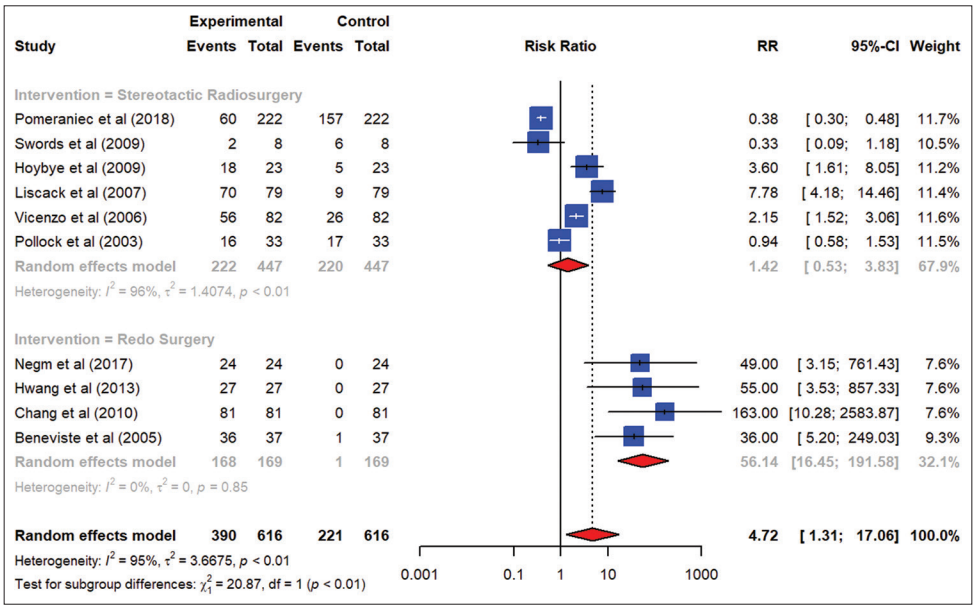

Figure 3: Forest plot comparing preintervention tumor size (Redo surgery vs. stereotactic radiosurgery).

was observed here (I^2 = 97%, P < 0.01), as displayed in Figure 12.

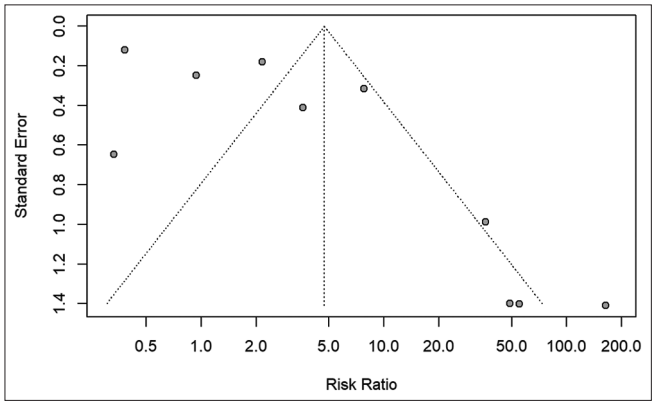

Figure 4: Funnel plot comparing preintervention tumor size (Redo surgery vs. stereotactic radiosurgery).

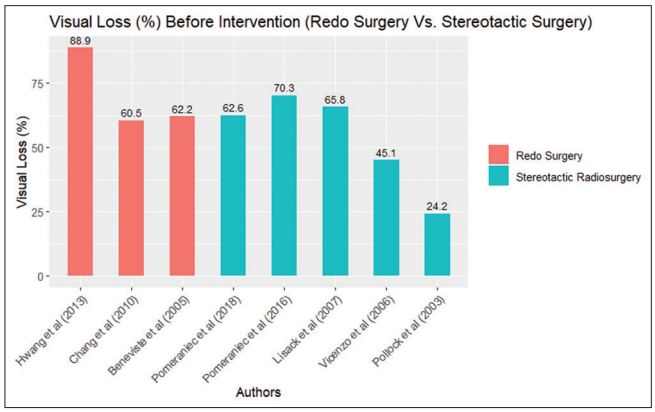

Figure 5: Bar chart for preintervention visual loss (Redo surgery vs. stereotactic radiosurgery).

DISCUSSION

To the best of our review, no systematic review or a meta-analysis exists that compares the two major intervention arms of redo/revision surgery and stereotactic radiosurgery/radiotherapy in recurrent, residual or tumors with progression in NFPAs. The probability of tumor growth is estimated to be 7.8% and 14.5% at 3 and 5 years without any intervention in the form of surgery or radiotherapy.[8] A recurrent pituitary adenoma is defined as a newly developed pituitary adenoma without the evidence of residual tumor on radiological scans at least six months after previous surgery or a growing residual pituitary adenoma on serial postoperative MRI scans. Around 50–60% of adenomas continue to progress after subtotal resection and on long-term follow-up, may recur after GTR in up to 30% of cases.[20] The extent of resection at the time of primary surgical intervention highly depends on factors such as tumor size, tumor consistency, dural invasion, and parasellar and suprasellar extension.[15]

Hypopituitarism is defined as a deficiency of one or more pituitary hormones. Patients with NFPAs develop hypopituitarism due to mechanical compressive forces generated on the pituitary gland with the consequent effects on the gland's portal circulation. Hypopituitarism is a relative indication of surgery in patients with NFPAs and is found more commonly in patients who are symptomatic, of male gender, and those harboring macroadenomas.[7] The patients who recover from hypopituitarism are more likely as compared to the ones who develop new endocrinopathies;[16] thus, repeat endocrinological evaluation is not routinely recommended unless there is evidence of tumor growth. Visual compromise can occur due to the proximity of the tumor to the optic chiasm and is estimated to be 0.2% of the NFPAs presenting with tumor growth.[8] It is important to

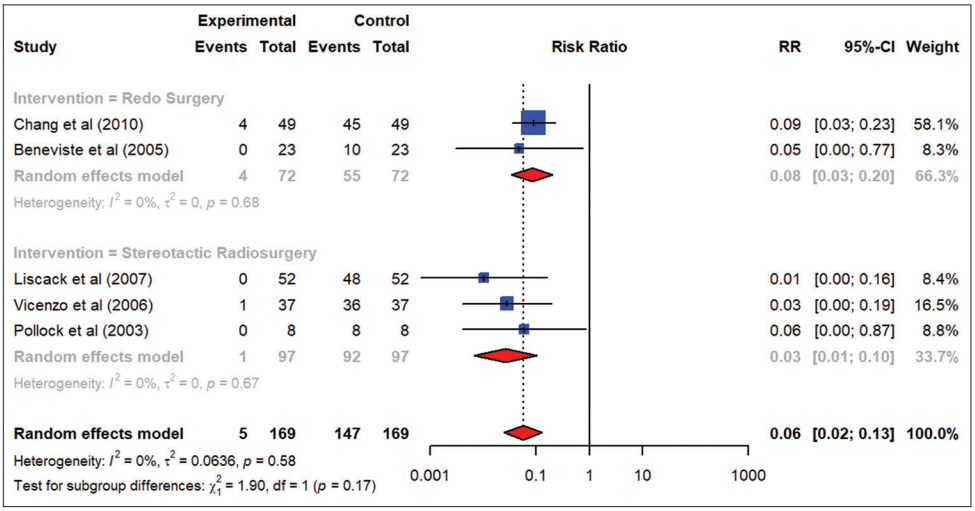

Figure 6: Forest plot comparing postintervention visual loss (Redo surgery vs. stereotactic radiosurgery).

address the visual field defects as the improvement of quality of life in patients with NFPAs treated with surgical resection is directly related to the visual field improvement.[26]

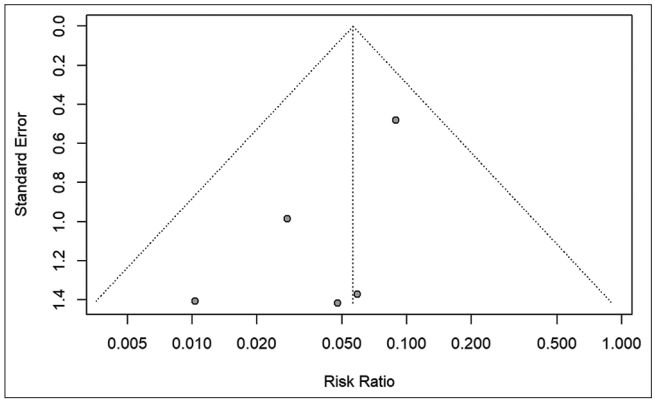

Figure 7: Funnel plot comparing postintervention visual loss (Redo surgery vs. stereotactic radiosurgery).

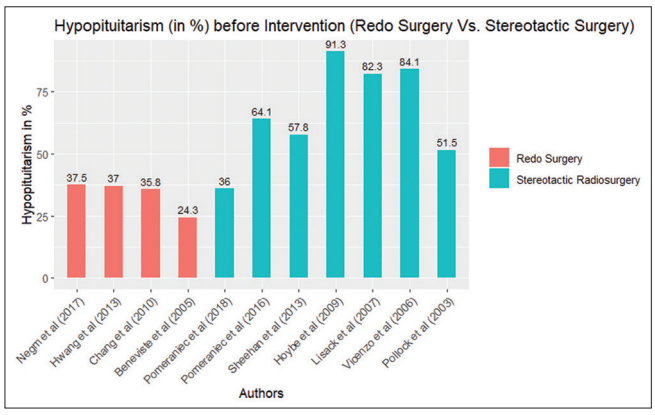

Figure 8: Bar chart for preintervention endocrine status (Redo surgery vs. stereotactic radiosurgery).

Revision surgery results in a more exhaustive tumor mass removal due to the physical nature of removal, leading to the prompt alleviation of pressure exerted on adjacent anatomical structures as compared to stereotactic radiosurgery (SRS). The transsphenoidal surgical approach is proven to be safe and effective but is unable to remove tumors fully; thus, a combination of transcranial and transsphenoidal approaches (TSAs) can be utilized to maximize tumor removal. The microscopic and endoscopic TSAs are similar in their safety profiles; however, endoscopic is the superior modality in terms of preserving the postoperative hormonal profile.[3] Surgical resection was preferred in larger tumor sizes and led to the debulking of tumors with Chang *et al*.[4] and Negm *et al*.[18] reporting satisfactory rates of GTR (ranging between 40% and 63%). The surgical invasiveness with increased manipulation inherently carries higher risks and longer recovery times, with an increased propensity to pituitary damage, thereby elevating the likelihood of precipitating new endocrine disturbances (both transient and permanent). However, the GTR rate after TSS for NFPAs was not associated with improvement or deterioration of hypopituitarism.[30] In redo surgery, the pituitary gland and its adjacent tissues often bear the scars of previous surgical interventions, making it challenging to preserve the pituitary gland's function. There is a risk of damage to the optic nerves or other critical structures in the vicinity, which can lead to visual loss. However, the extent of this risk depends on the complexity of the surgery and the surgeon's ability to preserve visual function. Revision surgeries also carry an increased risk of developing new postoperative complications such as CSF leaks, meningitis, and sinusitis. Chang *et al*.[4] reported one mortality from the postoperative hematoma that required a repeat immediate evacuation.

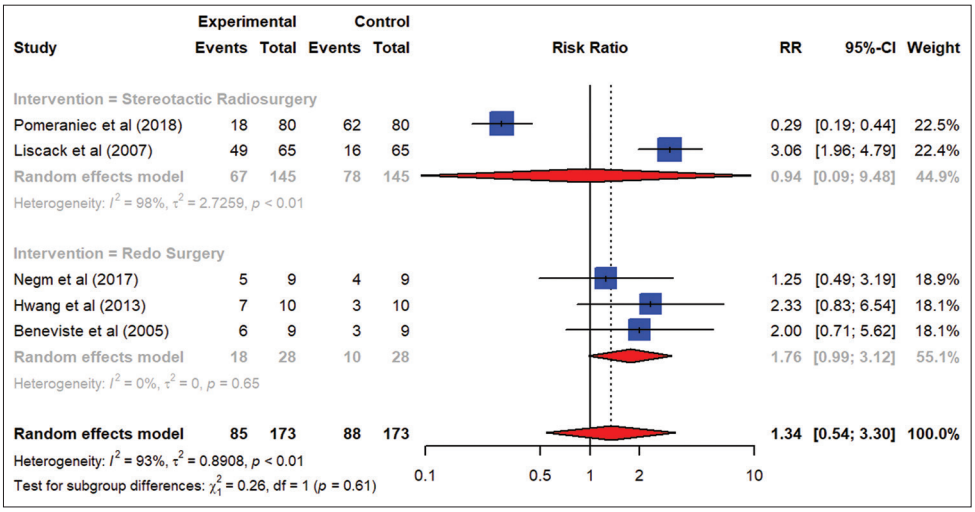

Figure 9: Forest plot comparing preintervention endocrine status (Redo surgery vs. stereotactic radiosurgery).

Table 4: Preintervention endocrine status.

Study	Intervention	Sample	Endocrinopathy	Panhypopituitarism	GH deficiency	Hypogonadism	Hypothyroidism	Hypocortisolism	DI
Pomeraniec *et al.* (2018)[22]	Stereotactic Radiosurgery	222	60	18	-	22	29	11	-
Negm *et al.* (2017)[18]	Redo Surgery	24	26	5	-	1	1		2
Pomeraniec *et al.* (2016)[23]	Stereotactic Radiosurgery	64	25	13	-	4	8	9	-
Hwang *et al.* (2013)[11]	Redo Surgery	27	10	7	2	-	-	-	-
Sheehan *et al.* (2013)[25]	Stereotactic Radiosurgery	512	-	-	77	166	207	158	32
Chang *et al.* (2010)[4]	Redo Surgery	81	29	-	-	-	-	-	-
Swords *et al.* (2009)[27]	Stereotactic Radiosurgery	8	-	7	-	-	-	-	-
Höybye and Rähn (2009)[10]	Stereotactic Radiosurgery	23	-	-	-	-	-	-	-
Liscák *et al.* (2007)[13]	Stereotactic Radiosurgery	79	-	49	-	-	-	-	-
Mingione *et al.* (2006)[17]	Stereotactic Radiosurgery	82	-	-	-	-	-	-	6
Benveniste *et al.* (2005)[2]	Redo Surgery	37	21	6	-	-	-	-	-
Pollock and Carpenter (2003)[21]	Stereotactic Radiosurgery	33	-	-	-	-	-	-	-

DI: Diabetes insipidus, GH: Growth hormone

Table 5: Postintervention development of new endocrinopathies.

Authors	Intervention	Sample	Hypopituitarism	Hypogonadism	Hypocortisolism	Hypothyroidism	Panhypopituatirsm
Pomeraniec *et al.* (2018)[22]	SRS	80	48	12	9	15	12
Negm *et al.* (2017)[18]	Redo surgery	9	6				
Pomeraniec *et al.* (2016)[23]	SRS	41	15	5	2	2	6
Hwang *et al.* (2013)[11]	Redo surgery	10	0		1		0
Sheehan *et al.* (2013)[25]	SRS	296	92	24	29	40	
Höybye and Rähn (2009)[10]	SRS	21	0				
Liscák *et al.* (2007)[13]	SRS	65	2		1	1	
Mingione *et al.* (2006)[17]	SRS	69	12		4	9	
Benveniste *et al.* (2005)[2]	Redo surgery	9	8				7

SRS: Stereotactic radiosurgery

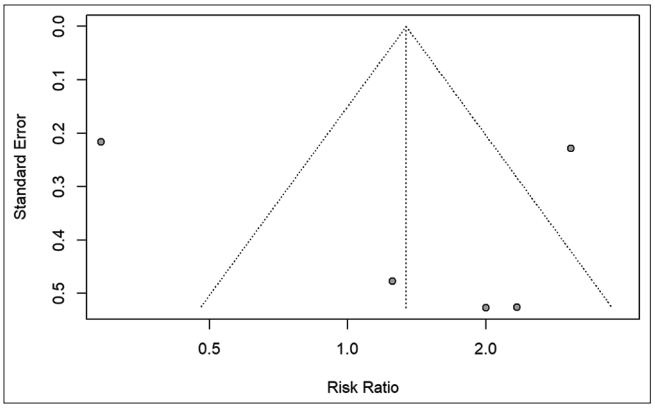

Figure 10: Funnel plot comparing the preintervention endocrine status of hypopituitarism (Redo surgery vs. stereotactic radiosurgery).

SRS, however, precisely and non-invasively delivers targeted radiation therapy to the tumor site to shrink or control the tumor and judiciously preserves surrounding healthy tissue. This makes SRS an inherently less invasive therapeutic option uniquely tailored to smaller intracranial lesions, and thus not suitable for large or complex tumors. It is a viable option when surgery is not advisable, especially in frail and elderly populations. It is designed to minimize damage to surrounding healthy tissue, including the optic nerves and pituitary gland. In our review, besides Cho *et al*.[5] and Pollock and Carpenter [21], all of our stereotactic radiosurgery (SRS) articles used GammaKnife. As elucidated by Sheehan *et al*.,[25] SRS has a far more promising result when the tumor size is smaller due to a greater breakdown of cells. This is also substantiated by the limited utility of SRS in tumors, which are often large and are abutting or compressing the optic apparatus where SRS is not indicated. Our records also demonstrate that SRS was primarily used for the management of smaller recurrent NFPA lesions. It should be noted, however, that SRS primarily focuses on assessing outcomes through tumor control, aiming to prevent tumor growth over a specified period rather than directly reducing tumor size. This explains why SRS may be less effective in directly reducing tumor size compared to repeat surgery in our review. It is important to note that SRS does not produce immediate or dramatic reductions in tumor size; its effects may take several months to years to manifest. Therefore, while our study did not demonstrate this, SRS may not be a suitable choice for patients with preexisting compromised visual function, as it does not offer rapid relief in such cases. While SRS offers a lower rate of complications when compared to redo surgery, it is not without its own set of potential issues. Among these complications, cranial nerve damage, particularly affecting the optic nerve, stands out as one of the most frequent. To mitigate this risk, it becomes necessary to carefully reduce the radiation dose in areas near the optic apparatus during SRS. In the NFPAs that are touching or

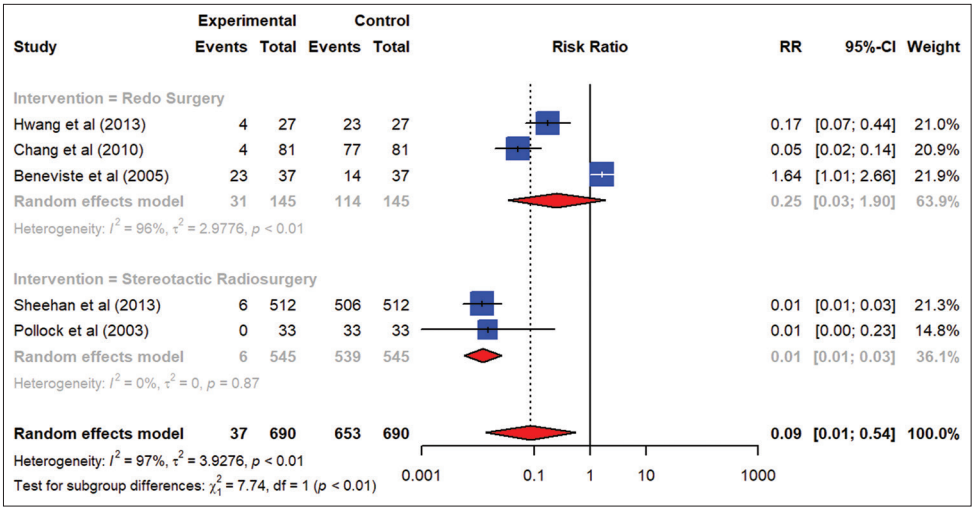

Figure 11: Forest plot comparing postintervention endocrine status (new diabetes insipidus) (Redo surgery vs. stereotactic radiosurgery).

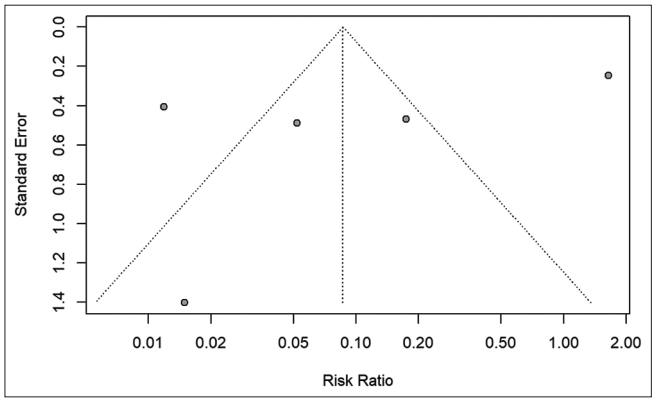

Figure 12: Funnel plot comparing postintervention endocrine status (new diabetes insipidus) (Redo surgery vs. stereotactic radiosurgery).

compressing the optic apparatus, SRS can achieve satisfactory long-term outcomes.[29] Another approach to minimize this complication is to consider switching from a fractionated to a hypofractionated SRS treatment regimen. It is important to note that the radiation dose typically administered during SRS is not usually sufficient to impair endocrine function. This explains the relatively low occurrence of aggravated endocrine dysfunction when compared to the rates seen in repeat surgery and may further support the utility of SRS in elderly patients as they may have greater difficulty in recovering from preintervention hypopituitarism.[12]

The choice between redo surgery and SRS should be made on a case-by-case basis, taking into consideration the specific characteristics of the tumor (such as initial tumor size) and the condition of the patient. Patients must discuss their treatment options with their medical team to determine the most appropriate approach.

Limitations

There is a notable scarcity of prospective studies and clinical trials available to offer definitive guidance for treatment decisions in cases of recurrent pituitary adenomas. Our study encountered a significant limitation in the form of a lack of class I articles that would have allowed for direct comparisons with our study models. Moreover, the new records from 2021 to 2023 were not included in our systematic review. Furthermore, our SRS studies were constrained by a follow-up period averaging <5 years. Typically, SRS requires approximately 5–10 years to manifest its complete effects. The inherent delay in the response to SRS poses a logistical challenge when considering the feasibility of conducting a RCT for an effective comparison of these two treatment modalities. This delay may, in part, contribute to the potential underestimation of the outcomes associated with SRS in our review. We did not include the comparison based on histopathological subtypes or immunohistochemical analysis. In addition, there was no long-term data available to address radiation-induced neoplasms, rates of tumor recurrence, and development of new endocrinopathies.

CONCLUSION

Redo surgery is the superior choice in the treatment of recurrent/residual tumors showing progression in diagnosed NFPA cases if the tumor size is large and an immediate reduction in tumor burden through debulking is warranted. However, redo surgery is associated with a higher risk of visual loss, new endocrinopathies, and other complications, in contrast to SRS. SRS, with a conformal regimen that spares the pituitary gland and optic apparatus, can be a viable alternative in tumors of small size, frail or elderly populations, and can achieve a satisfactory tumor control as well as avoid complications.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's was consent not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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