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ORIGINAL ARTICLE

Evaluation of surgery and radiosurgery for acromegaly: A review of efficacy, complications, and follow-up

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ABSTRACT

Background: Acromegaly is a rare disease caused by an over-increase in growth hormone (GH) and insulin-like growth factors. If left untreated, acromegaly is associated with many complications and increased mortality. The three modalities of treatment for this disease are surgery, pharmacotherapy, and radiotherapy. Another treatment option is stereotactic radiosurgery (SRS), which is used as an adjunct and alternative treatment in patients with acromegaly who are not suitable options for surgery.

Methods: The present study is a review study conducted by searching the databases of Elsevier, PubMed, Springer, and Wiley, and using the keywords of acromegaly, treatment, transsphenoidal surgery, and radiosurgery. Fifteen studies, which had been performed between 2010 and 2021, were selected for review.

Results: The results of these studies indicated that the use of SRS (LINAC SRS and GKRS) after surgery and medical treatment, before surgery and during radiotherapy improve biochemical and endocrine control and the quality of life of patients. However, due to some side effects of these treatments, it is necessary to conduct further studies in this field.

Conclusion: All three modalities of treatment would be effective in acromegaly if used with appropriate indication in right sequence.

Keywords: Pituitary Neoplasms, Pituitary Gland, Radiotherapy, Radiosurgery, Acromegaly

INTRODUCTION

Acromegaly is a rare disease caused by an over-increase in growth hormone (GH) and insulin-like growth factors [1] . Familial syndromes associated with GH overgrowth include multiple endocrine neoplasia type 1, McCune-Albright syndrome, and Carney syndrome [2] . Acromegaly, in addition to affecting the optic nerve and causing hypopituitarism due to adenoma, is characterized by somatic overgrowth and numerous complications. The course of this disease is gradual and there is a 5–10-year delay in the diagnosis of this disease. In the pre-diagnosis period, the symptoms of the disease are annoying, and after the definitive diagnosis, effective treatments can be performed [1] . Acromegaly is associated with significant complications such as hypertension, type 2 diabetes, cardiomyopathy, obstructive sleep apnea, musculoskeletal malignancies and abnormalities, and increased mortality [3] . The overall prevalence of this disease is between 2.8 to 13.7 cases per 100,000 people and its annual incidence is between 0.2 to 1.1 cases per 100,000 people [4] . On average, the disease is diagnosed in the fifth decade of the patient's life. At the time of diagnosis, most tumors are macroadenomas, which may be related to diagnostic delays, and it would pose challenges in the management of surgery. Increasing awareness about acromegaly in the medical community with the aim of reducing side effects due to delayed diagnosis and treatment, and improving outcomes in patients is of particular importance [4] . Appearance changes during this complication are due to skeletal growth and include overgrowth and enlargement of the nose and lips, prominent forehead and skull, overgrowth of the mandible and maxilla, increased interdental spacing, jaw malocclusion (jaw abnormalities), and overbite (one of the inherited problems of the jaw); Narrowing of the ring and changes in the size of the patient's shoes have also been reported [2] . In the absence of proper and timely treatment, acromegaly is associated with many complications and increased mortality. The three treatments for this disease are surgery, pharmacotherapy, and radiotherapy. Surgery is the treatment of choice for most patients and is the only method that can lead to immediate treatment. Unfortunately, in almost 50% of cases, surgery is not possible, and adjuvant treatment is required. In these cases, pharmacotherapy is recommended. Currently, the following three classes of drugs are used for the treatment of acromegaly:

Somatostatin receptor ligands (SRL), dopamine agonists, and GH receptor antagonists.

Radiotherapy is the third line of treatment, which is mainly used for invasive tumors that are not controlled by surgery or medical treatment [5] . Another adjunctive and effective treatment in this field is the use of stereotactic radiosurgery (SRS), which leads to recovery in 40-50% of patients [6, 7] . SRS refers to single-dose radiation therapy using precisely focused radiation to kill the target cell, while normal tissues receive the least amount of radiation. The ideal target in SRS is a tumor with a small diameter (less than 35 mm) and the radiation dose reached to the optical system is less than 8 Gy [8] . In this technique, there should be a suitable distance from the optic tract and the patient should be carefully selected.

MATERIALS AND METHODS

The present study is a review study performed by searching the databases of Elsevier, PubMed, Springer, and Wiley, and using the keywords of acromegaly, treatment, trans-sphenoidal surgery, and radiosurgery.

These words were often used separately and, in some cases, as a combination of two words. Inclusion criteria were full-text articles in the field of the role of radiosurgery and surgery in the treatment of acromegaly, and articles published since 2010; exclusion criteria included articles without full-text, and studies published before 2010. In the analysis phase, the information collected from the studies included the author (s), year, purpose, method of work, and research results. No interpretation was used during the data collection and the main phrases of the articles, which were used by the author (s), were used.

Treatments: There are several methods of treatment for acromegaly that aim to normalize IGF-1 levels, lower GH levels to below 1.0 ug/L, reduce tumor volume, and improve clinical signs and symptoms. Depending on the patient's characteristics and the size of the tumor, these methods vary from surgery, medical treatment, or radiotherapy [9] .

Surgery: Among the various treatments for acromegaly, the goal of surgery is to remove the tumor while maintaining normal pituitary function and maintaining patient safety. Removal of GH-secreting pituitary adenomas leads to improvement in 50-70% of patients. Patients with acromegaly often have other problems and diseases and anatomical changes that complicate anesthesia and surgical management. Despite these challenges, complications such as CSF (cerebrospinal fluid) leak or hypopituitarism do not occur after surgery [6] . Currently, more than 90% of somatotroph tumors are removed by transsphenoidal surgery (TSS). Although TSS is usually performed selectively, surgery is necessary in cases with rapid and progressive disease, increased intracranial pressure, and in some cases of pituitary apoplexy. There are two types of TSS, microscopic (MTSS) and endoscopic (ETSS), and both of which are performed through three different pathways: sublabial, direct endonasal, and submucosal endonasal. Although the choice of surgery largely depends on the surgeon's experience and preference, microscopic sublabial surgery is more appropriate for large tumors, while for smaller lesions, endonasal routes are preferred. In recent years, the endoscopic type of TSS has become highly popular due to its sharpness and the possibility of creating a wider view of the surgical field, but since this method only provides a two-dimensional view, it causes problems in understanding depth. This surgery is very useful when a part of the tumor is hidden from the surgeon's point of view. The endoscopic method has certain differences with the microscopic type, which include a narrower surgical space, a two-dimensional view, performing surgery by observing a monitor (as opposed to direct observation in the microscopic type of surgery), and the need for a secondary surgeon (usually an otorhinolaryngologist). The main advantage of the microscopic type of TSS is the ability to allow relatively free movement of the instruments in surgery. Another type of surgery is transcranial surgery, which is usually performed on very large macroadenomas with posterior extension or parasellar invasion into the cavernous sinus. TSS is associated with a much lower risk of mortality (below 0.6) and fewer complications (including bleeding, meningitis, CSF leak, and transient diabetes insipidus), in comparison with transcranial surgery [10] . Patients with refractory acromegaly require medication or radiation therapy after surgery [6] .

Medications: Medical treatment options for acromegaly include dopamine agonists (e.g., cabergoline), first-generation long-acting somatostatin receptor ligands such as octreotide and lanreotide (SRLs), GH receptor antagonists such as Pegvisomant (PEGV), and the second generation of long-acting somatostatin receptor ligands such as pasireotide (PAS-LAR). The first line of pharmacotherapy is monotherapy with the first generation of SRLs using octreotide and lanreotide. By affecting subgroup 2a of the somatostatin receptor (SST2a), SRLs inhibit GH secretion and normalize GH and IGF-1 levels with an efficacy of about 25%-45%. If biochemical control is not achieved after consuming the maximum dose of first-generation SRLs, treatment should be based on the presence or absence of residual tumor and impaired glucose tolerance in the patient. Monotherapy with dopamine agonists (e.g., cabergoline), which act on dopamine 2 receptors, can serve as the first line of postoperative drug therapy only for patients with relatively high GH and IGF-1 levels (IGF-1 levels less than 2.5x the upper limit of normal (ULN)). Combination therapy using first-generation SRLs and PEGV is also the best second-line treatment option in all non-responders (defined as IGF-1 levels greater than ULNx1.3) [11] . Although drug treatments that suppress GH production can be effective in the initial management of recurrent acromegaly, these treatments are not permanent and require lifelong treatment for hormonal control [12] .

Radiotherapy and radiosurgery: In general, the first line of treatment for acromegaly is transsphenoidal surgery (TSS) with/without somatostatin analogues such as octreotide and lanreotide. If previous treatment interventions are not successful, subsequent options include radiotherapy [13] . Various methods of radiation therapy include conventional radiotherapy, fractionated stereotactic radiotherapy (RT), or stereotactic radiosurgery (SRS) [14] . Among the different types of radiotherapy, RT and SRS, which typically reflect a significant dose of radiation in 1-5 target sections with an accuracy of less than millimeters, are more common [13] . Stereotactic radiosurgery has several methods, such as gamma knife, cyberknife, and linear accelerator or proton beam therapy that radiate the high energy of photons to the target. stereotactic radiosurgery can be used as a single dose (such as gamma knife), or fractionated that means the radiation delivered in three to five sessions. This technique is considered as an effective and appropriate method in the treatment of acromegaly [14] . Among the various types of SRS, gamma knife is the most widely used. Due to its long-term follow-up in clinical trials, it is likely to compete with drug therapy as the first line of treatment after surgery [15] . Gamma knife radiosurgery is a type of SRS that uses 200 sources of cobalt-60 (the radioactive isotope of cobalt) to irradiate a high dose of radiation to the target (tumor). In this technique, healthy and vital tissues of the brain receive the least amount of radiation and are not damaged [16] .

Damage to the optic apparatus is an important factor in selecting the radiation treatment modality. In the fractionated radiotherapy, even 3 dimensional conformal radiotherapy is more protective for optic chiasma and optic

tract compare to conventional (two-dimensional) radiotherapy. [17] Similarly, the patients should be selected properly for SRS with appropriate indications.

Some studies indicate less toxicity and faster recovery of endocrine using SRS compared to RT [13] . Fractionated conventional radiotherapy takes several months to years to control hyper secretion of tumor and it is also associated with the risk of pituitary insufficiency, which may limit its use; on the other hand, treatment with SRS may be less effective, but the patient recovers in shorter time. Also, better control on the radiation dose received by critical organs such as the pituitary stalk, pituitary gland, optic chiasm, and cranial nerve in the cavernous sinus, makes this method more accurate for targeting the adenoma [15] . Multidisciplinary decision making is critical for approach to patients with brain tumor such as acromegaly which has failure on treatment modalities [18] .

RESULTS

Efficacy of treatment, side effects, and follow-up

In order to evaluate the Efficacy of treatment, complications, and follow-up of SRS and TSS therapies in patients with acromegaly, 19 studies were selected for further review and the results of which are presented in Tables 1 and 2. Table 1 shows the role and side effects of SRS in the treatment of acromegaly, with 9 studies on GKRS and LINAC SRS. The results of these 9 studies indicated the positive relationship between the use of SRS (LINAC SRS and GKRS) after surgery and drug therapy, before surgery and simultaneously with radiotherapy, with biochemical and endocrine improvements, and better tumor control. A total of 1773 patients with acromegaly were studied in these 19 articles, and the results demonstrated that the use of SRS was associated with improved physical condition, tumor control, and biochemical improvement, as well as side effects, but no mortality was observed among the cases treated with this method. Side effects were reported in 325 patients (18.33%) following the use of this treatment method, including hypopituitarism, neurological disorders, panhypopituitarism, endocrine disorders, vision impairment and ocular motor nerve palsy, and adrenocorticotropin or thyrotropin deficiency [19-27] .

Knappe et al. showed that the rate of pituitary insufficiency in patients treated with FRT (fractional radiotherapy) is significantly higher than patients treated with SRS [21] . On the other hand, in 37 patients (2.09%) after SRS application, recurrence of the disease was observed [20, 22, 23, 27] . The follow-up period in these patients was between 40.8-166.5 months [19-24, 27] .

Table 2 shows a summary of the studies on the role and side effects of TSS (MTSS and ETSS) in acromegaly treatment, of which 5 studies are related to ETSS and 5 studies are related to the use of both types of MTSS and ETSS. The results of these 10 studies indicated a positive relationship between the use of TSS (MTSS and ETSS) with biochemical and endocrine improvements and tumor control. A total of 3251 patients with acromegaly were studied in these 19 articles, and the results demonstrated that the use of TSS was associated with improved physical condition, tumor control, biochemical improvement, and increased quality of life of patients, as well as side effects, but no mortality was observed among the cases treated with this method. In one patient, recurrence was observed after ETS. Complications of this treatment include epistaxis, transient diabetes mellitus, seizures, sinusitis, changes in taste and smell, pituitary insufficiency, panhypopituitarism, and deficiency of new hormones. The results of these studies showed that the patients treated with MTSS experienced more complications such as postoperative diabetes insipidus and pituitary insufficiency compared to patients treated with ETSS, while sinusitis and changes in taste and smell were more common in ETSS. However, in terms of recovery rate after surgery, no significant difference was observed between the two groups. In general, the success rate of treatment was higher in patients with microadenomas than in patients with larger lesions (macroadenomas). The follow-up period in these patients was between 11- 64 months [28-36] .

Table 1- Results related to the role of radiosurgery in the treatment of acromegaly

Author(s)	Title	Method/Follow-up	Results
Yan et al. (2013) [27]	Long-term follow-up of patients with surgical intractable acromegaly after linear accelerator radiosurgery	Number of cases and method: 22 patients with acromegaly with residual or recurrent pituitary tumor (high levels of IGF-1 and GH, and confirmation of tumor by imaging) were treated with LINAC-SRS after surgery (radiosurgery with Linear accelerators). Biochemical recovery was defined as the fasting GH level less than 2.5 ng / mL and IGF-1 adjusted for age and sex. Follow-up: The average follow-up period was 94.7 months.	Overall, the mean biochemical recovery time was 53 months. Biochemical control was obtained in 15 patients (68.2%) during the follow-up period. One patient experienced a recurrence after SRS and underwent another operation. Primary and pre-SRS GH levels were associated with biochemical diagnosis and control, respectively. Further evaluation showed that in these patients, biochemical control was stable after 7.5 years and hormone deficiency continued after SRS in five patients (22.7%).
Lee et al. (2014) [16]	Stereotactic radiosurgery for acromegaly	Number of cases and Method: A total of 136 patients with acromegaly underwent Gamma knife SRS (GKRS). The diagnosis of acromegaly was based on a combination of clinical features and biochemical evaluations, including serum GH and serum IGF-1 levels, according to age and sex. All patients underwent a complete endocrine evaluation, neuroimaging, and eye examinations before SRS. After discontinuation of GH or IGF-1 modifying drugs, patients who underwent oral glucose	With an average follow-up period of 61.5 months, 65.4% of patients recovered. The mean recovery time was 27.5 months. The rate of sustained recovery at 2, 4, 6, and 8 years after radiosurgery was 31.7%, 64.5%, 73.4%, and 82.6%, respectively. Optimal prognostic factors for recovery included higher marginal radiation dose, higher maximum dose, and lower primary IGF-1 levels. New pituitary hormone deficiencies occurred in 43 patients (31.6%). Two patients (1.5%) developed panhypopituitarism (deficiency of two or more

		tolerance tests and had a GH of less than 1 ng / mL or normal IGF-1, were considered as recovered. Pituitary insufficiency after radiosurgery was defined as a decrease in one or more hormones. Follow-up: The mean duration of follow-up was 61.5 months.	pituitary hormones). Risk factors associated with the new pituitary hormone deficiencies included one marginal dose greater than 25 Gy and a tumor volume greater than 2.5 ml. Other complications included adverse effects of radiation in one patient, vision impairment in four patients, and ocular motor nerve palsy in one patient.
Alonso et al. (2019) [19]	Safety and efficacy of repeat radiosurgery for acromegaly: an International Multi-Institutional Study	Number of cases and method: 398 patients with acromegaly who underwent treatment with GKRS. After repetition of SRS, 21 patients were followed up for endocrine function and 18 patients were followed up for imaging. Tumor control was defined as the lack of adenoma progression in imaging, and endocrine recovery was defined as the normal concentration of IGF-1. Follow-up: The mean duration of follow-up for imaging and endocrine function after the repetition of SRS were 3.4 and 3.8 years, respectively.	The mean interval between the initial and repeated SRS was 5 years. The mean marginal initial and repeated radiation doses were 17 and 23 Gy, respectively. Among the 18 patients who were followed for imaging, 15 patients (83.3%) had tumor control, and amongst the 21 patients who were followed for assessment of endocrine function, 9 patients (42.9%) had endocrine recovery at the last follow-up visit. Four patients (19%) experienced new complications and disorders after repeated radiosurgery, of which 3 patients had neurological disorders and 1 patient had endocrine disorders.
Ding et al. (2019) [20]	Stereotactic Radiosurgery for Acromegaly: An International Multicenter Retrospective Cohort Study	Number of cases and method: 371 patients with acromegaly who were treated with GKRS and endocrine follow-up period ≥ 6 months. Follow-up: The average duration of endocrine follow-up was 79 months.	IGF-1-lowering drugs were discontinued in 56% of patients receiving pharmacotherapy before SRS. The mean volume treated with SRS and marginal dose were 3 cm^3 and 24.2 Gy, respectively. The primary and stable endocrine recovery rates at 10 years were 69% and 59%, respectively. The mean time of stable recovery after SRS was 38 months. Biochemical recurrence occurred after initial recovery in 9% of patients with a mean recurrence time of 17 months. There seems to be a statistical correlation between discontinuation of IGF-1-reducing drugs before SRS and sustained recovery. Side effects of radiation included the development of 1≤ new endocrinopathy (endocrine disorders) in 26% of patients and 1≤ cranial neuropathy in 4% of patients.
Sims-Williams et al. (2019) [24]	Radiosurgery as primary management for acromegaly	Number of cases and method: 20 patients with acromegaly treated with primary GKRS. In these patients, biochemical control (GH / IGF1), pituitary insufficiency, complications, and mortality were evaluated and measured. Follow-up: The average duration of follow-up was 166.5 months.	At 20 years of follow-up, control was observed in all consumers of specific acromegaly medications (n = 12) and 75% of patients who did not receive the drug (n = 4). The time required to reach and achieve 50% control was 3 years for patients receiving the drug and 7.4 years for patients not receiving the drug. The mean marginal dose of radiation was 27.5 Gy and the mean follow-up period was 166.5 months. At a mean follow-up time of 146 months, 53% of patients developed pituitary insufficiency, and the first onset of this complication occurred 20 years after treatment. Also, no other complications were observed in MRI findings. Three patients underwent TSS (transsphenoidal surgery) due to poor biochemical control. During follow-up, 7 patients died at an average age of 65 years. No STRS-related mortality was reported
Pai et al. (2019) [23]	Low-Dose Gamma Knife Radiosurgery for Acromegaly	Number of cases and method: 76 patients with acromegaly treated with GKRS at a low dose (less than 25 Gy). The mean marginal dose, isodose line, and treated volume were 15.8 Gy, 57.5%, and 4.8 mL, respectively. All patients underwent a complete endocrine, visual, and imaging assessment before and after GKRS treatment and the results were analyzed. Follow-up: The mean duration of follow-up for imaging and endocrine assessment were 65.8 and 72.8 months, respectively.	Biochemical recovery was achieved in 33 patients (43.4%). The recovery rates at 4, 8, and 12 years were 20.3%, 49.9%, and 76.3%, respectively. Lack of invasion to the cavernous sinus and low levels of IGF1 were predictors of improvement. New hormone deficiencies were observed in 9 patients (11.8%). The frequencies of hormone deficiency at 4, 8, and 10 years were 3%, 14%, and 22.2%, respectively. In two patients (2.6%) with initial recovery, recurrence of the disease was observed. No visual impairment was reported. These results indicated that the rate of improvement and new hormone deficiency in acromegaly patients treated with GKRS at low doses and standard doses are comparable and equal.
Mohammed et al. **(2019)**	Primary versus postoperative stereotactic radiosurgery for acromegaly: a multicenter matched cohort study	Number of cases and method of work: 78 patients with acromegaly were treated with SRS. These patients were divided into two groups:	The study population consisted of 78 patients, 26 of whom were in group 1 and 52 in group 2. In the first group, the rate of endocrine recovery at 2 and 5 years was 20% and 42%,

[22]		in the first group SRS was used as the primary treatment and in the second group SRS was used after surgery (1: 2 ratio) and the results of the two groups were compared. Follow-up: The average follow-up period was 66.4 months.	respectively. Low IGF1 levels were the predictor of endocrine recovery, and a lower marginal dose of SRS was the predictor of biochemical recurrence after initial recovery. There was no difference between the two groups in terms of tumor control, primary endocrine recovery, biochemical recurrence after initial recovery, survival without recurrence, or pituitary insufficiency.
Knapp et al. (2020) **[21]**	Fractionated radiotherapy and radiosurgery in acromegaly: analysis of 352 patients from the German Acromegaly Registry	Number of cases and method: 352 patients with acromegaly treated with SRS and FRT (fractional radiotherapy) with a follow-up period of 1.0-45.1 years after radiotherapy. Successful treatment with low or normal levels of IGF-1 and without the use of inhibitor drugs was defined as recovery, and with the use of inhibitor drugs was considered as disease control. Follow-up: The time between radiotherapy and the last follow-up session for the FRT group (233 patients) and the SRS group (119 patients) was 13.0 ± 8.2 and 9.0 ± 8.5 years, respectively.	The mean level of basal growth hormone before radiotherapy in FRT and SRS groups was 6.3 and 3.5 ng / mL, respectively. The mean time of uncontrolled conditions after FRT and SRS was 3.0 and 2.1 years, respectively. The 10-year recovery rate and controlled disease rate for FRT and SRS were 48%, 52%, 23%, and 26%, respectively. The odds ratio of adrenocorticotropin or thyrotropin deficiency in SRS compared to FRT was 0.54, indicating that the rate of pituitary insufficiency was significantly higher in patients treated with FRT.
Sims-Williams et al. (2021) [25]	Long-term safety of gamma knife radiosurgery (SRS) for acromegaly	Number of cases: 118 patients with acromegaly, who were treated with gamma knife SRS. Data were collected from the hospital database and patients' questionnaires.	88% (104 out of 118) of the cases had complete documentation for patient follow-up and analysis. The mean follow-up was 134 months and the mean dose of SRS was 30 Gy. In 81% of cases, the cavernous sinus was invaded by the tumor. No association was found between stroke and age and sex. In 68 patients who had MRI-guided SRS and did not receive any radiation therapy (SRS or fractional radiotherapy), no deterioration in visual acuity was observed, and 3% required examination by an ophthalmologist. There was a positive correlation between radiation therapy and ophthalmology and deterioration of visual acuity.
Yang et al. (2021) [26]	Comparing primary gamma knife radiosurgery and postoperative gamma knife radiosurgery for acromegaly: A monocenter retrospective study	75 patients with acromegaly were included in this study. Endocrine recovery was defined as the normal level of IGF-I based on age and sex, or a GH level <1 ng/ml after OGTT, or a random GH level less than 2.0 ng/ml.	There were no significant differences in terms of endocrine recovery, biochemical recurrence, imaging regression, imaging progression, and radiation complications between the primary GKS and the postoperative GKS groups. The practical rate of endocrine recovery lasting in 3, 5, 8 years was 10.6, 33.80, and 70.6 %, respectively, in the primary GKS group, and 60.70, 43.40, and 78.80%, respectively, in the postoperative GKS group. Only nadir GH after OGTT was found to be the predictor of the duration of endocrine recovery.

Table 2- Results related to the role of surgery in the treatment of acromegaly

Author(s)	Title	Method/Follow-up	Results
Gondim et al. (2010) [32]	Pure endoscopic transsphenoidal surgery for treatment of acromegaly: results of 67 cases treated in a pituitary center	Number of cases and method: 67 acromegaly patients treated with endoscopic transsphenoidal surgery (ETSS). Disease control criteria included normal IGF-1 level and GH levels less than 1 ng/ml after the oral glucose tolerance test. Follow-up: The average duration of follow-up was at least 1 year.	After ETSS, disease control was achieved in 50 cases (74.6%). The success rate of treatment in patients with microadenoma was higher than in patients with larger lesions (macroadenoma); so that disease control was reported in 12 out of 14 cases (85.7%). Suprasellar and parasellar invasions were associated with lower disease control. Complications of ETSS included epistaxis or nosebleeds (6%), transient diabetes insipidus (4.5%), and 1 case of seizures (1.5%).
Starke et al. (2013) [36]	Endoscopic vs microsurgical transsphenoidal surgery for acromegaly: outcomes in a concurrent series of patients using modern criteria for remission	Number of cases and method of work: 113 acromegaly patients treated with TSS. Recovery was defined as normal IGF-1 level, random GH level less than 0.1 ng/ml, and reduction of GH level to less than 0.4 ng/ml after oral glucose tolerance test. Follow-up: The average follow-up period was 18.4 months.	These patients were divided into two groups. Endoscopic transsphenoidal surgery (ETSS) was performed in 72 patients and microscopic transsphenoidal surgery (MTS) was used in 41 patients. There was no significant difference between the two groups in terms of tumor characteristics. Overall, postoperative recovery was achieved in 20 of 23 cases with microadenomas (87%) and 59 of 90 cases with macroadenomas (66%). The rate of recovery and postoperative complications, except sinusitis and changes in taste or smell, were not significantly different between the groups treated with ETSS and MTS; But the complications mentioned above were significantly higher in patients treated with ETSS. Preoperative

			variables including GH level less than 45 ng / mL, Knosp score = 0-2, and postoperative GH level less than 1.15 ng / mL were the best predictors for recovery.
Sarkar et al. (2014) [34]	Endocrinological outcomes following endoscopic and microscopic transsphenoidal surgery in 113 patients with acromegaly	Number of cases and method: 113 patients with acromegaly treated with ETSS and MTSS. Recovery was defined as normal IGF-1, GH level less than 0.1 ng/ml, and decrease in GH level to less than 0.4 ng/ml after oral glucose tolerance test. Follow-up: The mean duration of follow-up was 33.26±5.8 months.	These patients were divided into ETSS and MTS treatment groups. In this study, 86% of tumors were macroadenomas. The average adenoma size was 21.1 ± 9.7 mm, but 56% of all tumors were 2 cm in size and 43.4% were invasive. There was no significant difference between the two groups in terms of recovery rate (28.8% vs. 36.2%). Preoperative GH levels of less than 4 ng/ml, adenoma size less than 20 mm, and non-invasive tumors were predictors of improvement during the follow-up period. There was no significant difference between the two groups in terms of surgical complications except pituitary insufficiency, which was more frequent in the group treated with MTSS.
Fathalla et al. (2014) [30]	Endoscopic transphenoidal surgery for acromegaly improves quality of life	Number of cases and method: 20 patients with acromegaly treated with ETSS Recovery was defined as normal IGF-1, GH level less than 0.1 ng/ml, and decrease in GH level to less than 0.4 ng/ml after oral glucose tolerance test. Follow-up: The mean follow-up period was 11 months.	In this study, 90% of tumors were macroadenomas and 70% had an invasion into the cavernous sinus based on preoperative imaging. In 90% of patients, improvement in postoperative symptoms was observed, and 80% stated that treatment with ETSS has improved their quality of life. 35% of cases were biochemically recovered, 35% had inconsistent results, and 30% were not treated; also, panhypopituitarism was reported in 4 patients. Physical health and pituitary symptoms were similar to the norms, while emotional health, social health, and energy levels were significantly lower than normal. 70% of patients stated that their relationship with the doctor has a great impact on their quality of life. Panhypopituitarism and adjuvant therapy were the most important predictors of low scores of quality-of-life.
Fathalla et al. (2015) [31]	Endoscopic versus microscopic approach for surgical treatment of acromegaly.	Number of cases and method: 65 patients with acromegaly treated with TSS. Elimination of common acromegaly symptoms as well as biochemical improvement was considered as recovery in patients. Follow-up: The average follow-up period was 56.6 months.	These patients were divided into two groups. ETSS was performed in 42 patients and MTS in 23 patients. There was no significant difference between the two groups in terms of age, preoperative endocrine status, percentage of macroadenomas, and suprasellar and parasellar invasion. There was no difference between the two groups in terms of postoperative recovery (45.2% vs. 34.7%). Nevertheless, in the ETSS group, the tissue removal rate was significantly higher (61% vs. 42%). Also, if there was an invasion to the cavernous sinus, there was a tendency to remove further tissue (48% vs. 14.2%). Postoperative diabetes insipidus was more common in patients undergoing microscopic treatment (34.7% vs. 17%). There was no significant difference between the two groups in terms of complications. These results show that there is no significant difference in the rate of biochemical recovery between the patients treated with ETSS and MTS.
Babu et al. (2017) [28]	Long-Term Endocrine Outcomes Following Endoscopic Endonasal Transsphenoidal Surgery for Acromegaly and Associated Prognostic Factors	Number of cases and method: 58 patients with acromegaly treated with ETSS Hormonal improvement was defined as normal IGF-1, serum GH level less than 2.5 ng/ml, and decrease in GH level to less than 1 ng/ml after oral glucose tolerance test (performed 3 months after the surgery). Follow-up: The mean follow-up period was 64 ± 32.2 months.	Among the 58 patients studied, there were microadenomas in 21 cases and macroadenomas in 37 cases. 3 and 6 months after the surgery, biochemical improvements were observed in 40 patients (69%) and 4 patients, respectively, and recurrence of the disease was observed in 1 patient in the first year after surgery. At the last follow-up, sustained improvement was reported in 43 of 44 patients (74.1%). The invasion of the tumor into the cavernous sinus was a predictor of no recovery.
Sasagawa et al. (2018) [35]	Transsphenoidal Surgery for Elderly Patients with Acromegaly and Its Outcomes: Comparison with Younger Patients.	Number of cases and method: 87 patients with acromegaly treated with TSS. Patients were divided into two groups: older (≥65 years) and younger (less than 65 years) and the clinical characteristics, anesthesia risks, and surgical results were evaluated and compared in these two groups. Follow-up: The average duration of follow-up was 5.2 years.	In the first group (older) 24 people (27.6%) and in the second group (younger) 63 people (73.4%) were present. Preoperative endocrine and radiological evaluations showed no significant difference between the two groups. However, the physical condition of the second group was significantly better based on the ASA Physical Status Classification System (75% vs. 3%). Also, due to the severity of related diseases, no significant difference in terms of preoperative complications was observed between the groups (17% vs. 6%).16 patients in the first group and 45 patients in the second group achieved endocrine recovery after surgery (67% vs. 71%). The incidence of postoperative pituitary deficiency was similar in the two groups (4% vs.

			3%). Approximately in one-third of patients in the first group, who had high blood pressure or diabetes mellitus, the drug use reduced after successful tumor removal. These results indicated that TTS can be considered as a safe treatment for young and old patients with acromegaly.
Coopmans et al. (2021) [29]	Predictors for Remission after Transsphenoidal Surgery in Acromegaly: A Dutch Multicenter Study	The collection of clinical data, from 2000 to the present, was performed as a multicenter retrospective study in three superior neurology and surgery centers in the Netherlands, and finally, 282 people were studied in this study.	Maximum tumor diameter and random GH concentration at diagnosis were the best predictors of recovery after TSS in acromegaly patients; so that cases with higher maximum tumor diameter and higher random GH concentration at diagnosis, were less likely to have long-term recovery.
Shengfu et al. (2021) [33]	A Meta-Analysis of Endoscopic vs. Microscopic Transsphenoidal Surgery for Non-functioning and Functioning Pituitary Adenomas: Comparisons of Efficacy and Safety	A meta-analysis review of the role of MTSS and ETSS in NFPA and FPA, which was performed by searching the PubMed, Cochrane, and EMBASE databases from the time that the databases were established until September 2020, and according to PRISMA guidelines.	There were 1003 patients in the ETSS group and 992 patients in the MTSS group. In patients with NFPA, the ETSS group was associated with a higher incidence of postoperative complications (GTR). In participants with FPA, the results showed that the ETSS group had a higher rate of improvement in vision and overall tumor removal, as well as a lower rate of meningitis. In participants with acromegaly, no significant difference was observed in postoperative complications. Based on the available evidence, participants with NFPA, who were treated with ETSS, had higher GTR rates. Patients with FTS treated with ETSS had higher rates of vision improvement and GTR, as well as lower rates of meningitis.

DISCUSSION AND CONCLUSION

Acromegaly is a rare condition that is often caused by excessive GH secretion from the pituitary adenoma. Clinical manifestations of acromegaly include enlarged arms and legs, enlarged face, arthralgia (joint pain), fatigue, and hyperhidrosis (Excessive sweating), as well as high blood pressure and diabetes, which affect the quality of life and life expectancy in these patients. Biochemical diagnosis of acromegaly is performed based on GH levels, and by measuring GH levels after glucose tolerance test and serum IGF-1 concentration. Although the primary treatment for acromegaly is usually TSS, most patients require combination therapy, which includes radiotherapy as well as medical treatment such as somatostatin analogues and dopamine agonists [37] . Another treatment option is stereotactic radiosurgery (SRS), which is used as an adjuvant and alternative treatment in patients with acromegaly who are not suitable options for surgery. The use of this method for the treatment of macroadenomas and tumors invading the cavernous sinus is associated with a significant reduction in tumor size, and endocrine recovery [38] . In this article, in order to evaluate the role of TSS and SRS treatments, 19 articles with similar topics were reviewed. Their results indicated a positive relationship between the use of these treatments and improving patients' physical condition and quality of life, tumor control, and biochemical recovery in patients with acromegaly. No deaths were reported from these methods. The positive effects of TSS and SRS in the treatment of acromegaly have also been reported in other studies [39-41, 14, 42] .

Although this review article showed that TSS and SRS were associated with biochemical and endocrine improvements, as well as tumor control in patients with acromegaly, due to some side effects of these treatments, further studies are required to further evaluate the effectiveness, tolerance, and safety of these treatment methods.

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