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RESEARCH ARTICLE

A review of treatment efficacy, side effects and follow-up of surgery and radiosurgery in patients with acromegaly

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ABSTRACT

Background: Acromegaly is an infrequent disorder where the body generates excessive growth hormone (GH) and other growth factors such as insulin-like agents. If remain untreated, it can cause various complications and an increased rate of mortality in these patients. There are three treatment modalities for acromegaly, including surgery, radiotherapy, and medical treatment. Stereotactic radiosurgery (SRS) can also be considered as an adjuvant or alternative option for cases where surgery is unsuitable.

Methods: In this study, a systematic review was done through PubMed, Elsevier, Wiley and Springer databases using the keywords acromegaly therapy, radiosurgery, and transsphenoidal surgery. At last, 15 studies were selected for review, all of which were conducted between 2010 and 2021.

Results: The result of this review showed that SRS (GKRS and LINAC SRS) can be performed after failure of surgery and medical therapy to improve endocrine and biochemical control as well as the quality of life in patients with acromegaly. However, further studies are recommended to evaluate the side effects of these treatments.

Conclusion: All three types of treatment (surgery, radiotherapy and medical treatment) can lead to positive outcomes in patients with acromegaly if performed in right sequence with proper indications.

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

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INTRODUCTION

Acromegaly is a rare condition where the body generates excessive growth hormone (GH) and some other growth factors such as insulin-like agents. [1] . Syndromes caused by excessive GH include McCune-Albright syndrome, endocrine neoplasia type 1, and Carney syndrome [2] . Acromegaly not only affects the optic nerve and causes hypopituitarism, but also causes corporal overgrowth and a variety of complications. The disease has a gradual course and its diagnosis is usually delayed for 5-10 years. Pre-diagnosis symptoms of acromegaly are annoying, and treatments can be begun after the definitive diagnosis [1]. Acromegaly is related with serious complications like hypertension, musculoskeletal abnormalities and malignancies, obstructive sleep apnea, cardiomyopathy, type 2 diabetes, and increased mortality [3]. The annual incidence of this disease is reported 0.2 to 1.1 and its overall prevalence 2.8 to 13.7 cases per 100,000 people [4]. Patients are usually diagnosed with the disease in the fifth decade of their lives. This delay in diagnosis is a challenge in surgical management, as most tumors at this stage of the disease are macroadenomas. Increasing the awareness of the medical community on acromegaly can help in achieving better outcomes and reducing side effects of this disease in the patients [4]. Due to skeletal growth during the course of the disease, the patients may experience changes in the appearance including enlargement and abnormal growth of lips and nose, jaw malocclusion and abnormalities, large interdental spacing, overbite (a hereditary problem of the jaw), excessive size of maxilla and mandible, and prominent skull and forehead. Moreover, changes in patients' foot size and tightness of patients' shoes have also been indicated [2]. If not treated promptly and appropriately, the disease can

cause various complications and increased mortality in the patients. Surgery is a better option than other treatments and can provide immediate treatment for these patients. However, surgery is not feasible in about half of patients and there is a need for adjuvant treatment such as pharmacotherapy. The following are the medications currently used to treat patients with acromegaly.

GH receptor antagonists, dopamine agonists, somatostatin receptor ligands (SRL)

In the third line of treating patients with acromegaly is radiotherapy, which is usually applied for patients with advanced stages of the disease that cannot be controlled by medical treatment or surgery [5]. Stereotactic radiosurgery (SRS) is another effective option for patients with acromegaly that can be used as adjuvant treatment. It is reported that SRS leads to 40-50% recovery in these patients [6, 7]. SRS is based on the delivering more radiation dose to the target cell (tumor) while doing less damage to nearby normal tissues. With a radiation dose less than 8 Gy to its optical system, SRS is better suited for small tumors (<35 mm in diameter) [8]. Patients undergoing SRS should be carefully selected and a suitable distance from the optic tract should be observed.

MATERIALS AND METHODS

In this study, a systematic review was done through PubMed, Elsevier, Wiley and Springer databases using the keywords acromegaly therapy, radiosurgery, and transsphenoidal surgery. The keywords were used both separately and in combination. Inclusion criteria included full-text articles published since 2010 on the therapeutic role of surgery and radiosurgery in patients with acromegaly. Exclusion criteria were articles published before 2010 ،and those without full-text. During the analysis phase, the required data were collected from the selected studies, including author name(s), year of publish, objective(s), method used in the study, and the results obtained in the research. During the data collection, no interpretation was used and the original phrases used by the author(s) were reported.

Treatments

The aim of treatment methods used for acromegaly is to reduce tumor volume, achieve GH levels lower than 1.0 ug/L, normalize IGF-1 levels, and improve clinical signs and symptoms in patients. Medical treatment, surgery, and radiotherapy are three types of treatment that are applied for patients with acromegaly based on the patient's specifications and the tumor size [9].

Surgery

As a treatment method for acromegaly, surgery aims to eliminate the tumor while preserving patient's safety and normal pituitary function. It is reported that removal surgery of GH-secreting pituitary adenomas can cause recovery in 50-70% of cases. Anesthesia and surgical management of patients with acromegaly are usually complicated by co-existence of other diseases and problems and anatomical changes in these patients. In spite of such challenges, the occurrence of complications like hypopituitarism and cerebrospinal fluid leak is rare after surgery [6]. Presently, transsphenoidal surgery (TSS) is accounted for over than 90% of surgeries for removal of somatotroph tumors. Although regarded as a selective treatment, TSS is necessary if there is a rapid and progressive condition, pituitary apoplexy, and an increased intracranial pressure. TSS is divided into two types of endoscopic (ETSS) and microscopic (MTSS), both of which are conducted via 3 pathways, i.e. direct endonasal, sublabial, and submucosal endonasal. Endonasal routes are preferred for smaller lesions while for large tumors, microscopic sublabial is more convenient. However, surgeon's experience and preference determine the final type of surgery. ETSS has recently become a popular choice for surgery because of its ability to provide a sharp and broad view of the surgical field, however it only offers 2D views that makes it difficult to understand the depth. This type of surgery is especially helpful when the surgeon cannot see a part of the tumor. ETSS differs from MTSS in some cases; it has a leaner surgical space, requires a surgical assistant (usually an otorhinolaryngologist), provides a 2D view, and finally, it is performed by observing a monitor (vs. direct observation in the MTSS).

On the other side, the possibility of relatively free movement of the surgical tools is the main advantage of the MTSS. Transcranial surgery is usually considered in the cases of parasellar invasion into the cavernous sinus or large posterior macroadenomas. As compared with transcranial surgery, TSS is associated with fewer complications (e.g., CSF leak, bleeding, transient diabetes insipidus, and meningitis) and a lower risk of mortality (<0.6) [10]. Medication or radiation therapy may also be required after surgery in patients with refractory acromegaly [6].

Medications

Medical options used to treat acromegaly are GH receptor antagonists such as Pegvisomant (PEGV), dopamine agonists such as cabergoline, and first- and second-generation of long-acting somatostatin receptor ligands such as lanreotide (SRLs) and pasireotide (PAS-LAR), respectively. Monotherapy by first-generation of SRLs using lanreotide and octreotide is the first line of pharmacotherapy. SRLs suppress the secretion of GH by its effect on subdivision 2a of the somatostatin receptor (SST2a) and normalize the levels of IGF-1 and GH with an effectiveness between 25% and 45%. If the maximum dose of first-generation SRLs fails to establish biochemical control in the patient, then the type of treatment is determined by the presence or absence of impaired glucose tolerance and residual tumor in the patient. Dopamine agonists such as cabergoline can affect dopamine 2 receptors and, when used as monotherapy, can be administered as the first option for post-op drug therapy. This types of treatment is only applicable for patients with relatively high levels of IGF-1 (<2.5 times of the upper limit of normal) and GH. In non-responsive

patients with IGF-1 levels over than 1.3 times of the upper limit of normal, combination therapy with PEGV and first-generation SRLs can be considered as the second-line treatment [11]. Although the use of GH suppressor drugs is an efficient treatment in the primary management of patients with recurring acromegaly, their effects are not permanent and lifelong therapy may be required for hormonal control [12].

Radiosurgery and radiotherapy

The application of transsphenoidal surgery (TSS) with/without somatostatin analogues like lanreotide and octreotide is the first line of treatment for patients with acromegaly. Radiotherapy is the next option if previous interventions failed to treat the disease [13]. There are three types of radiation therapy, including conventional radiotherapy, stereotactic radiosurgery (SRS), and fractionated stereotactic radiotherapy (RT) [14]. SRS and RT are two common types of radiotherapy, in which a considerable dose of radiation is reflected in 1-5 targets with an accuracy of millimeters [13]. SRS can be performed in several methods, including, but not limited to, cyberknife, gamma knife, linear accelerator, and proton beam therapy that irradiates photons with high energy to the target cells. SRS can be applied in single dose mode (e.g., gamma knife) or fractionated, in which radiation delivery is done during 3-5 sessions. SRS is an efficient and appropriate technique for treating patients with acromegaly [14]. Gamma knife is the most common technique among the various types of SRS.

Long-term follow-up trials have shown that this technique is comparable with pharmacotherapy as the first post-op treatment [15]. As a type of SRS, gamma knife radiosurgery employs 200 sources of cobalt-60, a radioactive isotope of cobalt, to deliver high doses of radiation to the target cells (tumorous cells), while the least amount of radiation is absorbed by the healthy and vital tissues around [16].

An important factor in choosing the type of radiation therapy is damage to the optic system. The fractionated (three-dimensional) radiotherapy provides more protection for optic tract and optic chiasma than conventional (two-dimensional) radiotherapy [17]. Patients undergoing SRS should be selected properly and a suitable distance from the optic tract should be observed.

Some studies have shown that the use of SRS leads to faster endocrine recovery and less toxicity compared to RT [13]. Prolonged efficacy time and the risk of pituitary insufficiency are two limiting factors in the use of conventional segmented radiation therapy. On the other side, the application of SRS leads to faster recovery of patients, but is less effective. Moreover, this technique provides a better control over the irradiated dose to the critical organs like cranial nerve in the cavernous sinus, optic chiasm, pituitary gland, and pituitary stalk, and is therefore a more accurate method for targeting adenomas [15]. It is necessary to adopt a multidisciplinary approach for patients with brain tumors, including patients with acromegaly, whose treatment process has failed [18].

RESULTS

Treatment efficacy, side effects, and follow-up

In the present study, 19 articles were included for further review to evaluate treatment efficacy, side effects, and follow-up of SRS and TSS therapies in acromegaly patients. The results of this review are shown in Table 1 and Table 2. Table 1 contains 9 studies on LINAC SRS and GKRS and presents the effectiveness of SRS and its side effects in the treatment of patients with acromegaly. According to the results of these 9 studies in Table 1, the use of SRS (GKRS and LINAC SRS) before and after surgery and during radiotherapy is associated with endocrine and biochemical improvements and better tumor control. The total number of the acromegaly patients studied in these 19 articles was 1773. The results showed that the patients underwent SRS showed biochemical improvement, better tumor control, and improved physical condition. Moreover, no mortality was reported among patients treated with this technique. The use of SRS was also associated with some side effects in 18.33% of patients (325 patients), including vision impairment, endocrine and neurological disorders, panhypopituitarism, hypopituitarism, ocular motor nerve palsy, and thyrotropin deficiency or adrenocorticotropin [19-27].

In a study by Knappe et al., it was found that the risk of pituitary insufficiency is higher in patients treated with fractional radiotherapy (FRT) than in those underwent SRS therapy [21]. In other side, disease recurrence after SRS was observed in 2.09% of patients (37 patients) [20, 22, 23, 27]. These patients were followed up for a period between 40.8 and 166.5 months [19-24, 27].

Table 2 contains the articles that studied the efficacy of TSS (ETSS and MTSS) in the treatment of acromegaly and the associated side effects. Out of 10 studies in this table, 5 studies are related to the use of ETSS in the treatment of acromegaly and the other 5 to both types ETSS and MTSS. According to the results of these studies, the use of TSS (ETSS and MTSS) is positively correlated with better tumor control and endocrine and biochemical improvements. The total number of the acromegaly patients studied in these 10 articles was 3251. The results showed that the patients underwent TSS showed biochemical improvement, better tumor control, improved physical condition, and increased quality of life. Moreover, no mortality was reported among patients treated with this technique. The use of SRS was also associated with some side effects, including epistaxis, panhypopituitarism, pituitary insufficiency, changes in smell and taste, deficiency of new hormones, sinusitis, seizures, and transient diabetes mellitus. Moreover, recurrence of the disease after ETS was also observed in one patient. The results also indicated that patients underwent ETSS therapy showed more side effects such as sinusitis and changes in taste and smell, while pituitary insufficiency and diabetes insipidus after surgery were more

common in patients treated with ETSS. However, no significant difference in postoperative recovery was observed between the two treatments. Generally, both treatment methods were more successful in patients with small lesions (microadenomas) than in those with larger lesions (macroadenomas). These patients were followed up for a period between 11 and 64 months [28-36].

Table 1: Results of reviewed studies on the effectiveness of radiosurgery in acromegaly treatment

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	22 acromegaly patients with recurrent or residual pituitary tumor were treated with radiosurgery with Linear accelerators after surgery. The patients had high levels of GH and IGF-1 with confirmed tumor by imaging. IGF-1 was adjusted for sex and age, and a fasting GH level of less than 2.5 ng/mL was defined as biochemical recovery. The average period of follow-up was 94.7 months.	During the follow-up period, biochemical control was achieved in 68.2% of patients (15 patients), and recurrence after SRS was observed in one patient who underwent another surgery. The mean duration of biochemical recovery was 53 months. Initial and pre-SRS levels of GH were related to biochemical diagnosis and biochemical control, respectively. Further investigations indicated that the stability of biochemical control continued after 7.5 years in these patients and in 5 patients (22.7%), hormone deficiency persisted after SRS.
Lee et al. (2014) [16]	Stereotactic radiosurgery for acromegaly	Totally, 136 patients with acromegaly were included, all of them received Gamma knife SRS (GKRS). Acromegaly diagnosis in patients was performed based on clinical specifications and biochemical assessments, including serum IGF-1 and GH levels, based on sex and age. Endocrine evaluation, eye examination, and neuroimaging were performed for all patients before undergoing SRS. Biochemical recovery was considered as having normal IGF-1 level or GH levels less than 1 ng/mL after discontinuation of GH or IGF-1 modifying drugs in patients. Moreover, a decrease in one or more hormones was defined as pituitary inadequacy after radiosurgery. The average period of follow-up was 61.5 months.	During the follow-up period (61.5 months, in average), biochemical control was achieved in 65.4% of patients. The mean duration of biochemical recovery was 27.5 months. After 2, 4, 6, and 8 years of radiosurgery, 31.7%, 64.5%, 73.4%, and 82.6% of patients achieved stable recovery, respectively. Lower primary IGF-1 levels, higher maximum dose, and higher marginal radiation dose were determined as optimal prognostic factors for recovery. New cases of pituitary hormone deficiency was observed in 31.6% of patients (43 patients). Panhypopituitarism, defined as a deficiency in two or more pituitary hormones, was developed in 2 patients. New pituitary hormone deficiency was associated with some risk factors in patients, including a tumor volume greater than 2.5 ml and one marginal dose greater than 25 Gy. Moreover, certain complications were also observed in some patients, including vision impairment (4 patients), ocular motor nerve palsy (1 patient), and adverse effects of radiation (1 patient).
Alonso et al. (2019) [19]	Safety and efficacy of repeat radiosurgery for acromegaly: an International Multi-Institutional Study	The number of patients with acromegaly in this study was 398, all of whom underwent GKRS therapy. After repetition of SRS, endocrine followed-up was performed in 21 patients and imaging followed-up in 18 patients. Normal IGF-1 concentration in patients was defined as endocrine recovery and the lack of adenoma progression in imaging as tumor control. The average period of follow-up was 3.8 and 3.4 years after the repetition of SRS for endocrine function and imaging, respectively.	Time interval between the first and second SRS was 5 years, in average. Mean radiation doses used in the first and second SRS were 17 and 23 Gy, respectively. Of the 21 patients followed up for endocrine function, 9 patients (42.9) were observed with endocrine improvement, while 15 (83.3%) of the 21 patients who were followed up for imaging were detected with tumor control at the last follow-up visit. New complications after repeated radiosurgery were observed in 4 patients (19%), three of which developed neurological disorders and the other patient experienced endocrine disorder.
Ding et al. (2019) [20]	Stereotactic Radiosurgery for Acromegaly: An International Multicenter Retrospective Cohort Study	Totally, 371 patients with acromegaly were included in the study, all of whom underwent GKRS therapy. Endocrine follow-up was performed for 79 months.	The use of IGF-1 suppressants was stopped in 56 patients who had received drug therapy prior to SRS. A mean marginal dose of 24.2 Gy were used and a mean volume of 3 cm3 were treated in SRS. The rate of endocrine recovery at primary and stable stages after 10 years of SRS was 69% and 59%, respectively. Mean stable recovery was achieved 38 months after SRS. It seems that there are a statistical relationship between discontinuation of IGF-1 suppressants

			and stable recovery. Side effects observed in patients were cranial neuropathy in 4% of patients and endocrine disorders in 26% of patients.
Sims-Williams et al. (2019) [24]	Radiosurgery as primary management for acromegaly	This study was performed on 20 patients with acromegaly who received primary GKRS. All patients were evaluated for pituitary insufficiency, biochemical control (GH / IGF1), morbidity and mortality. Follow-up duration was 166.5 months, in average.	The results of 20 years of follow-up showed that biochemical control was observed in all patients receiving specific acromegaly drugs (12 patients), while this rate was 75% in patients who did not receive the drug (4 patients). Drug-receiving patients achieved 50% control after 3 years, while the time required to achieve the same control in non-receiving patients was 7.4 years. A mean radiation dose of 27.5 Gy was used and the patients were followed up for 166.5 months. After 146 months of follow-up, pituitary insufficiency was developed in 53% of patients with the first onset after 20 years of the treatment. MRI findings showed no other complications and no TRS-related mortality was observed. However, 3 patients received TSS because of poor biochemical control and 7 patients died during the follow-up period at a mean age of 65 years.
Pai et al. (2019) [23]	Low-Dose Gamma Knife Radiosurgery for Acromegaly	This study included 76 acromegaly patients who received GKRS at a low dose (<25 Gy). The mean values of treated volume, isodose line and marginal dose were 4.8 mL, 57.5%, and 15.8 Gy, respectively. Before and after GKRS treatment, all patients underwent a complete evaluation of imaging, vision, and endocrinology, and the results were evaluated. The mean period of follow-up was 65.8 months for imaging assessment and 72.8 months for endocrine assessment.	The results showed that 43.4% of patients (33 patients) achieved biochemical recovery and a recovery rate of 20.3%, 49.9%, and 76.3% was obtained in the patients after 4, 8, and 12 years, respectively. In these patients, the recovery defined as low levels of IGF1 and lack of invasion to the cavernous sinus. New hormone deficiency occurred in11.8% of patients (9 patients) with a frequency of 3%, 14%, and 22.2% at 4, 8, and 10 years, respectively. Recurrence of the disease was reported in two patients, but no visual impairment was found in the patients. It was concluded that GKRS therapy at low and standard doses provides comparable and equal results in acromegaly patients regarding the rate of improvement and new hormone deficiency.
Mohammed et al. (2019) [22]	Primary versus postoperative stereotactic radiosurgery for acromegaly: a multicenter matched cohort study	This study involved 78 patients with acromegaly who underwent SRS therapy. The patients were distributed in 2 groups. Patients in the first group underwent SRS as the primary treatment, while patients in the second group received SRS as adjuvant treatment after surgery (1: 2 ratio). The results obtained from the 2 groups were compared. Follow-up was performed for 66.4 months, in average.	This study included 78 patients who were divided into two groups: group 1 with 26 patients and group 2 with 52 patients. Patients in group 1 achieved 20% and 42% endocrine recovery after 2 and 5 years, respectively. Endocrine recovery of the patients was defined as having a low level of IGF1. Moreover, biochemical recurrence was regarded as lower marginal doses of SRS after initial recovery. The two groups were not different in terms of primary endocrine recovery, pituitary insufficiency, survival without recurrence, biochemical recurrence after initial recovery, and tumor control.
Knapp et al. (2020) [21]	Fractionated radiotherapy and radiosurgery in acromegaly: analysis of 352 patients from the German Acromegaly Registry	The study included 352 acromegaly patients who received SRS and FRT treatments. The follow-up period after radiotherapy was 1.0-45.1 years. Disease recovery was defined as successful treatment with low-to-normal IGF-1 levels in the absence of inhibitor drugs. Disease control referred to cases in which inhibitory drugs were used. Follow-up periods (from the radiotherapy to the final session of follow-up) for patients in SRS group (119 patients) and FRT group (233 patients) were 9.0 ± 8.5 and 13.0 ± 8.2 13.0 ± 8.2, respectively.	Before radiotherapy, the mean values of basal growth hormone in SRS and FRT groups were 3.5 ng/mL and 6.3 ng/mL, respectively. Uncontrolled conditions after SRS and FRT continued for 2.1 and 3.0 years, respectively. Recovery rate and control rate at year 10 were 48% and 23% for FRT, and 52% and 26% for SRS, respectively. Patients treated with FRT experienced higher rates of pituitary insufficiency than those treated with SRS.

Sims-Williams et al. (2021) [25]	Long-term safety of gamma knife radiosurgery (SRS) for acromegaly	A total of 118 patients with acromegaly were included, all of whom underwent gamma knife SRS. Data collection was performed using patients' questionnaires and hospital database.	Out of 118 patients in the study, 104 patients (88%) had a complete record of analysis and follow-up. Mean SRS dose was 30 Gy and mean follow-up duration was 134 months. Tumor invasion to the cavernous sinus was observed in 81% of patients. There was no significant relationship between stroke risk and neither of sex nor age. Visual deterioration was absent in 68 patients who underwent SRS MRI and received no radiation therapy, and only 3% of patients were examined by an ophthalmologist. A positive correlation was found between radiation therapy and visual deterioration and ophthalmology .
Yang et al. (2021) [26]	Comparing primary gamma knife radiosurgery and postoperative gamma knife radiosurgery for acromegaly: A monocenter retrospective study	A number of 75 patients with acromegaly were studied. Endocrine recovery was determined as normal IGF-I levels based on sex and age, or a random GH level below 2.0 ng/ml, or a GH level less than 1 ng/ml after OGTT.	the results obtained for the two groups of primary GKS and the postoperative GKS were not significantly different in terms of biochemical recurrence, endocrine recovery, radiation complications, imaging regression and progression. In the primary GKS group, endocrine recovery rates after 3, 5, 8 years were 10.6, 33.80, and 70.6%, respectively, while these rates was 60.70, 43.40, and 78.80% in the postoperative GKS group. Only GH level after OGTT was significantly associated with the duration of endocrine recovery.

Table 2: Results of reviewed studies on the effectiveness of surgery in acromegaly treatment

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	This study was performed on 67 patients with acromegaly who underwent endoscopic transsphenoidal surgery (ETSS). Disease control were considered as having GH levels below 1 ng/ml and normal levels of IGF-1 after the oral glucose tolerance test. The patients were followed for at least 1 year.	The disease was controlled after ETSS in 74.6% of patients (50 patients). ETSS treatment was more efficient in patients with microadenoma than in those with larger lesions, so that the disease was controlled in 85.7% of patients with microadenoma. Lower disease control was associated with parasellar and suprasellar invasions in patients. The side effects associated with ETSS were nosebleeds or epistaxis in 6% of patients, transient diabetes insipidus in 4.5%, and seizures in 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	This study was performed on 113 patients with acromegaly who underwent TSS treatment. Recovery criteria were having a random GH level below 0.1 ng/ml, a normal level of IGF-1, and a reduced GH level below 0.4 ng/ml after oral glucose tolerance test. The patients were followed for 18.4 months, in average.	The patients were placed in two groups; the first group included 72 patients who underwent endoscopic transsphenoidal surgery (ETSS) and the second group included 41 patients who treated with microscopic transsphenoidal surgery (MTS). Tumor characteristics were not significantly different between the two groups. Of 23 patients with microadenomas, 20 patients (87%) recovered after surgery, while postoperative recovery was achieved in 59 of 90 patients with macroadenomas (66%). There was no significant difference between the two groups in terms of recovery rate and postoperative complications, except for sinusitis and changes in smell or taste, which were significantly higher in patients with ETSS treatment. A Knosp score between 0 and 2, a GH level below 45 ng/mL or a postoperative GH level below 1.15 ng/mL were found as effective 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.	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

		Follow-up: The mean duration of follow-up was 33.26±5.8 months.	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 an infrequent disorder where the pituitary adenoma secrets excessive GH. Patients with acromegaly may develop some clinical symptoms, including enlargement of face, arms and legs, hypertension, excessive sweating (hyperhidrosis), fatigue, diabetes, and joint pain (arthralgia). Such symptoms can negatively affect the expectancy and quality of life in these patients. Biochemical diagnosis of acromegaly is made by measuring serum IGF-1 concentration and serum GH level after glucose tolerance test. Although TSS is the first and most common treatment for acromegaly, some patients may also need adjuvant therapy, including radiotherapy and pharmacotherapy like dopamine agonists and somatostatin analogues [37]. Stereotactic radiosurgery (SRS) can also be considered as an adjuvant and alternative therapy for cases where surgery is unsuitable. The use of SRS in patients with macroadenoma has resulted in improved endocrine recovery and reduced tumor size [38]. In the present study, 19 related articles were reviewed to evaluate the effectiveness of SRS and TSS treatments. The results showed that the use of these treatment techniques in patients with acromegaly leads to an improvement in their physical condition, tumor control, biochemical recovery, and quality of life. Fortunately, there were no reports of deaths from these methods. Several studies have also reported the positive effects of SRS and TSS treatments in patients with acromegaly [39-41, 14, 42].

Although the use of SRS and TSS was associated with better tumor control and endocrine and biochemical improvement in patients with acromegaly, it caused some side effects in these patients. Further studies are recommended to examine various aspects of these treatment methods, including their effectiveness, safety and tolerability.

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