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Role of stereotactic radiosurgery in the treatment of acromegaly.

Komal Naeem
Aga Khan University

Aneela Darbar
Aga Khan University, aneela.darbar@aku.edu

Muhammad Shahzad Shamim
Aga Khan University, shahzad.shamim@aku.edu

Role of stereotactic radiosurgery in the treatment of acromegaly

Komal Naeem, Aneela Darbar, Muhammad Shahzad Shamim

Abstract

Acromegaly is a rare, indolent disease due to overproduction of growth hormone. Surgery is identified as primary treatment, but has its limitation, thus frequently requiring alternate treatment options as adjunct to surgery. Stereotactic radiosurgery (SRS) has been used as adjuvant and alternate therapy in patients with inoperable or residual disease; or those not fit for surgery. It has shown reasonable results for treating macroadenoma and tumours invading cavernous sinuses with significant reduction in tumour size and durable endocrinological remission. Factors favouring better outcomes include time from last resection to SRS, older age, peri-procedural withdrawal of medication, higher margin and maximum dose.Hypopituitarism is the most common side effects and requires yearly screening. With the new advances in the field Fractionated-stereotactic radiosurgery and cyber-knife robotic radiosurgery have been introduced with promising preliminary results..

Keywords: Pituitary adenoma, acromegaly, radiation therapy.

Background

Acromegaly has estimated prevalence of 36-69 per million population worldwide[1-4]. It is an endocrinological disorder of the pituitary gland due to abnormally increased secretion of Growth Hormone (GH)[1,4]causing pathagnomonic symptoms of increased blood pressure and enlarged hands and feet.[5] Acromegaly is associated with high morbidity and mortality rates, that are as high as 2-3 times compared to the general population.

The treatment goals for acromegaly are reduction of GH level, normal range Insulin-like Growth Factor-I (IGF-I), tumour shrinkage and control of clinical symptoms. According to a highly cited expert consensus, surgery is identified as the primary treatment, especially for small, well-circumscribed adenomas[5]. However, surgery is not curative for certain macroadenoma and invasive tumours, especially the ones invading cavernous sinus. In addition to traditional surgical and medical treatment options, SRS is now increasingly recognized as another treatment option[6,7].

Department of Surgery, Section of Neurosurgery, Aga Khan University Hospital, Karachi. Pakistan. **Correspondence:** Muhammad Shahzad Shamim. Email: shahzad.shamim@aku.edu

Review of Evidence

We searched "Stereotactic Radiosurgery (SRS) for acromegaly" on PubMed and the articles were reviewed. Radiosurgery has evolved tremendously in past 20 years, with increased efficiency and improved side effects profile. With the advent of new technology, now it is much focused and can be delivered in one dose after 3-D mapping of the lesion, called Stereotactic Radiosurgery (SRS), or in multiple smaller doses, called Fractionated-Stereotactic Radiosurgery (FSRT). Multiple technologies for radiation delivery are available, using photons (Gamma knife, Cyber knife, LINAC) or charged particles (protons)[6].

The role of radiosurgery in the treatment of acromegaly has been widely studied but paucity of a large patient population and longer follow-up has limited the evaluation of long term outcomes. Recently, a large, international, multi-centric study pooled and analyzed patient cohorts from 10 institutions participating in International Gamma Knife Research Foundation and reported promising results. In total 371 patients were enrolled with minimum follow-up of 6 months. The initial endocrinological remission rate was 69% and calculated durable endocrinological remission rate at 10 years, was 59%. Mean time for durable remission and recurrence after durable remission was 38 and 17months, respectively[8].

In a recent meta-analysis, a mean reduction of 93-100% in tumour size was been reported with mean tumour control of 98% and endocrinological remission of 44.3% at median follow up of 59 months.This meta-analyses showed a better disease control with SRS (52%) compared to conventional radiotherapy (36%) at 5 years but the difference was not significant[7]. The main goal of all the studies have been to identify important factors favouring early durable endocrinological remission, so that patient selection and efficiency of this rapidly evolving technology may be improved. The factors showing strong association with favourable outcomes can be divided into, patients dependent (older age, decreased time between last resection and first radiotherapy session,

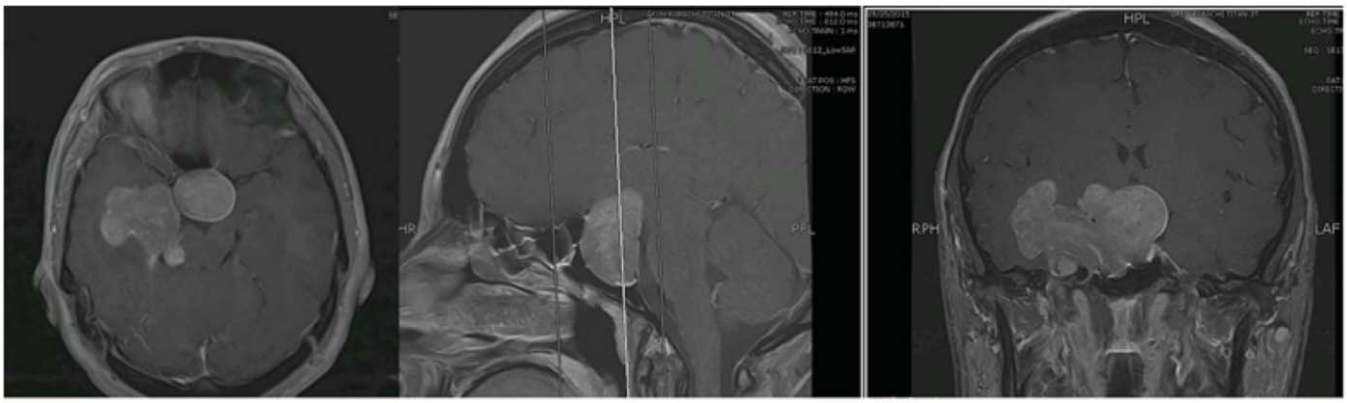

Figure-1: MRI brain T1 with contrast axial, sagittal and coronal images of a growth hormone secreting giant pituitary adenoma with temporal and suprasellar extension.

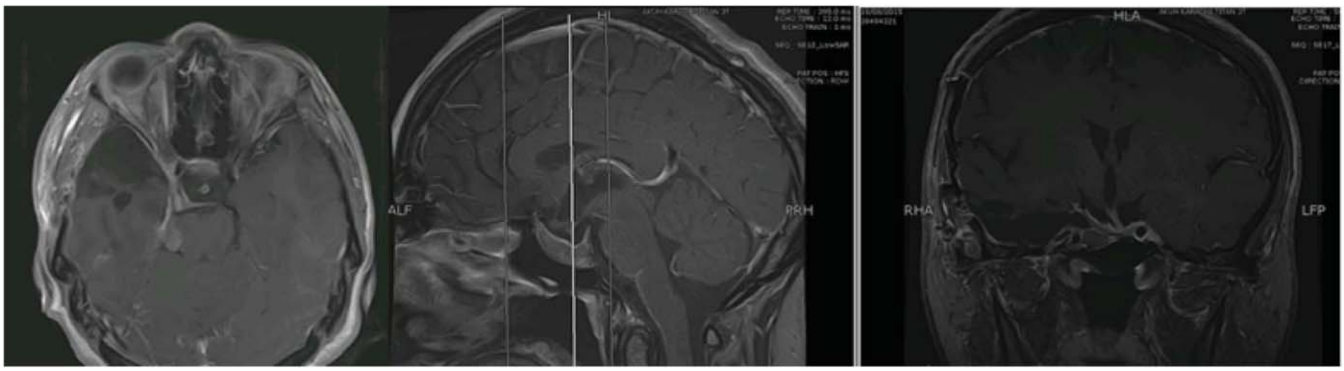

Figure-2: Post-operative images of the same patient after trans-cranial and trans-sphenoidal resection, showing a small residual tumor in right peri-mesencephalic cistern, that was managed with SRS.

densely granulated tumour and temporary withholding of IGF-I lowering medications prior to treatment and SRS dependent(higher margin radiation dose, higher maximum dose, whole sella radiosurgery and radiosurgery to cavernous sinus[7-9].

With the increasing use of this modality it is important to understand the limitations and side effects of SRS. The most important side effects include radiation induced hypopituitarism, optic neuropathy and other cranial neuropathies, radionecrosis and cerebrovascular disease. Hypopituitarism is the most commonly experienced side effect, which may present in a delayed fashion, and can be predicted by cavernous sinus extension in pre-SRS imaging. The risk for delayed hypopituitarism increases as a function of time, as Cohen-Inbar et al,. reported the actuarial rates of 2%, 12%, 26% after 3, 5 and 10 years of SRS, respectively. This mandates yearly assessment of endocrine profile of all patients undergoing SRS [5,10]. SRS is also not advised for large invasive adenoma and for those which are in closer proximity to optic chiasm[6].Joint venture of biotechnology sciences and physics have introduced many innovation in the field, including FSRT, a novel hybrid technology that may improve outcomes and overcome limitations of SRS. It allows the delivery of focused radiation in multiple doses, delivering on average a dose of 45-55Gy in 25-33 daily fractions. Its use is recommended for large adenomas (>3cm) and for tumours located at the distance of 3-5mm from optic chiasm.Although more outcome studies with longer follow up are still awaited for this modality, but initial results have been promising, showing tumour reduction comparable to that of SRS and conventional radiation therapy. The incidence of cranial neuropathies and cerebral necrosis is less than SRS but risk of cerebrovascular event is higher[6] Recently, experience with cyber-knife robotic surgery at a single institution was reported to have similar tumour control, but with much fewer visual complications and fewer cases of hypopituitaris.[11]

Conclusion

Surgery remains the treatment of choice for acromegaly, However, for cases with residual, recurrent or inoperable tumours, SRS is also a valid option especially as an adjunct to surgery. It may also be used in patients who cannot

undergo surgery. With improving technology, the existing limitations of SRS may be overcome, however, until then, referring patients for SRS must be weighed against the complications of treatment. Therefore, patient selection is extremely important.

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