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Epidemiology of pituitary tumors treated by gamma knife radiosurgery in Mexico: a single-center study

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Abstract

Objective: *Pituitary adenomas (PAs) represent the second most common intracranial tumors usually treated with surgery. Total resection is rare, so adjuvant radiosurgery is often indicated to control tumor growth. This study aims to describe a cohort of Mexican patients treated with Gamma Knife Radiosurgery (GKR) for PA over 17 years in a single center.* **Methods:** *The records of adult patients treated with GKR for PA at San Javier Hospital in Guadalajara, Mexico, from 1998 to 2015 were retrospectively reviewed. The analyzed factors included tumor imaging characteristics, visual field abnormalities, prior treatment, and radiographical improvement after radiosurgery.* **Results***: This study included 111 patients (70 females, median age 39.5 years, [IQR: 33-51]). The median tumor volume was 3.55 cm^3 (2.14-6.82), and the median diameter was 0.95 mm (0.5-1.4). We found an abnormal visual field pre-GKR in 33 (29%) patients. The most common type of tumor was prolactinoma (43%). The median dose of radiation was 21 Grays (16-25). Forty-five (39.5%) patients had radiographic improvement. The variables associated with significant radiographic improvement were having a normal pre-treatment visual field campimetry (p = 0.03; odds ratio [OR] = 2.4 [95% confidence interval (CI), 1.05-5.48]) and the absence of chiasmatic extension (p = 0.03; OR = 2.66 [95% CI, 1.06-6.99]) which are essential to anticipate and improve outcomes in patients with pituitary tumors.* **Conclusions***: GKR was safe and valuable for the volumetric control of PA. Nearly half the patients had radiographic improvement without reported adverse effects (different from hormonal deficiencies) within a median follow-up of 12 months.*

Keywords: *Gamma knife radiosurgery. Radiosurgery. Pituitary neoplasms. Pituitary adenoma.*

Epidemiología de los tumores hipofisarios tratados con radiocirugía con bisturí gamma en México: un estudio de un solo centro

Resumen

Objetivo: *Los adenomas pituitarios representan el segundo tumor intracraneal más frecuente y usualmente son tratados mediante cirugía y radiocirugía. El objetivo de esta cohorte es describir el uso de radiocirugía con bisturí de rayos gamma en México.* **Métodos:** *Se realizó una revisión retrospectiva de pacientes tratados mediante radiocirugía con bisturí de rayos gamma en el Hospital San Javier en Guadalajara, México de 1998 al 2015. Las variantes analizadas incluían las características imagenológicas del tumor, las anormalidades del campo visual previo al tratamiento y la mejoría radiográfica posterior a la radiocirugía.*

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Resultados: *En total 111 pacientes fueron incluidos (70 mujeres, edad media 39.5 años [IQR: 33-51]) en este estudio. El volumen promedio del tumor fue 3.55 cm^3 (2.14-6.82) y el diámetro de 0.95 mm (0.5-1.4). Encontramos alteraciones del campo visual previo a la radiocirugía en 33 pacientes (29%). La dosis promedio de radiación fue 21 Gy (16-25). Se observó una mejoría radiológica en 55 pacientes (39.5%); las variables asociadas con esta mejoría fueron un campo visual por campimetría normal previo al procedimiento (p = 0.03; OR 2.4 [95% CI, 1.05-5.48]) y la ausencia de extensión tumoral al quiasma óptico (p = 0.03; OR 2.66 [95% CI, 1.06-6.99]); los cuáles son esenciales para anticipar y mejorar los resultados a futuro con este tipo de ciurgía.* **Conclusiones:** *La radiocirugía con bisturí de rayos gamma fue segura y demostró utilidad en el control volumétrico de adenomas pituitarios. El 39.5% de los pacientes obtuvieron una mejoría radiológica sin reporte de efectos adversos, diferentes a deficiencias hormonales, en un seguimiento a 12 meses.*

Palabras clave: *Radiocirugía con bisturí de rayos gamma. Radiocirugía. Adenoma pituitario. Prolactinoma.*

Introduction

Pituitary tumors are categorized based on their size and endocrine function. The treatment of these tumors aims to control tumor growth and normalize hormone levels[1,2], utilizing various therapeutic approaches such as medication, surgery, and radiotherapy. Surgical resection is typically the initial management strategy for these tumors, except in specific instances where medical therapy, such as for prolactinomas (PRLs), is preferred. However, achieving total resection can be challenging, particularly in tumors that invade the cavernous sinus[3]. In such cases, adjuvant radiation therapy, with or without radiosurgery, has demonstrated excellent results in preventing post-surgical tumor growth while minimizing adverse effects[4]. A range of factors, including tumor volume, histology, previous use of radiation, proximity to optic nerves, and the preservation of endocrinological function, determines the prescribed radiation dose. The mortality rate associated with these tumors is low, but the morbidity related to surrounding structures in the sellar region can be significant[5,6].

Medical professionals increasingly recognize Gamma Knife Radiosurgery (GKR) as an adjunct treatment for recurrent or residual disease, particularly in lesions that invade parasellar structures. Although complications following GKR are rare, chronic issues can arise, including cranial neuropathies (such as optic neuritis), panhypopituitarism, secondary neoplasms, stroke, and radionecrosis. Acute complications are infrequent, but symptoms such as headache, dizziness, seizures, syncope, optic neuritis, and localized infection may occur at the site where stereotactic frame posts were inserted[7-9]. GKR has long been used in Mexico to treat patients with pituitary adenomas (PA); however, there is no epidemiological information or clinical results. This study aims to describe a cohort of patients with pituitary tumors treated with GKR, a topic that has yet to be explored in our country.

Material and methods

In this retrospective study, we collected information from adult patients (≥ 18 years) treated with GKR for pituitary tumors at Hospital San Javier in Guadalajara, Mexico, from 1998 to 2015. Table 1 summarizes the patient's characteristics and prognosis factors associated with radiographical improvement. We extracted data from medical records, which included tumor imaging characteristics (such as size), endocrine function, visual field abnormalities, previous medical or surgical treatments, and radiographic outcomes following GKR. Cases with incomplete data and those with an alternative histopathological diagnosis were excluded from the study.

Radiographic improvement was defined as a reduction in tumor size of at least 1 mm, as detected by contrast-enhanced magnetic resonance imaging (MRI), utilizing 1-2 mm slices with a focus on the sellar region during any point in the follow-up period. We defined abnormal visual field campimetry as any irregularity observed through digital campimetry that could be attributed to the compression of the optical nerves caused by a pituitary tumor. The total radiation dose administered to each tumor was recorded in Grays (Gy). Prior medical treatments consisted of bromocriptine, cabergoline, octreotide, ketoconazole, or pegvisomant, each given for a minimum of 3 months before the radiosurgery – any surgical intervention before GKR, whether transsphenoidal or transcranial, was classified as prior surgery. Following a surgical procedure, partial resection was defined as any indication of residual disease observed through contrast-enhanced MRI of the sellar region.

Differences between categorical variables were analyzed using the χ^2 test, while differences in continuous variables were evaluated using the Mann-Whitney U test. A $p < 0.05$ was considered statistically significant. IBM SPSS Statistics, version 23 (IBM Corp., Armonk, NY, USA), was used for statistical analysis. The Local Ethical Committee approved this study.

Table 1. Population and tumor baseline characteristics

Variables	Total
Sex (%) Female Male	 70 (64) 41 (36)
Age (years)	39.5 (33-51)
Abnormal visual field test by campimetry	33 (29%)
Tumor radiographical features Volume (cm^3) Diameter (cm) Chiasmatic extension Cavernous sinus extension	 3.55 (2.14-6.82) 0.95 (0.5-1.4) 24 (21.1%) 30 (26.3%)
Previous treatment (%) Previous medical treatment Previous surgery	 63 (55.3) 60 (52.6)

Results

We analyzed 135 medical records, with 24 cases excluded for specific reasons: 10 patients were diagnosed with craniopharyngioma, and 14 were pediatric cases. This resulted in a final cohort of 111 patients, of which 70 (64%) were female, with a median age of 39.5 years (33-51). Thirty-three patients (29%) presented abnormal visual field campimetry. The median tumor volume was 3.55 cm^3 (2.14-6.82), with a median diameter of 0.95 cm (0.5-1.4). Among the 111 patients, 63 (55.3%) had received medical treatment before GKR, 60 (52.6%) had undergone previous surgical interventions, and 51 (47.4%) had not. (Table 1) The most frequently identified tumor type was PRL, present in 48 cases (43.2%), followed by growth hormone (GH) producing tumors in 18 cases (16.2%), and adrenocorticotropic hormone (ACTH) producing tumors in 8 cases (7.2%). In addition, there were three cases (2.7%) of mixed co-producing tumors and 37 (33.3%) non-functional tumors (Fig. 1).

The median administered radiation dose was 21 (16-25) Gy, and it was determined by various factors, mainly tumor volume, histology, previous radiation, and endocrine function. Radiographic improvement following GKR was observed in 45 patients (39.5%). Throughout the follow-up period, which had a median duration of 12 months (range 8-36), no acute or chronic complications were reported, including cranial neuropathies, optic neuritis, hypopituitarism, cerebrovascular events, secondary neoplasms, or cognitive disorders. Two significant variables were identified as being associated with improved radiographic outcomes post-GKR: patients who exhibited a normal pre-treatment visual field campimetry were more likely to experience favorable results (p = 0.03; odds ratio [OR] = 2.4 [95% confidence interval (CI), 1.05-5.48]), as were those without chiasmatic extension (p = 0.03; OR = 2.66 [95% CI, 1.06-6.99]) (Table 2). No significant relationship was found between the radiation dose (p = 0.40) or tumor type and the degree of radiographic improvement (Fig. 2).

Table 2. Variables associated with radiographical improvement

Variable	Odds ratio	95% confidence interval	p
Normal visual field test	2.4	1.05-5.48	0.03
Non-chiasmatic involvement	2.66	1.06-6.69	0.03
Non-cavernous sinus involvement	1.8	0.77-4.18	0.17
Previous medical treatment	1.01	0.47-2.17	0.95
Previous surgery	1.9	0.88-4.09	0.09

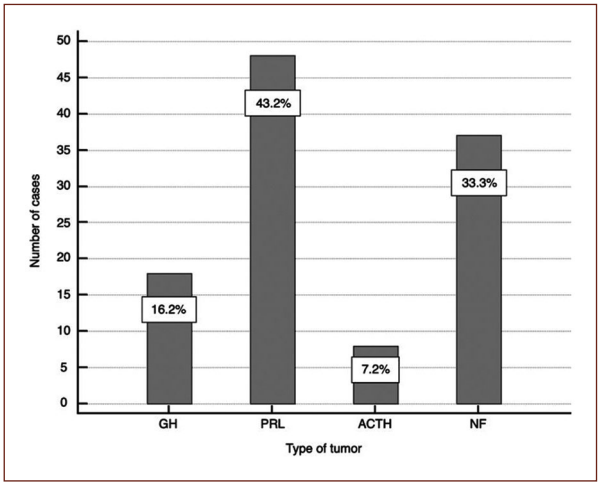

Figure 1. Frequency of tumor subtype. GH: growth hormone; PRL: prolactin; ACTH: adrenocorticotropic hormone; NF: non-functioning.

Discussion

The prevalence of pituitary tumors within our study population is consistent with findings documented in the literature by researchers worldwide[10-19]. Prolactinoma was identified as the predominant subtype, followed by non-functioning adenomas, GH-producing

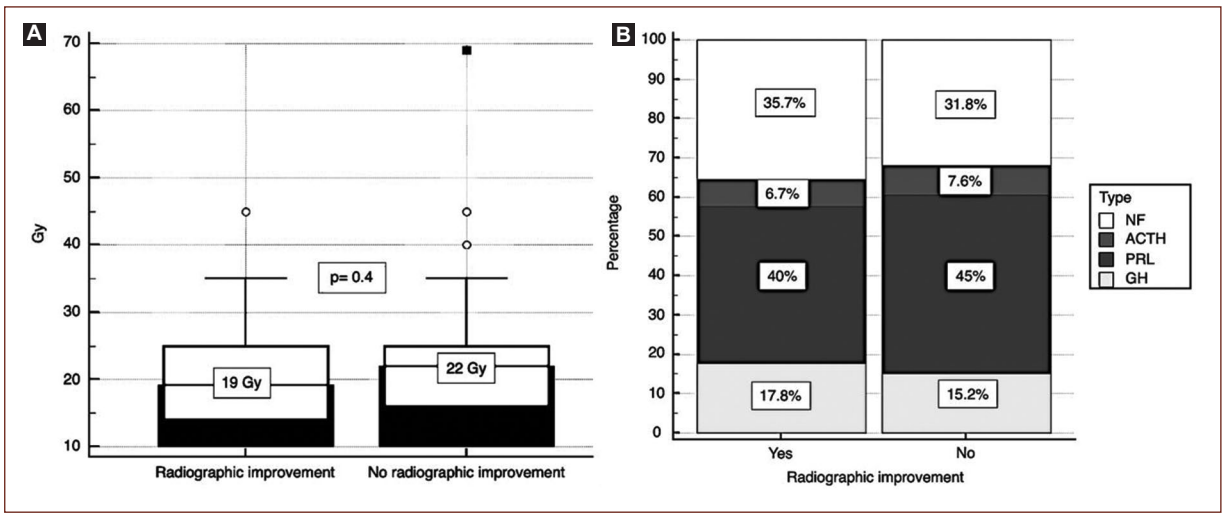

Figure 2. Radiographic improvement after GKR according to radiation dose and tumor type. **A:** patients who did not have radiographic improvement received more radiation than those with radiographic improvement, but the difference was not significant (p = 0.40). **B:** there were no statistically significant differences regarding the type of tumor and its association with radiographic improvement, meaning that no tumor by itself was more associated with presenting radiographic improvement with GK treatment. GH: growth hormone; PRL: prolactin; ACTH: adrenocorticotropic hormone; NF: non-functioning.

tumors, and ACTH-producing tumors. Notably, no cases of thyroid-stimulating hormone-producing tumors were observed. In addition, we recorded three cases of mixed co-producing tumors (GH and PRL), one of which was confirmed through positive immunobiological markers and the other by elevated serum hormone levels.

This study determined that the absence of extension to the optic chiasma and a normal pre-treatment visual field campimetry were significant factors associated with radiographic improvement following GKR. These results align with observations reported in other studies[10-19]. We documented no adverse effects related to GKR during the median follow-up duration of 12 months, demonstrating the safety of this procedure and paving the way for establishing its conventional use in this type of tumor. Tumors subjected to prior surgical resection demonstrated a requirement for a lower radiation dose, indicating a tendency for radiographic improvement in long-term follow-up, supporting the theory that GKR should be used as an adjuvant to conventional neurosurgery.

We also noted that the type of tumor did not exhibit a significant correlation with radiographic improvement post-GKR. The results suggest that radiosurgery is effective and safe for patients with residual or recurrent disease, with nearly half of the tumors demonstrating radiographic improvement and no complications. This study did not include information regarding hormonal deficiencies due to a lack of records.

Conclusion

The management of pituitary tumors has advanced significantly in recent years and should include a comprehensive team of neurosurgeons, endocrinologists, and radio oncologists. At present, transsphenoidal surgery appears to be the treatment of choice in patients with low surgical risk, mainly when the tumor produces a mass effect on the optical system, or there is hormone overproduction. However, approximately 20-50% of patients may experience recurrent or residual disease, particularly when the tumors invade difficult-to-reach areas like the cavernous sinus. GKR can be pivotal in such cases[15]. The limitations of our study include its retrospective nature, where data obtained from medical records may be biased due to medical record accuracy. Furthermore, since hormone levels before and after GKR were not systematically available, no conclusions can be made about the biochemical effect of GKR in these tumors, which is as essential as volumetric control.

In this study, GKR was safe and beneficial for the volumetric control of PAs. Nearly half of our patients had radiographic improvement without any report of adverse effects (unrelated to hormonal deficiencies)

associated with treatment within a median follow-up period of 12 months. Positive prognosis factors associated with radiographical improvement include a normal pre-treatment campimetry and the absence of a tumor affecting the optic chiasm. More research is needed in our country to replicate these findings in other centers.

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The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of humans and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality of data. The authors declare that they have followed their center's protocols on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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