Gamma Knife Radiosurgery as a Surgical Alternative in Tolosa–Hunt Syndrome: A Comprehensive Literature Review

Beni Wibowo [1], Arif Ismail[2]

[1]Faculty of Medicine, Lampung University

Abstract

Tolosa–Hunt Syndrome (THS) is a rare idiopathic granulomatous inflammatory disorder involving the cavernous sinus, superior orbital fissure, or orbital apex, and is clinically characterized by painful ophthalmoplegia. Corticosteroids remain the first-line therapy due to their rapid anti-inflammatory effects and significant symptom relief. However, long-term use is often limited by recurrence, steroid resistance, and adverse systemic or psychiatric effects. This literature review aims to evaluate the role of Gamma Knife radiosurgery (GKR) as an alternative or adjunctive treatment in patients with refractory or steroid-intolerant THS. A comprehensive search of recent literature was conducted, focusing on case reports and small case series discussing radiosurgical management of THS. The findings suggest that GKR offers a targeted, minimally invasive approach that delivers precise radiation to affected areas while minimizing exposure to surrounding neural structures. Clinical outcomes from the reviewed studies demonstrate effective pain relief, improvement of cranial nerve function, and sustained symptom control with relatively low complication rates. Although there is a theoretical risk of delayed radiation-induced effects, no significant radiological or clinical complications were reported during the available follow-up periods. GKR appears to be a promising therapeutic option in selected patients, particularly those with recurrent or steroid-resistant disease. Further prospective studies are required to establish standardized protocols and confirm long-term safety and efficacy of this treatment modality.

Keywords : Corticosteroid resistance, gamma knife, radiosurgery, refractory case, Tolosa–Hunt Syndrome

Abstrak

Sindrom Tolosa–Hunt (THS) merupakan kondisi langka berupa peradangan granulomatosa idiopatik yang melibatkan sinus kavernosus, fissura orbitalis superior, atau apeks orbita, dengan manifestasi klinis berupa oftalmoplegia disertai nyeri. Kortikosteroid menjadi terapi lini pertama karena memberikan perbaikan gejala secara cepat melalui efek antiinflamasi yang kuat. Namun, penggunaan jangka panjang sering terbatas akibat kekambuhan, resistensi terhadap steroid, serta efek samping sistemik maupun psikiatrik. Tinjauan pustaka ini bertujuan untuk mengevaluasi peran Gamma Knife Radiosurgery (GKR) sebagai terapi alternatif atau tambahan pada pasien THS yang refrakter atau intoleran terhadap kortikosteroid. Metode yang digunakan adalah penelusuran literatur dari berbagai sumber ilmiah yang relevan, terutama laporan kasus dan seri kasus dalam beberapa tahun terakhir. Hasil kajian menunjukkan bahwa GKR memberikan terapi yang terarah dan minim invasif dengan paparan radiasi yang rendah pada jaringan sekitar. Beberapa studi melaporkan perbaikan nyeri, pemulihan fungsi saraf kranial, serta kontrol gejala yang bertahan lama dengan angka komplikasi yang rendah. Meskipun terdapat risiko teoretis efek radiasi jangka panjang, tidak ditemukan komplikasi klinis maupun radiologis yang bermakna selama masa tindak lanjut. GKR dapat dipertimbangkan sebagai pilihan terapi pada kasus tertentu, khususnya pada pasien dengan kekambuhan atau resistensi terhadap steroid. Penelitian prospektif lebih lanjut diperlukan untuk menentukan standar terapi serta memastikan efektivitas dan keamanan jangka panjang.

Kata kunci: Gamma knife, kasus refrakter, radiosurgery, resistensi kortikosteroid, Sindrom Tolosa Hunt

Correspondence: Beni Wibowo, Villa Citra 2 Blok G1 No. 8B, Bandar Lampung, e-mail: beniwibowo.bw8@gmail.com

Background

Tolosa Hunt Syndrome (THS) is a rare, idiopathic granulomatous inflammation involving the cavernous sinus, superior orbital fissure, or orbital apex.[1] It typically presents as unilateral orbital pain with ophthalmoplegia due to involvement of cranial nerves III, IV, and VI.[2] Rarely, THS may affect cranial nerves V and VII or the pupillary sympathetic pathways.[3] The diagnosis is made clinically and radiologically after excluding neoplastic, inflammatory, or vascular etiologies. [4]

Epidemiologically, THS is exceedingly rare, with an estimated incidence of approximately one case per 1,000,000 person-years.[5] Due to its rarity, evidence-based management remains limited. While corticosteroid therapy remains the mainstay of treatment, the optimal parameters for radiosurgical intervention such as indication, timing, and dosage are yet to be standardized. But the use of corticosteroids is not always feasible due to specific contraindications or patient conditions.

Generally, invasive surgical decompression of lesions in the cavernous sinus region carries significant risk. The anatomical confines of the cavernous sinus and neighboring structures

render surgical access challenging with potential morbidity such as cranial neuropathies, vascular injury, or permanent ophthalmic sequelae. Cavernous sinus and superior orbital fissure are surgically inaccessible without high morbidity, making radiosurgery a valuable noninvasive alternative.[6,7]

So that stereotactic radiosurgery (SRS) has evolved as a minimally invasive alternative for a widening spectrum of skull-base inflammatory and neoplastic lesions. This review aims to critically evaluate current evidence regarding the role of radiosurgery as a potential adjunct or alternative therapeutic approach in the management of THS.[8]

Discussion

Magnetic Resonance Imaging (MRI) is the primary imaging modality for diagnosing and monitoring Tolosa–Hunt Syndrome (THS), providing excellent soft-tissue contrast and multiplanar views while excluding other causes of painful ophthalmoplegia. Typical findings include unilateral enlargement of the cavernous sinus, superior orbital fissure, or orbital apex, with isointense T1, iso- to slightly hypointense T2 signals, and homogeneous gadolinium enhancement. Additional features may include effacement of adjacent fat, orbital apex extension, and occasional vascular changes of the intracavernous internal carotid artery. High-resolution MRI also guides treatment planning for image-guided interventions, such as stereotactic radiosurgery, by delineating lesion boundaries, involvement of critical neurovascular structures, and monitoring lesion regression on follow-up.[9]

Glucocorticoids have long constituted the primary treatment approach for this syndrome, yet standardized recommendations concerning dosage, duration, and administration route remain undefined.[9] In selected THS cases, immunosuppressive agents such as methotrexate or azathioprine have been employed, while radiotherapy has been considered for refractory or steroid-dependent cases.[10,11,12]

Several factors may contraindicate or limit the use of corticosteroids. Long-term therapy is associated with multiple adverse effects, including Cushingoid habitus, hyperglycemia, peripheral edema, peptic ulcer, and glaucoma.[13] Although corticosteroids exert potent anti-inflammatory effects, they may induce psychiatric adverse effects. Delirium, depression, mania, and other psychotic disorders have been reported as treatment-related neuropsychiatric symptoms. The mechanism of steroid-induced psychosis remains unclear, and symptoms can appear as early as 3 to 5 days after initiation of therapy.[14]

Although corticosteroids are generally effective in managing THS, partial recovery or non-responsiveness may occur in certain cases.[15] Moreover, recurrence and steroid resistance have been reported.[16] Although it is improbable that this therapy will replace steroids as the first-line treatment, Gamma Knife radiosurgery (GKR) could serve as an alternative and may be employed as an early intervention for THS in the future.[17]

Radiosurgery has emerged as a promising option for patients unsuitable for corticosteroid therapy or those with recurrent disease.[18] Because Tolosa-Hunt Syndrome is an exclusion diagnosis, steroid response and imaging alone may not confirm the disease, and reduced efficacy of steroids can result from misdiagnosis with mimicking entities like Rosai–Dorfman disease. Therapy for this disease can vary, one of which is radiosurgery.[19]

In cases of THS associated with other underlying conditions, radiosurgery may be considered following corticosteroid therapy. Such as Tolosa-Hunt Syndrome can manifest as Hypertrophic Pachymeningitis (HP), a chronic condition characterized by recurrent remissions and relapses. Response to steroid therapy is variable, and in refractory cases, radiosurgery may be considered as an alternative treatment option.[20] It may be considered following a biopsy-confirmed diagnosis.[21]

Prior to the introduction of GKR, conventional radiotherapy was used as an alternative approach to minimize surgical risks. Several reports demonstrated favorable clinical outcomes following radiotherapy, where relatively high fractionated doses (>3 Gy per fraction) were deemed effective for managing cavernous sinus–related conditions. However, the use of high-dose radiation was associated with potential complications involving the central

nervous system.[22]

Recently, radiosurgery has been considered for medically refractory recurrences of THS. The GKR, a single-fraction, highly precise technique, delivers a low radiation dose to surrounding normal tissues while targeting the lesion, resulting in significant clinical improvement. Although GKR carries a theoretical risk of late complication, its submillimetre accuracy substantially minimizes radiation exposure to adjacent tissues, thereby markedly reducing the likelihood of secondary oncogenesis.[23] Supporting this, a case report documented sustained symptom relief in a steroid-intolerant THS patient following GKR, with no subsequent recurrence.[24]

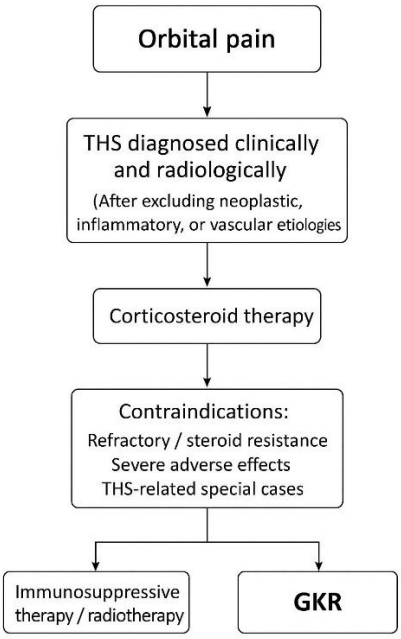

Figure 1. Management pathway of THS using GKR

Within the last decade there are very few THS-specific reports of focal radiotherapy or stereotactic radiosurgery, most contemporary guidance on radiation dose and safety is therefore extrapolated from skull-base SRS literature (cavernous sinus meningiomas, hemangiomas, orbital-apex lesions). Consequently, direct high-level evidence for Gamma Knife radiosurgery (GKR) in THS is lacking and available reports remain limited to case-level evidence and small series. However, there is still no specific evidence defining the optimal GKR dose exclusively for THS.

Given that THS is a diagnosis of exclusion, future studies integrating molecular or immunopathological markers could improve diagnostic precision and guide therapeutic selection. Given that THS is a diagnosis of exclusion, future studies integrating molecular or immunopathological markers could improve diagnostic precision and guide therapeutic selection.

Management of THS requires multidisciplinary collaboration between neurosurgeon and other fields of science such as neurology, internal medicine, radiology to determine whether the patient receives sufficient corticosteroids, immunosuppressants, or radiosurgery.

Summary

Radiosurgery, particularly Gamma Knife radiosurgery, offers a targeted and minimally invasive alternative for refractory Tolosa-Hunt syndrome, resistant to corticosteroids, severe side effects, and cases associated with specific diseases. For surgeons, GKR offers a safe, noninvasive solution to manage Tolosa–Hunt Syndrome located in surgically high-risk regions, achieving symptom control without the morbidity of open approaches. It also represents a precision-based, image-guided treatment that can achieve both clinical and radiologic remission in steroid-refractory Tolosa–Hunt Syndrome. Although evidence is limited, promising results in selected cases justify further clinical investigation to establish standard protocols and long-term efficacy. Future studies should focus on prospective surgical-radiosurgical registries to evaluate standardized outcomes, refine patient selection criteria, and establish evidence-based protocols for dose, targeting, and long-term efficacy

References

1. Yuliati A, Rajamani K. Tolosa-Hunt Syndrome. *Neurohospitalist.* 2018 Apr;8(2):104-105. doi: 10.1177/1941874417714147. Epub 2017 Jun 13. PMID: 29623162; PMCID: PMC5882006.
2. Ramirez JA, Ramirez Marquez E, Torres G, Muns Aponte C, Labat EJ. Tolosa Hunt Syndrome: MRI Findings. *Cureus.* 2023 Oct 7;15(10):e46635. doi: 10.7759/cureus.46635. PMID: 37936989; PMCID: PMC10626213.

3. Park SH, Jang SI, Lee EJ, Kim NH. Case report: Tolosa-Hunt syndrome—expanding the neuromyelitis optica spectrum disorder phenotype? *Front Neurol.* 2024 Feb 14;15:1326867. doi: 10.3389/fneur.2024.1326867. PMID: 38419701; PMCID: PMC10899484.
4. Dinaki K, Sarafidou A, Papadopoulos C, Triaridis S, Karkos P. Intracavernous Aneurysm Mimicking Tolosa-Hunt Syndrome. *Maedica (Bucur).* 2024 Sep;19(3):634-640. doi: 10.26574/maedica.2024.19.3.634. PMID: 39553346; PMCID: PMC11565145.
5. Kumar S. Ophthalmoplegia syndrome or Tolosa Hunt syndrome – A review. *IP Int J Ocul Oncol Oculoplasty.* 2023;9(4):166-169. doi: 10.18231/j.ijooo.2023.037.
6. Rennert RC, Ravina K, Strickland BA, Bakhsheshian J, Fredrickson VL, Russin JJ. Complete Cavernous Sinus Resection: An Analysis of Complications. *World Neurosurg.* 2018 Nov;119:89-96. doi: 10.1016/j.wneu.2018.07.206. Epub 2018 Aug 1. PMID: 30075273.
7. Goldman MJ, Teh BS, Lo SS, Butler EB, Baskin DS. Radiosurgery for Intracranial Meningiomas: A Review of Anatomical Challenges and an Update on the Evidence. *Cancers.* 2025;17:45. doi: 10.3390/cancers17010045.
8. Umekawa M, Shinya Y, Hasegawa H, Shin M, Kawashima M, Katano A, et al. Long-term outcomes of stereotactic radiosurgery for skull base tumors involving the cavernous sinus. *J Neurooncol.* 2022 Jan;156(2):377-386. doi: 10.1007/s11060-021-03921-5. Epub 2022 Jan 14. PMID: 35028788.
9. Amrutkar CV, Lui F, Burton EV. Tolosa-Hunt Syndrome. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. Updated 2025 Jun 22. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459225/
10. Badakere A, Patil-Chhablani P. Orbital Apex Syndrome: A Review. *Eye Brain.* 2019 Dec 12;11:63-72. doi: 10.2147/EB.S180190. PMID: 31849556; PMCID: PMC6913296.
11. Wiener J, Cron RQ. Successful treatment of pediatric Tolosa-Hunt syndrome with adalimumab. *Eur J Rheumatol.* 2020 Feb;7(Suppl 1):S82-S84. doi: 10.5152/eurjrheum.2019.19149. PMID: 31804175; PMCID: PMC7004262.
12. Qasim B, Siddiqui F, Saleem M, Zohaib M, Khan MK, Siyal NA. Clinical presentation and management of Tolosa-Hunt syndrome: a case report. *J Pak Med Assoc.* 2025 Jan;75(1):115-118. doi: 10.47391/JPMA.10593. PMID: 39828842.
13. Behera G, Gupta V, Mishra UP, Chaurasia JK. Tolosa-Hunt Syndrome: A Challenging Diagnosis from Otorhinolaryngologist Perspective – A Case Report. *Indian J Otolaryngol Head Neck Surg.* 2022 Dec;74(Suppl 3):5681-5684. doi: 10.1007/s12070-021-02992-0. Epub 2021 Nov 29. PMID: 36742718; PMCID: PMC9895722.
14. Ishikawa R, Ishikawa Y, Kubota T, Shirahama K. A case of delirium in Tolosa-Hunt syndrome during corticosteroid therapy. *JA Clin Rep.* 2018 Jul 31;4(1):58. doi: 10.1186/s40981-018-0193-y. PMID: 32026006; PMCID: PMC6967251.
15. Ata F, Yousaf Z, Arachchige SNM, Rose S, Alshurafa A, Muthanna B, et al. The demographics of Tolosa-Hunt syndrome in Qatar. *eNeurologicalSci.* 2021 Jul 22;24:100359. doi: 10.1016/j.ensci.2021.100359. PMID: 34355072; PMCID: PMC8325092.
16. Thu PW, Chen YM, Liu WM. Recurrent Tolosa-Hunt syndrome. *Tzu Chi Med J.* 2020 Oct 15;33(3):314-316. doi: 10.4103/tcmj.tcmj_137_20. PMID: 34386372; PMCID: PMC8323652.
17. Kemeny AA. Tolosa-Hunt Syndrome: Another legitimate target for radiosurgery? *Acta Neurochir (Wien).* 2016 Jan;158(1):141. doi: 10.1007/s00701-015-2649-4. Epub 2015 Nov 27. PMID: 26611688.
18. Usha, Sowmini PR, Velayutham SS, Jeyaraj MK, Kumar MS, Saravanan SV, Mugundhan K. Remarkable Benefit of Infliximab Therapy in Recurrent Tolosa Hunt Syndrome. *Neurol India.* 2022 May-Jun;70(3):1289-1291. doi:

10.4103/0028-3886.349597. PMID: 35864695.

19. Nóbrega PR, Rodrigues PGB, de Sousa Pereira I, de Figueiredo Santos C, Gerson G, et al. Steroid responsive cavernous sinus syndrome due to Rosai-Dorfman disease: beyond Tolosa-Hunt syndrome – a case report. *BMC Neurol.* 2021 Jul 5;21(1):264. doi: 10.1186/s12883-021-02255-z. PMID: 34225703; PMCID: PMC8256567.
20. Dutta P. Tolosa-Hunt syndrome as a manifestation of Hypertrophic Pachymeningitis. *Eur J Rheumatol.* 2021 Jan;8(1):51-52. doi: 10.5152/eurjrheum.2020.20114. Epub 2020 Sep 8. PMID: 32910772; PMCID: PMC7861639.
21. Mullen E, Rutland JW, Green MW, Bederson J, Shrivastava R. Reappraising the Tolosa-Hunt Syndrome Diagnostic Criteria: A Case Series. *Headache.* 2020 Jan;60(1):259-264. doi: 10.1111/head.13692. Epub 2019 Nov 4. PMID: 31681980.
22. Cho JM, Sung KS, Jung IH, Chang WS, Jung HH, Chang JH. Temporal Volume Change of Cavernous Sinus Hemangiomas after Gamma Knife Surgery. *Yonsei Med J.* 2020 Nov;61(11):976-980. doi: 10.3349/ymj.2020.61.11.976.
23. Msigwa SS, Li Y, Cheng XL. Tolosa Hunt Syndrome: Current Diagnostic Challenges and Treatment. *Yangtze Medicine.* 2020;4:140-156. doi: 10.4236/ym.2020.42014.
24. Lee JM, Park JS, Koh EJ. Gamma Knife radiosurgery in steroid-intolerant Tolosa-Hunt syndrome: case report. *Acta Neurochir (Wien).* 2016 Jan;158(1):143-145. doi: 10.1007/s00701-015-2648-5. Epub 2015 Nov 27. PMID: 26611689.