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Stereotactic radiosurgery for intracranial Langerhans cell histiocytosis: A multi-institutional case series with long-term follow-up

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ABSTRACT

Introduction: Intracranial Langerhans cell histiocytosis (iLCH) is rare and optimal local therapy remains undefined. Stereotactic radiosurgery (SRS) has emerged as a focused alternative to surgery or conventional radiotherapy for selected lesions.
Research question: To report long-term outcomes of Gamma Knife radiosurgery (GKRS) for iLCH across multiple institutions.
Material and methods: We retrospectively reviewed four patients (eight lesions) treated with GKRS between 2003 and 2015 at four institutions affiliated with the International Radiosurgery Research Foundation (IRRF). Inclusion required histopathologic LCH, single- or hypofractionated SRS to brain lesions, and ≥6 months radiological follow-up. Responses were assessed volumetrically (regression ≥20 %; progression ≥20 %). SRS-related toxicity was evaluated using the Radiation Therapy Oncology Group criteria for CNS toxicity.
Results: The median age at GKRS was 27 years. Four patients were treated, three with single lesions and one with five lesions across three sessions; most affected the cerebellum (n = 5). Median dose was 13 Gy (range: 8–14 Gy) with a median tumor volume of 2.7 cc. All lesions regressed with no local failures. Side effects were minimal, limited to one case of grade 2 edema. No necrosis or major morbidity occurred.
Discussion and conclusion: GKRS provided durable radiographic regression and local control of iLCH with minimal toxicity, using a median prescription dose of 13 Gy. This approach represents a valuable, minimally invasive option for localized iLCH, while endocrine dysfunctions typically persist. Further prospective and collaborative investigations are essential to standardize dosing, evaluate combination approaches with systemic regimens, and refine guidelines for patient selection.

1. Introduction

Langerhans cell histiocytosis (LCH) is a rare disorder of unknown origin, characterized by clonal proliferation of Langerhans histiocytes that can infiltrate bones, lungs, liver, spleen, lymph nodes, and skin (Hong et al., 2013). LCH primarily occurs in children, with an annual incidence of 2–10 cases per 1 million individuals under 15 years of age (D'Ambrosio et al., 2008), and can manifest with diverse clinical presentations with a variable disease course, ranging from self-limiting to rapidly progressive (Doberauer and Bornemann, 2022). The pathogenesis of LCH remains unclear, with ongoing debate as to whether it is primarily an inflammatory condition or behaves more like a tumor (Hong et al., 2013).

LCH is classified as single-system (SS-LCH), involving one organ, or multi-system (MS-LCH), involving two or more. In pediatric cases, "risk organs" linked to poorer outcomes include the bone marrow, liver, and spleen, with the lungs sometimes also considered high-risk in multisystem disease (Aricò et al., 2003).

The central nervous system (CNS) involvement is rarely reported, particularly in the adult population, occurring in less than 4 % of cases when excluding the pituitary gland, and approximately 10–25 % when considering all neurological structures (Cohen Aubart et al., 2021). The

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hypothalamo-pituitary axis is the most frequently affected CNS site, with diabetes insipidus (DI) as the most common endocrine manifestation (Sagna et al., 2019).

Management strategies for LCH are individualized. Surgical resection is preferred for symptomatic or solitary lesions, particularly for diagnostic clarification. Conventional radiotherapy (RT) has limited efficacy for CNS or soft tissue involvement and often does not reverse endocrine deficiencies (Kotecha et al., 2014). Stereotactic radiosurgery (SRS) with Gamma Knife or CyberKnife has recently emerged as a minimally invasive, targeted option, providing local tumor control and symptom relief with a favorable safety profile, although endocrine deficits like DI frequently persist (Tripathi et al., 2021).

Given the rarity of intracranial LCH (iLCH) treated with SRS, further research and longer follow-up are required to optimize treatment protocols and assess long-term outcomes. This study aims to describe the feasibility, safety, and preliminary efficacy outcomes of SRS as an emerging option for localized iLCH in a selected patient cohort.

2. Material and methods

This retrospective study included 4 patients (8 tumors in total) treated between June 2003 and November 2015 (with the last survival data collected in July 2024) at four institutions affiliated with the International Radiosurgery Research Foundation (IRRF). Inclusion criteria were histopathological diagnosis of LCH (either intracranial or extracranial), treatment with single-fraction or hypo-fractionated SRS for brain lesions, and at least six months follow-up with magnetic resonance imaging (MRI) study after SRS. Clinical, radiological, and treatment-related data were retrospectively collected from institutional medical records and prospectively maintained databases. The study was conducted in adherence to the principles of the Helsinki Declaration. All procedures were performed in compliance with relevant laws and institutional guidelines and have been approved by the institutional committee (01/13/2022, 2022.022.IRB1.017).

All patients underwent treatment using a frame-based SRS approach. Gamma Knife (Elekta AB, Stockholm, Sweden) systems were employed, with the specific model differing based on the institution and the year of treatment. Each treatment plan was reviewed and approved by the respective institution's multidisciplinary team prior to implementation. Comprehensive data on SRS parameters were collected, including marginal dose, maximum dose, prescription isodose line, number of isocenters, LCH volume, and treatment volume.

All patients were followed with serial brain MRI at intervals determined by the treating physicians, or as clinically indicated. Treatment response was evaluated based on tumor volume changes observed at the last imaging follow-up. A volume change of $\geq$20 % was categorized as progression (local failure, LF), a change of $\pm$20 % as stable, and a reduction of $\geq$20 % as regression. Stable or regressed tumors were considered to have achieved local control (LC).

Clinical evaluations, including neurological examination and documentation of symptoms or treatment-related adverse events, were performed at each follow-up visit. SRS-related toxicity was evaluated using the Radiation Therapy Oncology Group (RTOG) criteria for CNS toxicity (Shaw et al., 2000). The duration of radiological and clinical follow-up was measured from the date of SRS to the last available evaluation or death.

Given the rarity of iLCH and the small sample, analyses were descriptive. Continuous variables were summarized as medians with ranges, and categorical variables as counts with percentages. Time-based outcomes such as radiographic follow-up and time to local progression were reported as medians with ranges; no hypothesis testing, survival modeling, or adjustment for within-patient clustering was attempted.

3. Results

This series included four iLCH patients (three male, one female) treated with GKRS. Median age at diagnosis was 23 years (range 10–28) and at GKRS was 27 years (20–29). Three patients had a single lesion, while one underwent GKRS for five distinct lesions across three sessions (2006, 2010, 2015).

All patients had multisystem LCH with controlled primary disease status at the time of GKRS. Risk organ involvement was observed in three patients (75 %), with hepatic involvement present in one case and pulmonary involvement identified in two cases.

Presenting symptoms were heterogeneous and included incidental findings, endocrine dysfunction, and neurological complaints. At the time of GKRS, most of the patients (75 %) exhibited neuroendocrine dysfunction—panhypopituitarism, DI and hypogonadism—along with additional symptoms such as sleep disturbances, hearing loss, headache, and visual impairment.

The anatomical distribution of lesions included five cerebellar lesions in one case, two pituitary lesions, and a single lesion situated intracanalicular with extension into the cerebellopontine angle.

One patient underwent prior gross total resection for iLCH before GKRS. One lesion underwent previous RT; however, the administered doses were not uniformly recorded. Two patients had previously undergone chemotherapy, with a median interval of 177 months (range: 64–287 months) between the last chemotherapy session and SRS. No patients had received immunotherapy, targeted therapy, or stem cell transplantation before SRS. None of the patients were receiving systemic therapy, and there were no cases in which systemic agents were held or continued at the time of GKRS. No concurrent or recently discontinued systemic therapies were noted for any lesion. All patients received corticosteroids at the time of GKRS. The primary LCH disease was controlled in all patients at the time of GKRS.

The indication for SRS was initial management in seven lesions and treatment of residual disease in one lesion. All procedures were administered as single-fraction treatments. The prescription dose had a median of 13 Gy (range, 8–14). Tumor volume at the time of SRS had a median of 2.7 cc (range, 0.16–5.3).

At the time of GKRS, performance status by Eastern Cooperative Oncology Group (ECOG) scale ranged from fully active (ECOG 0, three lesions) to limited self-care (ECOG 3, four lesions), and one lesion was recorded in a patient completely disabled (ECOG 4).

The median interval from GKRS to last imaging was 157.5 months (range, 70–181). At last imaging, all lesions demonstrated regression, defined as greater than 20 % reduction in volume compared with baseline (Fig. 1). No treated lesion showed local progression. Nonetheless, four distant progressions occurred in one patient, with a median time to progression of 45 months (range, 45–65). Leptomeningeal dissemination was not observed in any case.

GKRS was generally well tolerated. Seven lesions had no treatment-related adverse events. One lesion developed RTOG grade 2 edema, which was managed medically and subsequently resolved. No radiation necrosis or severe/life-threatening complications were reported.

No patient underwent salvage surgery or RT following GKRS. At the final follow-up, all patients demonstrated stable performance status. The median follow-up after GKRS was 156 months (range, 102–253). One patient died during the study period, and another was lost to follow-up. In the case that resulted in death, clinical documentation indicated that the cause was unrelated to iLCH, and included sepsis, gastrointestinal perforation, hemorrhage, and aspiration pneumonia.

Table 1 presents demographic data, primary clinical features, treatment details, and associated outcomes.

4. Discussion

Treatment of iLCH is a complex and evolving field, with no single, universally standardized treatment protocol due to the disease's rarity

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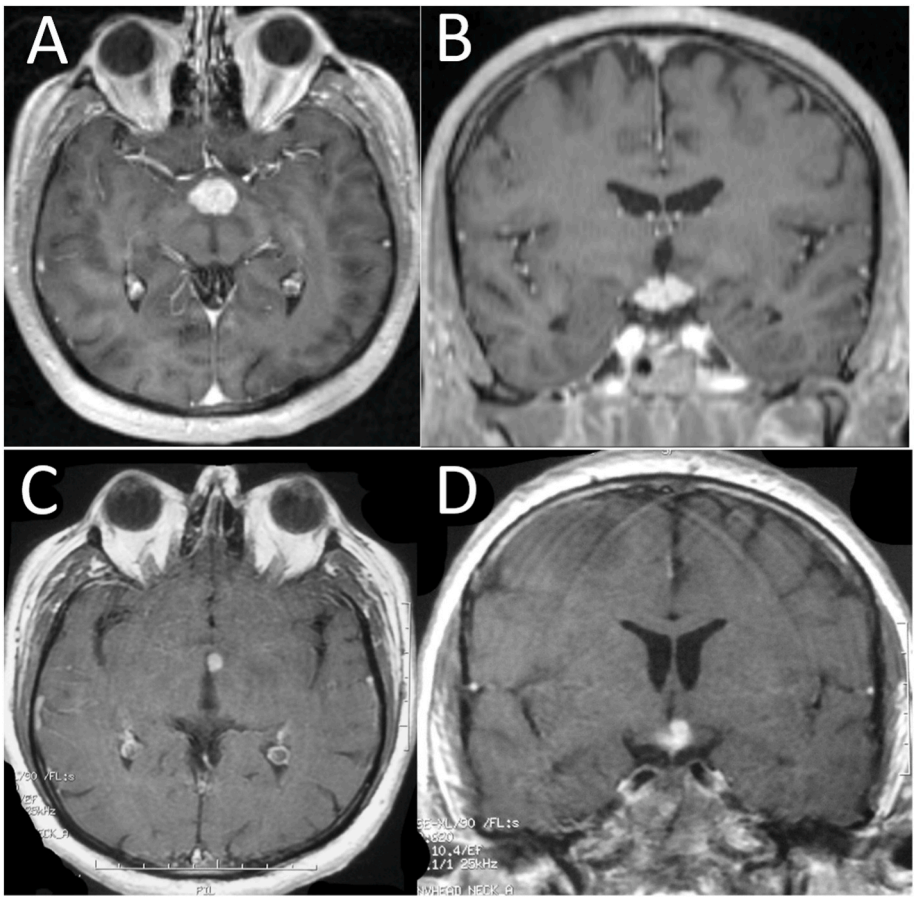


Fig. 1. Contrast enhanced magnetic resonance images of a patient with pituitary Langerhans cell histiocytosis. (A, B) Axial and coronal images on the day of radiosurgery. (C, D) axial and coronal images 126 months after radiosurgery.

and heterogeneous presentation, especially in adults. Ongoing debate over whether LCH is inflammatory or neoplastic continues to shape therapeutic strategies (Hong et al., 2013).

Conventional management of iLCH has included chemotherapy, corticosteroids, surgery, and occasionally RT. However, no standardized approach exists, and treatment is typically individualized.

In iLCH, surgery plays a distinct role, primarily for diagnosis, since histopathology is essential to distinguish it from other intracranial neoplasms or inflammatory diseases due to nonspecific imaging and broad differential diagnoses (Gersey et al., 2020; Belen et al., 1996; Wei et al., 2024). Biopsy, whether open or stereotactic, remains the diagnostic gold standard, especially for inaccessible lesions or when multifocal disease is suspected.

Surgical resection is typically reserved for solitary, accessible lesions causing mass effect or neurological symptoms such as intracranial pressure, focal deficits, or obstructive hydrocephalus (Belen et al., 1996). However, even after complete resection, recurrence may occur, especially in multifocal or multisystem cases, highlighting the importance of long-term follow-up and multidisciplinary care.

Surgical limitations are most evident in multifocal, deep-seated, or anatomically complex lesions, particularly those involving the hypothalamic-pituitary axis or skull base. In such cases, surgical risks—including neurological morbidity and endocrinopathies—may outweigh benefits, making biopsy with subsequent systemic therapy the preferred approach (Gersey et al., 2020; Krishna et al., 2004). Furthermore, the natural history of LCH is highly variable, with spontaneous regression—especially in children—supporting conservative management in select cases (Irving et al., 1994; Gargano et al., 2019). Advances in systemic therapies, including chemotherapy and targeted agents, have shifted management away from aggressive surgery, particularly in multisystem or refractory disease (Muthiah et al., 2021).

Systemic chemotherapy has long been the mainstay for multisystem and high-risk LCH, including CNS disease. Regimens like vinblastine with prednisone, and cytarabine or cladribine for refractory cases, have demonstrated efficacy, but are associated with notable toxicity and high risks of recurrence or progression, especially in risk organ involvement or iLCH (Windebank and Nanduri, 2009; Zinn et al., 2016).

A key advance in understanding LCH pathogenesis is the discovery of recurrent MAPK pathway mutations, especially BRAFV600E, in many cases. This discovery has enabled targeted therapies, particularly BRAF and MEK inhibitors, which show rapid and robust responses in refractory or relapsed LCH, including CNS cases, and are now promising options for high-risk patients or those failing conventional chemotherapy (Zinn et al., 2016; Feng et al., 2021). Despite these advances, challenges persist, with incomplete responses, resistance, and frequent relapses after stopping therapy, as targeted agents do not appear to eradicate the mutated clone (Francis et al., 2021; Lin and Cao, 2024). Furthermore, the ability of BRAF and MEK inhibitors to penetrate the CNS and control neurologic disease may be limited in some cases, necessitating ongoing research into optimal dosing, duration, and combination strategies (Francis et al., 2021).

Immunotherapy represents an emerging and potentially transformative approach in LCH. The immune microenvironment in LCH lesions shows dysregulated cytokine expression and immune cell infiltration, potentially affecting disease severity and treatment response (Feng et al., 2021). Recently, selective CD1a expression on LCH cells has been explored for monoclonal antibody therapy. Preclinical studies with a human anti-CD1a antibody show high specificity and effective cytotoxicity, suggesting targeted immunotherapy may provide a less toxic and more effective future treatment (Bechan et al., 2005).

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Table 1
Demographic data, primary clinical features, treatment details, and associated outcomes.

Case	Sex	Age at iLCH Dx/ SRS (yrs)	Lesion location	Lesions treated	Presenting symptoms	Risk organ involvement	Other extracerebral involvement	Prior therapy	Diagnostic confirmation	Tumor volume (cc)	Margin dose (Gy)/ Isodose (%)	Max dose (Gy)	FU (mo)	Radiographic response	Distant progression	Endocrine outcome	SRS-related toxicity	ECOG at SRS/ at last FU	Survival status
1	F	10/ 25-28-34	Cerebellum	5 (3 × 2006, 1 × 2010, 1 × 2015)	DI, PHP, sleep disturbance	Yes (liver)	Skin	Chemo (vincristine, MTX, etoposide), surgery (GTR), RT (dose NR)	Brain biopsy (CD1a +, langerin +)	5.3–0.17 – 0.16–2.5 – 2.8	13/50, 13/50, 13/50, 14/50, 14/50	26, 26, 26, 28, 28	186	Regression (all)	Yes	Stable	RTOG grade 2 in last session	3-3-4/ 4	Deceased (unrelated to iLCH)
2	M	28/ 29	Intracanalicular + CPA extension	1	Hearing loss, vertigo	None	Bone	None	Bone biopsy	1.2	10/85	11.8	253	Regression	No	Stable	None	0/0	Lost to FU
3	M	19/ 20	Pituitary	1	DI, headache, hypogonadism, vision impairment	Yes (lung)	Colon	Chemo (vinblastine)	Lung biopsy	3.8	8/50	16	102	Regression	No	Stable	None	0/0	Alive
4	M	27/ 29	Pituitary	1	DI, PHP	Yes (lung)	None	None	Lung biopsy	3.2	10/45	22.2	126	Regression	No	Stable	None	0/0	Alive

Dx = diagnosis; SRS = stereotactic radiosurgery; FU = clinical follow-up; iLCH = intracranial Langerhans cell histiocytosis; MS = multisystem; RT = radiotherapy; GTR = gross total resection; DI = diabetes insipidus; PHP = panhypopituitarism; CPA = cerebellopontine angle; MTX = methotrexate; RTOG = Radiation Therapy Oncology Group; ECOG = Eastern Cooperative Oncology Group; NR = not recorded.

RT has been employed in the management of LCH for many years, with its application often dictated by the lesion's location, size, number, and associated symptoms (Gramatovici and D'Angio, 1988; Kaltsas et al., 2000). Studies have consistently shown high rates of LC and symptomatic improvement for RT-treated LCH lesions (Kotecha et al., 2014; Olschewski and Seegenschmiedt, 2006; Kriz et al., 2013). A multi-institutional retrospective study reported a complete remission rate of 77 % and a long-term control rate of 80 % following RT, with a median total dose of 15 Gy and minimal acute or late toxicity, even over extended follow-up periods (Kriz et al., 2013). Similarly, LC rates exceeding 90 % have been documented in both adult and pediatric cohorts, with most patients experiencing stabilization or improvement in lesion-related symptoms such as pain (Kotecha et al., 2014; Olschewski and Seegenschmiedt, 2006).

Bone lesions, which are the most common site of LCH, are described as "exquisitely radio-responsive" and are often well-controlled even with low doses of radiation(Laird et al., 2018). However, LCH in non-bone tissues, such as the skin and brain, are more difficult to control and may require higher doses or additional treatment modalities (Hong et al., 2013; Laird et al., 2018). For iLCH, LC rates are lower compared to bone lesions, with studies reporting a 3-year freedom from LF of 63 % for non-bone lesions, including the brain, versus 100 % for bone lesions (Laird et al., 2018). Some cases demonstrate initial symptomatic and radiographic response to RT, but recurrence can occur within months, suggesting that higher doses or additional modalities may be needed for durable control (Laird et al., 2018; Funk et al., 2012). Combination therapies, such as surgery and chemotherapy alongside RT, have shown higher success in preventing recurrence (Gersey et al., 2020).

A major point of debate concerns the efficacy of RT for managing DI, which frequently occurs as part of LCH affecting the hypothalamic-pituitary axis. While earlier reports suggested some benefit (Laird et al., 2018), more recent data, including a study where none of eight patients treated to the pituitary experienced a reduction in vasopressin requirements, questioned its efficacy for DI symptoms (Kotecha et al., 2014). Patients in one case series with pituitary stalk LCH continued to require endocrine replacement therapy even after SRS, and their DI did not improve (Park et al., 2023). This suggests that while RT might control lesion growth, it may not reverse established endocrine deficiencies.

Long-term RT side effects strongly influence treatment choices, particularly in children, with risks including impaired musculoskeletal development, secondary malignancies, facial asymmetry, and bone growth abnormalities (Kotecha et al., 2014). Despite these concerns, studies using modern conformal techniques report few adverse events (Laird et al., 2018).

RT for iLCH is generally well tolerated. Most studies report minimal acute or late side effects, even with higher doses, and no significant radiogenic toxicity has been observed in long-term follow-up (Olschewski and Seegenschmiedt, 2006; Kriz et al., 2013). In rare cases, re-irradiation has also been well tolerated without acute side effects (Funk et al., 2012). However, the risk of recurrence and progression to multisystem disease remains, especially in adults, indicating the need for careful long-term monitoring(Duan et al., 2013).

SRS is a promising treatment for iLCH, particularly in localized, recurrent, or refractory lesions. While surgery remains the mainstay for isolated CNS disease and chemotherapy for systemic involvement, SRS offers a non-invasive, precisely targeted alternative. SRS may help achieve LC when surgery is unfeasible or has failed, and when conventional RT carries high risk. A recent systematic review of nine patients with intracranial histiocytic disorders treated mainly with Gamma Knife or CyberKnife showed promising results: ~40 % of lesions resolved completely, 44 % regressed, only one progressed, and no adverse effects were reported over nearly seven years of follow-up. Delivered doses ranged from 8 to 28 Gy, targeting lesions in the pituitary stalk, posterior pituitary, petrous region, and pons, underscoring the versatility of SRS in treating anatomically challenging sites (Tripathi et al., 2021).

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In our multi-institutional case series, GKRS achieved durable LC in all treated iLCH lesions, with a median follow-up of over 13 years. Notably, every lesion demonstrated radiographic regression, and no LFs were observed. These results align with prior reports suggest that LCH is radiosensitive, yet our series extends the literature by providing the longest follow-up to date and demonstrating consistent long-term tumor control with relatively modest prescription doses (median 13 Gy). Dose selection was individualized, with lower marginal doses typically prioritized for larger target volumes or lesions adjacent to critical structures such as the optic apparatus to mitigate toxicity risks, while taking advantage of the high radiosensitivity of LCH. Importantly, SRS was well tolerated, with only one case of transient grade 2 edema and no severe radiation-induced toxicity.

While distant progression was observed in one patient, LC remained consistent across cases, indicating that SRS maintained its effectiveness as a local treatment. This pattern of distant failure, occurring despite durable LC of the treated lesion, underscores that SRS is inherently a focal therapy. It acts solely on the targeted volume and provides no prophylactic benefit against the development of new intracranial disease, which is driven by the underlying systemic pathophysiology. It is also important to note that due to the heterogeneous treatment histories in our cohort, the favorable LC observed may partly reflect the cumulative benefit of multimodal management strategies, although the temporal association with SRS suggests a direct therapeutic effect.

Consistent with prior studies, SRS did not reverse pre-existing endocrine dysfunction, underscoring that while lesion shrinkage can be reliably achieved, neuroendocrine deficits may represent irreversible sequelae of hypothalamo-pituitary axis involvement. In our series, the two lesions involving the pituitary region achieved LC, yet pre-existing endocrinopathies persisted. While standardized radiologic assessment of the pituitary stalk was not available to document specific anatomical changes in these cases, this clinical outcome aligns with existing literature on pituitary stalk LCH. Previous reports indicate that even when radiologic improvement—such as the resolution of stalk thickening—is documented, it rarely translates to functional recovery, suggesting irreversible damage to the neurohypophyseal tract (Hong et al., 2013; Park et al., 2023).

Despite promising results from our series and earlier reports, evidence for SRS in iLCH remains limited by small cohorts and the lack of prospective, controlled studies. While no major adverse effects have been reported, further assessment of long-term safety, particularly in pediatric patients, is necessary.

Considering the consistent tumor control achieved in our series and others, coupled with the established radiosensitive nature of the disease, a dose de-escalation paradigm warrants further investigation. Future studies with larger cohorts should explore whether lower marginal doses (e.g., $<$12 Gy) can maintain high local control rates while further minimizing the integral dose to surrounding eloquent structures, such as the optic pathways and hypothalamic-pituitary axis.

Overall, these observations support the potential role of SRS as a safe and viable option for iLCH, particularly as part of a multimodal treatment approach alongside systemic therapies and surgery. However, additional prospective studies and pooled analyses are needed to clarify appropriate dose selection, evaluate long-term control in different anatomical locations, and further establish its place in the wider treatment framework.

5. Limitations

As a retrospective case series of only four patients, its findings lack generalizability and preclude meaningful statistical analysis.

The cohort exhibits marked heterogeneity regarding lesion location, prior therapeutic interventions, and baseline performance status (ECOG 0–4). Patients presented with varying degrees of systemic involvement and prior exposure to chemotherapy or surgery, which complicates the isolation of SRS-specific treatment effects. Consequently, it is difficult to definitively distinguish the therapeutic benefit of SRS from the delayed effects of prior systemic therapies or the natural variability of the disease course. This variability limits the internal validity of the study and precludes direct comparisons between patients.

Follow-up imaging and clinical assessments were not standardized, with variations in MRI protocols, timing, and endocrine evaluations, combined with retrospective response assessment, introduce potential measurement bias.

Toxicity reporting relied on routine documentation rather than prospective collection, likely underestimating minor adverse events.

Another significant limitation of this study is the absence of molecular profiling, particularly for BRAF V600E and MAPK pathway alterations, as the treatment period for most patients predated the routine implementation of such testing. Consequently, we are unable to assess whether mutational status influences radiosensitivity or prognosis. This lack of genomic data limits the ability to integrate our findings directly into modern, genotype-informed treatment algorithms.

Finally, the lack of a comparator arm prevents definitive conclusions about the comparative effectiveness of SRS in relation to surgery, conventional radiotherapy, or systemic therapies.

6. Conclusion

This multi-institutional case series suggests that SRS may provide durable long-term LC of iLCH with minimal toxicity in selected patients. All treated lesions regressed radiographically, and no LFs occurred over a median follow-up exceeding a decade. While endocrine dysfunction did not improve following SRS, tumor regression was durable and clinically meaningful. These results indicate that SRS warrants consideration as a valuable, minimally invasive therapeutic option for selected patients with iLCH. Additional large-scale collaborative studies are necessary to validate these results and to better delineate the optimal role of SRS in the management of this rare disease.

Authorship

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Privacy rights and informed consent statement

Privacy rights of human subjects have been observed and informed consent was obtained for experimentation with human subjects.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT 5.1 in order to improve the readability and language of the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and took full responsibility for the content of the published article.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: L. Dade Lunsford reports a relationship with AB Elekta, Stockholm,

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