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REVIEW

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Primary Gamma Knife Radiosurgery for pineal region tumors: A systematic review and pooled analysis of available literature with histological stratification

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Abstract

Pineal region tumors (PTs) represent extremely rare pathologies, characterized by highly heterogeneous histological patterns. Most of the available evidence for Gamma Knife radiosurgical (GKSR) treatment of PTs arises from multimodal regimens, including GKSR as an adjuvant modality or as a salvage treatment at recurrence. We aimed to gather existing evidence on the topic and analyze single-patient-level data to address the efficacy and safety of primary GKSR. This is a systematic review of the literature (PubMed, Embase, Cochrane, Science Direct) and pooled analysis of single-patient-level data. A total of 1054 original works were retrieved. After excluding duplicates and irrelevant works, we included 13 papers ($n = 64$ patients). An additional 12 patients were included from the authors' original series. A total of 76 patients reached the final analysis; 56.5% ($n = 43$) received a histological diagnosis. Confirmed lesions included pineocytoma WHO grade I (60.5%), pineocytoma WHO grade II (14%), pineoblastoma WHO IV (7%), pineal tumor with intermediate differentiation WHO II/III (4.7%), papillary tumor of pineal region WHO II/III (4.7%), germ cell tumor (2.3%), neurocytoma WHO I (2.3%), astrocytoma WHO II (2.3%) and WHO III (2.3%). Presumptive diagnoses were achieved in the remaining 43.5% ($n = 33$) of cases and comprised of pineocytoma (9%), germ cell tumor (6%), low-grade glioma (6%), high-grade glioma (3%), meningioma (3%) and undefined in 73%. The mean age at the time of GKSR was 38.7 years and the mean lesional volume was 4.2 ± 4 cc. All patients received GKSR with a mean marginal dose of 14.7 ± 2.1 Gy (50% isodose). At a median 36-month follow-up, local control was achieved in 80.3% of cases. Thirteen patients showed progression after a median time of 14 months. Overall mortality was 13.2%. The median OS was not reached for all included lesions, except high-grade gliomas (8mo). The 3-year OS was 100% for LGG and pineal tumors with intermediate differentiation, 91% for low-grade pineal lesions, 66% for high-grade pineal lesions, 60% for germ

cell tumors (GCTs), 50% for HGG, and 82% for undetermined tumors. The 3-year progression-free survival (PFS) was 100% for LGG and pineal intermediate tumors, 86% for low-grade pineal, 66% for high-grade pineal, 33.3% for GCTs, and 0% for HGG. Median PFS was 5 months for HGG and 34 months for GCTs. The radionecrosis rate was 6%, and cystic degeneration was observed in 2%. Ataxia as a presenting symptom strongly predicted mortality (odds ratio [OR] 104, $p = .02$), while GCTs and HGG histology well predicted PD (OR: 13, $p = .04$). These results support the efficacy and safety of primary GKSR treatment of PTs. Further studies are needed to validate these results, which highlight the importance of the initial presumptive diagnosis for choosing the best therapeutic strategy.

KEYWORDS

Gamma Knife Radiosurgery, pineal tumors, primary treatment

1 | INTRODUCTION

Pineal region tumors (PTs) represent extremely rare pathologies, characterized by highly heterogeneous histological patterns.[1–5]

Due to the regional density of critical neurovascular structures, surgery has always represented a technical challenge. Surgical treatment has been extensively studied in the past and has been burdened by an extremely high rate of neurological deficits and death, although progress in micro-neurosurgical techniques led to a progressive reduction in postoperative mortality and complications, especially in high-volume centers. Large surgical series reported surgical-related mortality ranging from 7%[6] to 1.5%[7] and postoperative complications including life-threatening hemorrhage in up to 15% of cases in older reports.[6] In recent years, the relatively high rates of iatrogenic morbidity and mortality have pushed the neurosurgical community to search for alternative approaches to the diagnosis and treatment of pineal lesions.[8–12]

From a diagnostic perspective, the evolution of radiological techniques and biomolecular analyzes have progressively outclassed the need for surgical samplings; by the same extent, surgical resection has given way in most cases to less invasive therapeutic approaches.

In this context, growing evidence has shown Gamma Knife Radiosurgery (GKRS) as a safe and effective alternative to surgery. Nevertheless, given the rarity of the disease, literature reports on the topic are limited to small series and sporadic case reports, thus making it difficult or even impossible to draw any conclusive observations.[13–23]

The lack of formal evidence on the efficacy/safety profile of GKRS as primary treatment in this specific field makes it fundamental to analyse results from the clinical experiences reported to date in the literature.

The present is the first systematic review and pooled analysis of available single-patient level data with histological stratification of primary Gamma Knife radiosurgical (GKSR) treatment of PTs. Predictive factors on survival, radiologic/oncologic outcome, and treatment safety/efficacy have been studied and quantitatively analyzed.

2 | MATERIALS AND METHODS

2.1 | Study retrieval, selection, and data collection

We performed a systematic review of available literature in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statements[24] to identify retrospective or prospective clinical studies addressing primary GKSR treatment of PTs, using a combination of "pineal," "pineal gland," "pineal region," "stereotactic radiosurgery," "radiosurgery," "gamma," "gamma knife," "primary treatment," and "primary" keywords. Two authors (F. G. and P. D. D.) independently searched different international databases (MEDLINE via PubMed, Embase, Cochrane, Science Direct) to identify pertinent papers using Endnote X9.2, Clarivate, 2013. Databases were searched from inception until September 2022. We only included articles written in English.

Papers reporting other radiant treatment regimens and studies reporting single case reports, review articles, meta-analyses, abstracts, pure surgical reports, and papers not reporting the radiation therapy regimen or technology were excluded.

Data were manually extracted by two authors (P. D. D. and E. G.) using standardized forms. All data were retrieved following an already-defined PICO strategy. The risk of bias was assessed using the National Institutes of Health (NIH) quality assessment tool for nonrandomized interventional studies.[25] The PICO table and risk of bias are outlined in the Supporting Information Material Supporting Information: Table S1.

Only patients with reported individual outcomes were included in the present analysis. Aggregated measures of outcomes were, contrarily, excluded. Similarly, we excluded patients undergoing surgery for subtotal (STR) or gross total resection (GTR) or receiving radiotherapy or chemotherapy before radiosurgery. We only allowed biopsy and CSF shunting procedures before GKSR. Histology was suspected based on radiological and/or biochemical markers when surgical sampling was not performed and reported as originally stated by the authors. Outcomes were recorded at the last available follow-up.

The current 2021 WHO classification of intracranial tumors[26] introduced molecular markers as grading criteria for selected histotypes. It was not possible to retrospectively apply the novel criteria to the included lesions described in early studies. For this reason, the histological grade of the included lesions with histological confirmation was retrieved and analyzed as originally determined by the authors.

2.2 | Statistical analysis

This is a pooled analysis of single-patient level data from available literature using STATA Statistical Software 2015: Release 14 (StataCorp LP). We first presented an overall analysis of all included cases ($n = 76$), where similar lesions (either pathologically confirmed or suspected) were gathered under the same definition. In details:

Pineal low-grade ($n = 29$): suspected ($n = 3$) or confirmed pineocytoma WHO I ($n = 26$).

Pineal tumors of intermediate differentiation ($n = 10$): pineal region papillary tumor WHO II/III ($n = 2$), pineal tumor of intermediate differentiation WHO II/III ($n = 2$), and pineocytoma WHO II ($n = 6$).

Pineal high-grade ($n = 3$): pineoblastoma WHO IV ($n = 3$).

Low-grade glioma and glial-neuronal (LGG, $n = 4$): suspected low-grade glioma (n = 2), confirmed neurocytoma WHO II ($n = 1$), and astrocytoma WHO II ($n = 1$).

High-grade glioma (HGG, $n = 2$): suspected glioblastoma ($n = 1$) and confirmed astrocytoma WHO III ($n = 1$).

Germ cell tumors (GCTs, $n = 3$) = suspected GCT based on peripheral markers ($n = 2$), confirmed GCT on histology ($n = 1$).

Subsequent subgroup analysis of pathologically confirmed ($n = 43$) and nonpathologically confirmed lesions ($n = 33$) has been performed and presented later in the text.

Descriptive statistics and univariate analyses were performed using the *t*-test or Mann–Whitney (*U*-test) in accordance with the normality of the distribution and Chi-square or Fisher's exact tests were used where appropriate. The Kaplan–Meier method was used to estimate the predicted overall survival (OS) and progression-free survival (PFS). The predictive role of pretreatment variables was sought through univariate logistic regression analysis of relevant parameters on efficacy and safety outcomes. Categorical variables are reported as absolute numbers and/or percentages whereas continuous variables are reported as mean ± standard deviation (SD) or median (interquartile range [IQL]). The results of all tests are presented as *p* Values and statistical significance was set as a probability value of .05 (95% confidence interval).

3 | RESULTS

3.1 | Included studies

The systematic review yielded 1054 references. After an initial evaluation and removal of duplicates, we screened the records on title/abstract and excluded irrelevant papers. The search process is illustrated in Figure 1.

After scanning, 69 studies were retained for further analysis, and a total of 14 papers were considered eligible for inclusion.[13–23,27,28] Aiming at performing a histological stratification of the outcomes and to calculate predictive variables of response, the papers published by Li[28] and Yang,[29] although meeting the original inclusion criteria, needed to be excluded from data analysis because presented only aggregated outcomes from primary GKSR treatments. Data arising from the excluded articles are discussed along with the outcomes of this present analysis in the Discussion section.

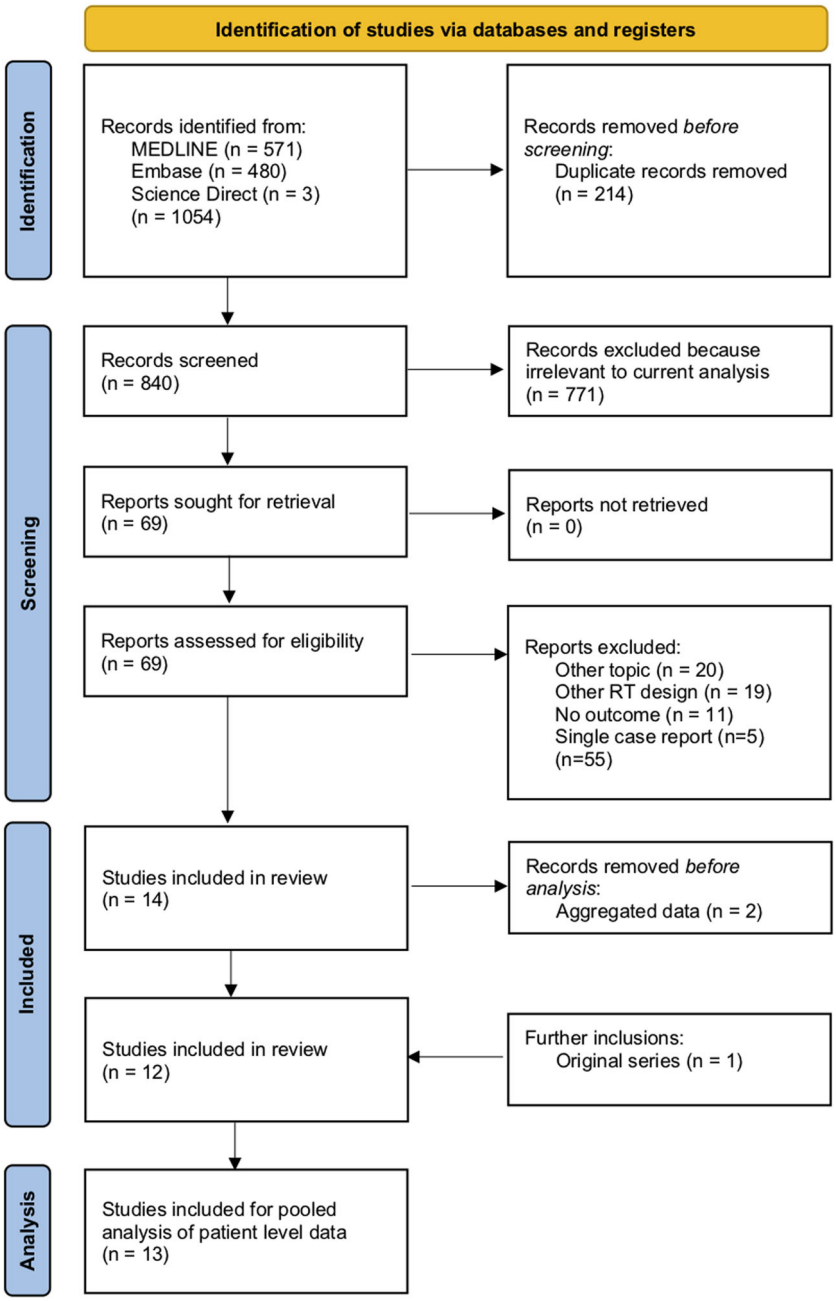

FIGURE 1 Systematic literature review process, including selection and exclusion criteria.

Eventually, 12 original works[13–23,27] reached the final analysis. We included data from the authors' original series of 12 patients harboring PTs primarily treated with GKSR.

A list of the retrieved papers with an overall summary of characteristics is provided in Table 1.[13–23,27] The selected papers included 10 retrospective monocentric studies[13,14,16,18–23,27], and two small case series (number of patients < 5).[15,17] They were all published after 2001, with more than half of the patients (59.2%) reported in the last 10 years (since 2013)[13,15,19,21,23] reflecting the increasing interest of the scientific community in the topic.

3.2 | Patient population

Overall, the retrieved patients were 207 with only 76 completely fulfilling the selection criteria (radiosurgery as primary treatment, with only biopsy allowed as a previous surgical procedure and individual outcome available). The largest samples were reported by Wang et al. (17 patients; 22.4% of all cases)[23], and by *our group* (12 patients; 15.8% of all cases). The baseline characteristics of included patients and lesions are summarized in Table 2.

The median age of the patients' population was 38.7 ± 19.7 years, with patients aged less than 30 years

TABLE 1 List of studies and characteristics of lesions and treatments included in the final analysis.

Author	year	Original patients	Included patients[a]	F/M	Mean age (*y*)	Mean volume (*cc*)	Pts with HCP	Previous treatments			Histology					
								Biopsy	VPS	ETV	Pineal	GCT	Glial	Other/ unknown	Mean dose (*Gy*)	Follow-up (month)
Kobayashi[27]	2001	33	2	1:1	48	.	2 (100)	1 (50)	2 (100)	0	1 (50)	0	0	1 (50)	16.5	37.5
Hasegawa[16]	2002	16	10	2:3	40.8	.	9 (90)	9 (90)	7 (70)	2 (20)	10 (100)	0	0	0	15.7	61.9
Hasegawa[17]	2003	4	1	0:1	21.0	2.2	1 (100)	0	1 (100)	0	0	1 (100)	0	0	14.0	34.0
Deshmukh[14]	2004	9	1	0:1	24	1.9	1 (100)	1 (100)	0	1 (100)	1 (100)	0	0	0	15.0	12.0
Reyns[22]	2006	13	7	3:4	38.5	.	7 (100)	7 (100)	3 (42)	4 (57)	7 (100)	0	0	0	.	36.3
Lekovic[18]	2007	17	10	2:3	36.5	5.7	8 (88)	9 (100)	7 (77)	1 (11)	5 (55)	1 (11)	3 (33)	0	14.7	38.6
Mori Y[20]	2009	38	1	1:0	69	.	1 (100)	1 (100)	1 (100)	0	1 (100)	0	0	0	15.3	45.0
Balossier[13]	2013	12	9	1:2	59.8	3.5	8 (88)	9 (100)	0	8 (88)	9 (100)	0	0	0	15.3	23.3
Wang[23]	2013	17	17	1:7.5	25.4	2.2	13 (76)	0	13 (76)	0	.	.	.	.	13.7	33.3
Park[21]	2015	9	3	0:3	38	7.6	3 (100)	3 (100)	1 (33)	2 (66)	3 (100)	0	0	0	13.3	179.7
Fernandez-Mateos[15]	2018	2	2	1:1	36.5	8.5	2 (100)	2 (100)	2 (100)	0	2 (100)	0	0	0	11.0	210.0
Li[19]	2019	25	2	1:1	13.5	.	.	0	0	0	0	0	2 (100)	0	15–25	51.0
Authors' original series	2023	12	12	3:1	44.9	5.2	8 (66)	1 (8)	3 (25)	5 (41)	3 (25)	1 (8)	1 (8)	7 (58)	15	39.3

Abbreviations: ETV, endoscopic third-ventriculostomy; GCT, germ cell tumors; HCP, hydrocephalus; VPS, ventriculoperitoneal shunt.

[a]Only primary treatments with available individual case data. Frequencies are represented as absolute numbers (%).

TABLE 2 Baseline characteristics of included patients and lesions.

Overall population		$n = 76$
Demographics	Age	38.7 ± 19.7
	Age < 30 yo	29 (38.1)
	Age 30-60 yo	30 (39.4)
	Age > 60 yo	17 (22.5)
	Male	48 (63)
	Female	29 (39)
Lesions	Mean volume (mL)	4.2 ± 4
	– low-grade pineal lesions	4.3 ± 2.9
	– intermediate-grade pineal lesions	5 ± 3.4
	– high-grade pineal lesions	23[a]
	– low-grade glioma	1.4 ± 0.1
	– high-grade glioma	3.9[a]
	– GCTs	2.4 ± 1.3
	Histologically confirmed (biopsy)	43 (57)
Previous treatments	VPS	40 (53)
	ETV	23 (30)
Further treatments	VPS	3 (3.9)
	Surgery	1 (1.8)
	Chemotherapy	12 (15.8)
	WBRT	1 (1.3)
	Cranio-spinal RT	10 (13.2)
GKSR		
Treatment parameters	Single fraction	75 (98.7)
	Multiple fractions ($n = 4$)	1 (1.3)
	Mean marginal dose (Gy)	14.7 ± 2.1
	– low-grade pineal lesions	15.3 ± 2.2
	– intermediate-grade pineal lesions	14.3 ± 2.4
	– high-grade pineal lesions	14.5 ± 0.7
	– low-grade glioma	17.2 ± 2.5
	– high-grade glioma	17 ± 5.6
	– GCTs	15 ± 1
	Mean maximal dose (Gy)	29.1 ± 4.5
	Median isodose (%)	50
	Median no. Isocenters	10
	Median coverage (%)	99
Overall survival	Death	10 (13.1)
Follow-up	Median follow-up (m)	36 [15–60]

Note: Continuous variables are expressed as mean ± standard deviation or median [interquartile range], whereas dichotomic variables are expressed as absolute numbers (%).

Abbreviations: GKSR, Gamma Knife Radiosurgery; WBRT, whole brain irradiation; yo, years old.

[a]only one lesion with reported data.

and between 30 and 60 years equally distributed (38.1% and 39.4%, respectively). About one-fifth (22.5%) of the patients were older than 60. The relatively large SD in the mean age was mostly due to the inclusion of one study reporting a significantly higher mean age (59.8 years)[13] together with a case report (69 years)[20] and, on the other side, a small case series with two pediatric cases (13.5 years).[19]

Across the series, there was a strong male predilection (63 vs. 37%), in accordance with the general epidemiological data.[30]

The most frequent presenting symptoms were headache and nausea (52.7%), followed by diplopia (10.9%) and ataxia (7.3%).

Before radiosurgery, 56.5% of patients underwent surgical biopsy, 53% ventriculo-peritoneal shunt placement (VPS), and 30% endoscopic third-ventriculostomy (ETV).

3.3 | Lesions characteristics

The tumor volume was only reported in 71% of cases and showed a mean value of 4.2 ± 4 cc. The largest volumes were reported by Fernandez[15] (8.5 cc) and Park et al.[21] (7.6 cc).

Overall, the number of patients presenting with hydrocephalus was 63 (85% of cases with reported variable).

The biopsy rate ranged from 100% in some studies[13–15,18,20–22] to 0%.[17,19,23] Histological diagnosis was available in overall 43 cases (56.5%). Confirmed lesions included pineocytoma WHO grade I ($n = 26$, 60.5%), WHO grade II ($n = 6$, 14%), pineoblastoma WHO IV ($n = 3$, 7%), pineal tumor with intermediate differentiation WHO II/III ($n = 2$, 4.7%), papillary tumor of pineal region WHO II/III ($n = 2$, 4.7%), GCT ($n = 1$. 2.3%), neurocytoma WHO II ($n = 1$, 2.3%), astrocytoma

WHO II ($n = 1$, 2.3%) and WHO III ($n = 1$, 2.3%). Presumptive diagnoses were achieved in the remaining 43.5% ($n = 33$) of cases and comprised of pineocytoma ($n = 3$, 9%), GCTs ($n = 2$, 6%), low-grade glioma ($n = 2$, 6%), high-grade glioma ($n = 1$, 3%), meningioma ($n = 1$, 3%) and undefined in 24 cases (73%).

Taken together, all the included lesions ($n = 76$) reflected a predominance of intrinsic pineal lesions ($n = 42$, 55.2%) of which low-grade lesions represented 38% of cases, followed by pineal tumors with intermediate differentiation (13%) and high-grade tumors (4%). Other lesions included LGG (5%), germ cell tumors (4%), HGG (3%), and meningiomas (1%). The diagnosis was unclear in the remaining 32% of cases. See Table 3 for a detailed list. The six cases of astrocytoma WHO II reported by Balossier[13] have been classified among pineal tumors of intermediate differentiation, according to the current 2021 WHO classification.[26]

3.4 | Treatment parameters

In all studies, GKRS was the technology in use. Information about the GK model was provided only by Reyns et al.[22] (model B and C), Balossier et al.[13] (model C), and *our group* (model C, Perfexion, and Icon).

All but one lesion was treated in a single fraction with a mean prescription dose of 14.7 ± 2.1 Gy, and a mean maximal dose of 29.1 ± 4.5 Gy. The only exception was an 18-month-old girl harboring a large lesion (6.2 cc) with nonspecific neuroimaging characteristics who received dose fractionation (9 Gy in four fractions) in our original series. The treatment parameters as stratified per histological family are summarized in Table 2.

The variability among the prescription doses mostly depended on the presumptive diagnosis, lesional volume, and predicted collateral brainstem irradiation. This was also reflected in the different reported isodoses, which ranged from 50% to 60%, with a median value across all studies of 50%.

Beyond our series, the data on the number of isocenters used was available in only two more studies[15,18] the median value was 10, while in our experience it was 22.

3.5 | Survival analysis

The median follow-up across all studies was 36 months (IQL 15–60 months). The longest clinical and radiological observation was reported by Park et al., and Fernandez et al. (median values 179 and 210, respectively).[15,21]

TABLE 3 The histological diagnosis was first presumed based on neuroimaging or biochemical markers.

All included lesions		***n* = 76**
	Pineal low-grade	29 (38)
	Pineal intermediate differentiation	10 (13)
	Pineal high-grade	3 (4)
	Germ cell tumor	3 (4)
	Low-grade glioma and glial-neuronal (LGG)	4 (5)
	High-grade glioma (HGG)	2 (3)
	Meningioma	1 (1)
	Undefined/unknown	24 (32)
(43.5%) only suspected at imaging/laboratory markers		***n* = 33**
Suspected	Pineocytoma	3 (9)
	Germ cell tumor	2 (6)
	Low-grade glioma	2 (6)
	High-grade glioma	1 (3)
	Meningioma	1 (3)
	Undefined/unknown	24 (73)
(56.5%) histologically confirmed		***n* = 43**
Biopsy	Pineocytoma WHO I	26 (60.5)
	Pineocytoma WHO II[a]	6 (14)
	Pineal intermediate differentiation WHO II/III	2 (4.7)
	Papillary tumor of pineal region WHO II/III	2 (4.7)
	Pineoblastoma WHO IV	3 (7)
	Germ cell tumor	1 (2.3)
	Neurocytoma WHO II	1 (2.3)
	Astrocytoma WHO II	1 (2.3)
	Astrocytoma WHO III	1 (2.3)

Note: In 56.5%% of cases, the diagnosis was confirmed with a lesional biopsy, whereas in the remaining 43.5% the diagnosis was only suspected.

[a]Astrocytoma WHO grade II was reported by Balossier et al. We have subsequently treated these lesions among pineal tumors of intermediate differentiation, according to the current 2021 WHO classification.

At the last follow-up, 10 patients died due to tumor progression; the overall mortality rate was 13.2%; the mean mortality rate, calculated among the selected studies, was 6.4%, with the highest reported by Hasegawa et al.[16] (30%).

When analyzing all included lesions, Kaplan–Meier estimates of OS did not reach the median for either all intrinsic pineal lesions, pineal low-, intermediate- and high-grade tumors, GCTs, LGG, or unclear lesions.

Median OS, however, was 8mo for HGG (Figure 2A). Overall, no statistical difference in survival curves was detected for different histologies ($p = .14$).

The best results in terms of 3-year OS were observed in LGG and pineal tumors with intermediate differentiation (100%), followed by low-grade pineal tumors (91%), the worst in HGG (50%), and GCTs (60%). These survival rates were sustained at 4 years for intrinsic pineal lesions and LGG. The entire cohort reported an 85% 3-year OS.

Table 4 shows a summary of predicted survival probabilities based on Kaplan–Meier survival analysis.

The PFS estimation yielded a significant difference in outcome among the different histologies ($p < .001$), with a median PFS time of 34 months for GCTs, and 5 months for HGGs, while in all other cases, the median was not reached. (Figure 2B).

The highest 3-year PFS rates were observed in low-grade glial tumors and pineal tumors with intermediate

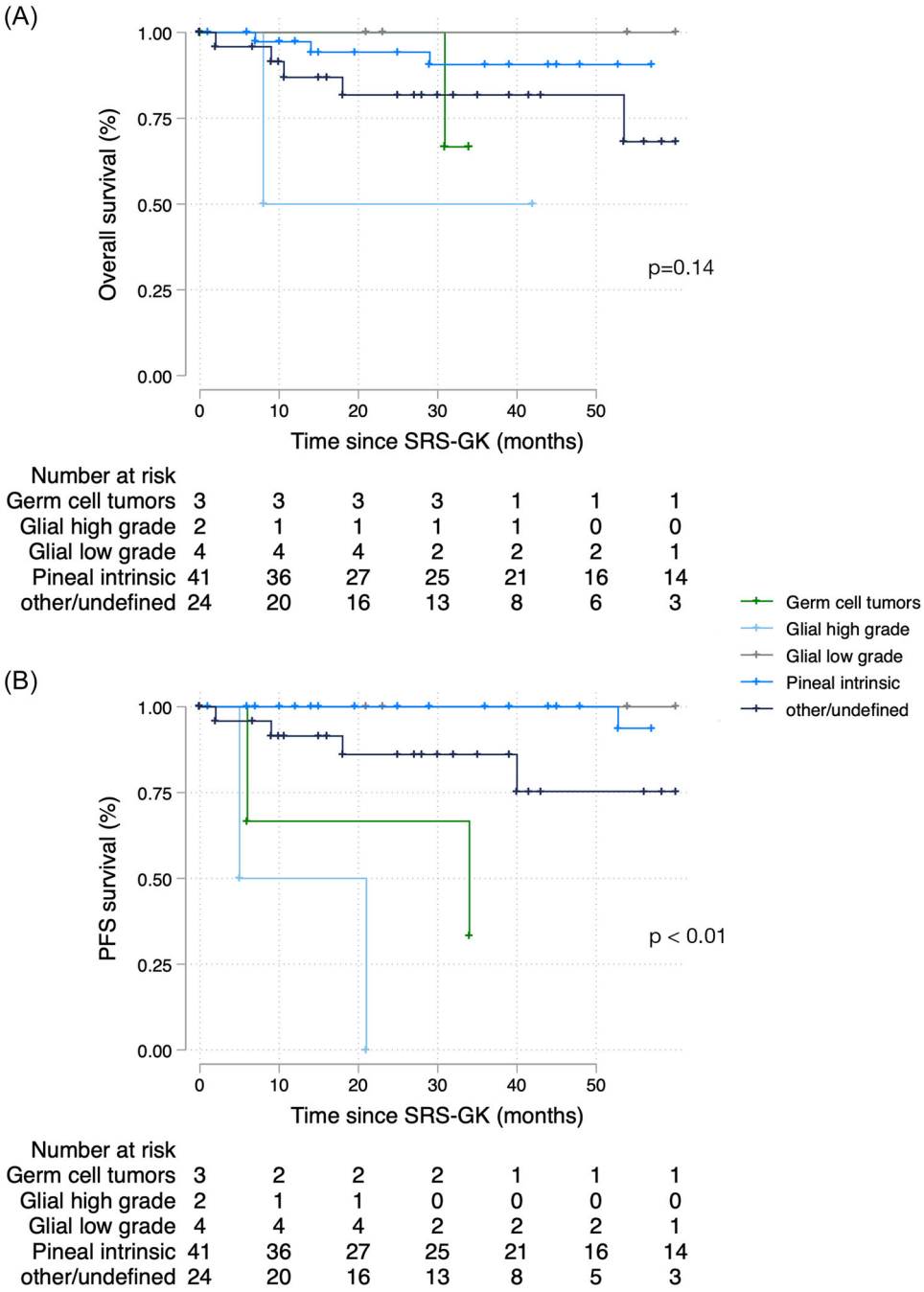

FIGURE 2 Kaplan–Meier estimates of overall survival (panel A) and progression-free survival (panel B) for pineal region tumors, histological stratification of outcomes.

TABLE 4 Kaplan–Meier estimates of overall survival and progression-free survival.

4.A OS (%)					
Histology		**1 year**	**2 years**	**3 years**	**4 years**
Overall	All included lesions	92%	89%	85%	81%
Pineal	All intrinsic pineal				
	– Low grade	100%	95%	91%	90%
	– Intermediate grade	100%	100%	100%	100%
	– High grade	66%	66%	66%	66%
Glial/neuro	All glial-neuro lesions				
	– LGG	100%	100%	100%	100%
	– HGG	50%	50%	50%	.
GCTs	Germ cell tumors	100%	60%	60%	.
Other	Other or unknown	86%	82%	82%	82%
4.B PFS (%)					
Histology		**1 year**	**2 years**	**3 years**	**4 years**
Overall	All included lesions	91%	85%	81%	77%
Pineal	All intrinsic pineal				
	– Low grade	100%	93%	86%	86%
	– Intermediate grade	100%	100%	100%	100%
	– High grade	66%	66%	66%	66%
Glial/neuro	All glial-neuro lesions				
	– LGG	100%	100%	100%	100%
	– HGG	50%	0%	0%	.
GCTs	Germ cell tumors	66%	33.3%	33.3%	.
Other	Other or unknown	91%	86%	86%	74%

Note: All values are presented as percentages (%). This table includes both suspected and histologically confirmed lesions. Pineal low-grade ($n = 29$): suspected ($n = 3$) or confirmed pineocytoma WHO I ($n = 26$). Pineal tumors of intermediate differentiation ($n = 10$): confirmed pineal region papillary tumor WHO II/III ($n = 2$), pineal tumor of intermediate differentiation WHO II/III ($n = 2$), and pineocytoma WHO II ($n = 6$). Pineal high-grade ($n = 3$): pineoblastoma WHO IV ($n = 3$). Low-grade glioma and glial-neuronal (LGG, $n = 4$): suspected low-grade glioma ($n = 2$), confirmed neurocytoma WHO II ($n = 1$), and astrocytoma WHO II ($n = 1$). Glial high-grade (HGG, $n = 2$): suspected high-grade glioma ($n = 1$), astrocytoma WHO III ($n = 1$). 4.A. Overall survival. 4.B. Progression-free survival.

differentiation (100%), followed by low-grade pineal tumors (86%). Conversely, GCTs reported a 3-year PFS rate of 33%, while HGG had a 0% PFS already at 24 months. Undefined lesions showed a 3-year PFS of 86%. The 3-year PFS for the entire cohort was 81%.

Overall, the mean time to progression across the included studies was 24.2 ± 27 months, with the longest reported by Park[21] and by *our group* (81 and 32.6 months, respectively).

We performed a sub-group analysis of histologically confirmed lesions ($n = 43$) and non-histologically confirmed lesions ($n = 33$).

3.5.1 | Histologically confirmed lesions

Kaplan–Meier analysis revealed a significant difference in OS probabilities curves among the histologically confirmed lesions ($p = .009$), however, median OS was not reached for either of the included tumors. Calculated OS probabilities are shown in Supporting Information: Table S2A. The 3-year OS was 100% for pineocytoma WHO II, pineal tumor with intermediate differentiation WHO II/III, papillary tumor of pineal region WHO II/III, neurocytoma WHO II and GCT, while it was 89% for pineocytoma WHO I and 0% for astrocytoma WHO III.

Pineoblastoma WHO IV reached a 66% OS probability at 2 years but the remaining two cases were lost to follow-up. Similarly, the single astrocytoma WHO II case was reported alive at 1 year but was later lost to follow-up.

As for PFS (see Supporting Information: Table S2B), Kaplan–Meier curves revealed a significant difference in PFS time among the included lesions ($p < .001$) but median PFS was not reached for either group. The 3-year PFS was 100% for pineocytoma WHO II, pineal tumor with intermediate differentiation WHO II/III, papillary tumor of pineal region WHO II/III, neurocytoma WHO II and GCT, 84% for pineocytomas WHO I and 0% for astrocytoma WHO III.

3.5.2 | Non-histologically confirmed lesions

Survival analysis (see Supporting Information: Table S3) failed in demonstrating a significant difference in OS curve probabilities ($p = .56$) and showed a median OS of 30.9 months for GCTs. The 3-year predicted OS probabilities were 100% for pineocytomas, meningiomas, and LGG, and 81% for the undefined lesions. The survival probability dropped to 33% for GCTs and 0% for HGG at 2 years follow-up.

The PFS analysis, contrarily, showed a significant difference in the PFS probability curve ($p = .007$) with a median PFS time of 6 months for GCTs, while for the other included lesions median was not reached. Predicted PFS rates largely reflected the reported OS probabilities and were the largest (100%) for pineocytomas and LGG, and 85% for undefined lesions at 3 years. As expected, the predicted PFS for GCTs was 50% at 1 year and 0% at 2 years, while HGG had a striking 0% PFS at 1 year.

3.6 | Tumor control

At the last follow-up, the data on radiologic response were available in 63 patients (82.9%). In 10 cases the outcome was not reported, while three patients were lost to follow-up immediately after GKSR. According to adapted RANO criteria, complete (CR) and partial response (PR), stable disease (SD), and disease progression (PD) were achieved in 26.9%, 33.3%, 23.8%, and 15.8%, respectively (Table 5A). At actuarial analysis after 36 months (3 years), CR, PR, and SD were achieved in 37.9%, 37.9%, and 10.3% of cases, while only 13.7% of lesions showed progression after a median time of progression of 14 (IQR 6–29) months.

The histological stratification showed a significantly higher rate of PD in HGG compared to intrinsic pineal (100% vs. 14.%, $p = .03$) at the last available follow-up. No differences were detected among the different intrinsic pineal histologies. High-grade gliomas showed progression in 100% of cases, while LGG did not show any progression ($p = .02$). Globally, low-grade pineal lesions showed local control of disease in 86.3% of cases, while intermediate differentiation lesions achieved control in 88.9%. High-grade pineal lesions, conversely, showed progression in 33.4% of cases, as did GCTs in 66.7% of cases.

Univariate analyses showed the following variables to be associated with CR: previous VPS ($p = .001$), relatively lower prescription dose to tumor margins (mean 13.7; $p = .05$), chemotherapy and craniospinal RT as further treatment in requiring lesions ($p = .05$ and 0.01, respectively), smaller tumor volume ($p = .08$), and the presence of hydrocephalus at the onset of the disease ($p = .08$). We observed ETV to be significantly less common in patients achieving CR ($p = .03$), however, when local control was assessed (defined as CR, PR, or SD), both ETV and VPS did not show a strong predictive role.

Conversely, GCTs and HGG tumors were associated with PD ($p = .05$, and $p = .01$, respectively), whereas intrinsic pineal tumors and, specifically, pineocytomas experienced local control more frequently ($p = .04$ and $p = .03$). Absence of headache as presenting symptom trended towards significance for higher local control ($p = .07$). Subgroup analysis is shown in Table 5B,C.

3.6.1 | Histologically confirmed lesions

Intrinsic pineal lesions

Pineocytomas WHO I showed an overall 85% tumor control rate after GKSR, with a CR attested at 15% and PR and SD at 35% each. Progression of disease was observed in 15%. The two cases of papillary tumor of the pineal region were reported as CR (100%), while one of the two pineal tumors with intermediate differentiation (WHO II/III) ultimately progressed (50%) and the other achieved PR (50%). The 6 reported pineocytoma WHO grade II remained stable at the last

TABLE 5 Radiological outcomes were assessed through adapted RANO criteria.

5.A					
All included lesions		**CR**	**PR**	**SD**	**PD**
Overall	All included lesions	26.9%	33.3%	23.8%	15.8%
Pineal	All intrinsic pineal				
	– low grade	13.7%	36.3%	36.3%	13.7%
	– intermediate grade	22.2%	11.1%	55.6%	11.1%
	– high grade	33.3%	0%	33.3%	33.4%
Glial/neuro	All glial-neuro lesions				
	– LGG	33.3%	66.7%	0%	0%
	– HGG	0%	0%	0%	100%
GCTs	Germ cell tumors	33.3%	0%	0%	66.7%
Other	Other or unknown	37.6%	41.6%	4.1%	16.7%

5.B					
Histology confirmed		**CR**	**PR**	**SD**	**PD**
Confirmed diagnosis (WHO grade)					
Pineal	Pineocytoma (I)	15%	35%	35%	15%
	Pineocytoma (II)	0%	0%	100%	0%
	Pineal intermediate differentiation (II/III)	0%	50%	0%	50%
	Papillary tumor of pineal region (II/III)	100%	0%	0%	0%
	Pineoblastoma (IV)	33.3%	0%	33.3%	33.4%
Glial/neuro	Neurocytoma (II)	0%	100%	0%	0%
	Astrocytoma (II)	100%	0%	0%	0%
	Astrocytoma (III)	0%	0%	0%	100%
GCTs	Germ cell tumors	100%	0%	0%	0%

5.C				
Suspected lesions	**CR**	**PR**	**SD**	**PD**
Suspected diagnosis				
Pineocytoma	0%	25%	75%	0%
Germ cell tumor	0%	0%	0%	100%
Glial low-grade	0%	100%	0%	0%
Glial high-grade	0%	0%	0%	100%
Meningioma	0%	0%	0%	100%
Undefined	39.1%	43.4%	4.3%	13.4%

Note: 5.A. includes both suspected and confirmed lesions. 5.B. only histologically confirmed lesions. 5.C. radiologically/markers suspected lesions.
Abbreviations: CR, complete response; PD, progression of disease; PR, partial response; SD, stability of disease.

follow-up. Conversely, pineoblastomas WHO IV reported PD in 33.4% of cases and tumor control in the remaining 66.6% being equally distributed among CR and SD.

Glial-neuronal lesions

Our literature review reported only three cases of glial and neuronal lesions primarily treated with GKSR. Among glial lesions, astrocytoma WHO III showed PD,

astrocytoma WHO II achieved CR, and the single case of neurocytoma WHO II remained stable.

Other lesions

One case of GCT was treated with primary GKSR and showed complete remission.

3.6.2 | Nonhistologically confirmed lesions

The numerosity of this group of lesions is smaller than histologically confirmed lesions and several tumoral histotypes have been only represented by one or two lesions. Pineocytomas were globally observed to achieve tumor control, with stability of disease in 75% and PR in 25% at the last follow-up. Two suspected LGG achieved PR (100%) while high-grade gliomas (100%), one meningioma (100%), and one GCT (100%) showed progression at the last follow-up. The response was mixed in the group of the undefined lesions which reported 39.1% of CR, 43.4% PR, only 4.3% SD, and 13.4% PD.

3.7 | Complications, progression, and further treatments

At the last follow-up, eight patients (10.5%) experienced treatment-related intracranial changes (TRICs). Five patients (6%) experienced radionecrosis, while only one presented with pseudoprogression (1%), and an additional two (2%) showed cystic degeneration.

Among the 10 patients with PD (13.5%), five had tumor recurrence/relapse; the distribution according to lesion histology was quite homogenous; the mean time to recurrence/relapse was 26.9 ± 20 months. The other five harbored leptomeningeal dissemination (LMD); among them, two cases were GCTs, one astrocytoma WHO grade II, one pineal tumor with intermediate differentiation, and one last lesion with unclear diagnosis; the mean time to LMD was 21.6 ± 34 months. Baseline hydrocephalus was relatively more common in patients experiencing LMD ($p = .08$).

After radiosurgery, 4% of patients ($n = 3$) underwent surgery for hydrocephalus (VPS or ETV), one patient (1%) underwent resective surgery, 16% ($n = 12$) chemotherapy, and 14.5% any type of radiation therapy (RT) (one case of WBRT, and other 10 cases of craniospinal RT) (see Table 2). No predictive factors of radionecrosis could be identified.

3.8 | Analysis of predictive variables

3.8.1 | Survival

After logistic regression analysis (Figure 3), ataxia as presenting symptom confirmed a strong predictive role for mortality (OR 104; $p = .02$). The presence of hydrocephalus at the onset of the disease (OR 0.25; $p = .09$), intrinsic pineal tumors (OR 0.29; $p = .09$), and pineocytoma WHO I or II (OR 0.25; $p = .09$) were slightly associated to a survival benefit. Contrarily, the need for post-GKSR chemotherapy was associated with an increased risk of death (OR 4.07; $p = .057$).

3.8.2 | Local failure

Germ cell tumors showed a higher risk for local failure (OR 13, $p = .04$). As opposed, intrinsic pineal tumors showed a trend towards a decreased risk (OR 0.2, $p = .06$) while data was not sufficient to calculate the risk for gliomas. Ataxia was associated with an increased risk of local failure (OR 8, $p = .06$).

3.8.3 | Complete response

Tumor histology was a strong predictor of complete response, as confirmed by true pineocytomas showing a relative resistance to achieve CR (OR 0.23; p 0.03). Germ cell tumors were not predictive for complete response ($p = .80$) and data was not sufficient for gliomas. Additional chemotherapy was associated with good CR rates in responding lesions (OR 4.47; $p = 0.03$). Previous VPS was associated with CR (OR 11.2, $p = .003$) while ETV to lower rates (OR 0.2, $p = .04$). Overall, VPS and ETV did not show significant predictive values in terms of global local control (CR, PR, and SD).

3.8.4 | Limitations

The major limitations of this systematic review and pooled analysis are the retrospective design, the lack of a control group, and the relatively small number of included lesions, mainly due to the rarity of the disease. Moreover, histological confirmation was only available in about half of patients, thus the histological stratification of outcomes relied on neuroimaging and biochemical markers in a considerable number of cases. Additional studies are therefore necessary to

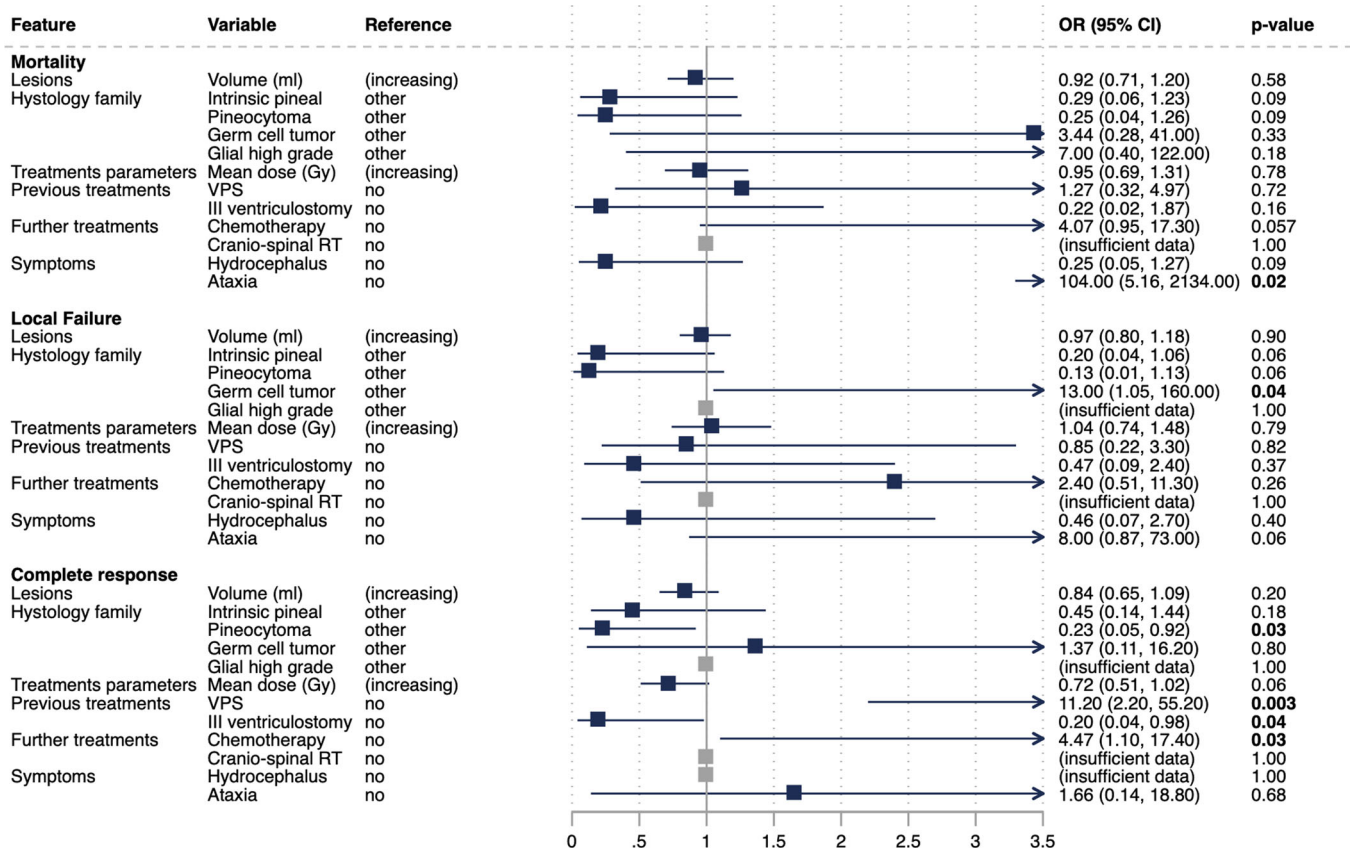

FIGURE 3 Predictors of efficacy and safety measures in primary GKRS of pineal region tumors. GKRS, Gamma Knife Radiosurgery.

further validate the results arising from this current analysis.

4 | DISCUSSION

According to available evidence and guidelines[31] treatment is currently always indicated in solid parenchymal pineal tumors, including grade I pineocytomas. This has been historically addressed with surgery aiming at maximal safe resection and adjuvant treatments in cases of lesions at risk of progression or local and distant dissemination. More recently, literature has increasingly indicated primary GKSR treatment for lesions arising in the pineal region, right after diagnosis and shunting of concurrent hydrocephalus. In detail, Park and colleagues[21] have elected stereotactic radiosurgery as a primary therapy following CSF diversion and biopsy in all pineal parenchymal tumors of adults, and to a similar extent, Reyns,[22] Mori,[20] Deshmukh,[14] Hasegawa,[16] and Lekovic[18] considered radiosurgery a safe alternative to surgery for pineal tumors, including WHO grade I, and reporting good local control rates, while avoiding mortality and morbidity associated to surgery. Nonetheless, aggressive tumors, including gliomas, still require multimodal treatments, where surgery generally remains the first-line strategy and GKSR may be considered an adjuvant or alternative method when surgery is contraindicated.[19] Other benign non pineal parenchymal lesions (e.g., meningiomas) are generally treated upon documented growth at serial imaging. For what concerns non-histologically confirmed lesions, Li et al.[28] reported a large cohort of patients ($n = 147$) reporting about 95% local control rate for non-GCT, and concluding that GKSR appears to be an effective, low-risk treatment option for only radiologically suspected pineal parenchymal tumors.

This systematic review presented the pooled outcomes of primary GKSR treatment of 76 PTs. Included lesions did not undergo surgical removal and only received surgery for hydrocephalus shunting. Among the included lesions, only 56.5%% of lesions received histological confirmation through biopsy before GKSR. The median follow-up duration was 36 months (3 years).

Patients receiving primary GKSR showed an overall 13.5% mortality and a 3-year OS rate of 85%, which is higher than the 72% recorded by Li[28] in their large cohort treated with primary GKSR for PTs without histological confirmation. In our analysis, LGG reported the best

3-year OS rates followed by intrinsic pineal tumors, while, expectedly, HGG had the lowest survival. Subgroup analysis of histologically confirmed true pineal lesions showed that pineocytomas WHO I reached 89% 3-year OS rate, while pineoblastomas WHO IV only achieved 66% at 2 years follow-up. Surprisingly pineal papillary and tumors with intermediate differentiation (WHO grade II/III) recorded a 3-year OS of 100%. This result may be partially explained by the extremely small representation of these rare lesions ($n = 6$) compared to the relatively more frequent pineocytomas.

Because of their specific pathobiology and treatment schedules, germ cell tumors deserve a dedicated discussion. Yang et al.[29] analyzed the outcomes of 12 patients with pineal or suprasellar GCTs receiving primary GKSR. Localized lesions did not receive adjuvant chemotherapy or routine radiotherapy after radiosurgery and invariably showed LMD, while widespread tumors received upfront chemotherapy and craniospinal irradiation. Overall, the authors reported a 5-yOS of 63.6%. Mortality only occurred in patients with localized lesions showing progression after primary GKSR not followed by adjuvant treatments. Of note, the primary GKSR cohort had the lowest 5-year OS compared to the primary chemotherapy (85%) and radiotherapy (75%) regimens. Accordingly, our current analysis revealed that patients only receiving primary GKSR without adjuvant treatment showed even lower survival rates at shorter follow-up (3-year OS 60%). This data is consistent with the 62% reported by Li.[28] These results highlight the need for immediate multimodality treatment of GCTs.

The largest available series[28] reported a 94% rate in non-GCTs without further data on the presumptive histology of included lesions, making it not possible to directly compare these outcomes.

Failure pattern was equally distributed between recurrence and LMD. True recurrence primarily occurred in HGG, meningioma, and pineal intrinsic tumors, while LMD was principally observed in GCTs, astrocytoma WHO grade III, and pineal tumors with intermediate differentiation WHO II/III. Further histological stratification of outcomes confirmed a significantly increased risk of all forms of progression in HGG and GCTs. Accordingly, the highest 3y-PFS rates were observed in LGG (100%), followed by intrinsic pineal lesions (90%).

Overall, we observed a 10.5% incidence of complications, mostly due to radionecrosis requiring increased steroid dosage. Of these patients, only one with suspected meningioma died because of a significant radionecrosis nonresponsive to medical treatment causing severe brainstem dysfunction, impaired consciousness, and pneumonia. In all the other cases medical treatment was sufficient to deal with this complication. Similar outcomes were seen by Li[28] who reported an overall 2% severe increased lesional volume following GKSR requiring intensive care, and only one death in their entire series. Yang[29] did not report GKSR-related complications. Taken together, these results build up a total of 3.5% RN incidence rate and treatment-related mortality of 0.8%.

In our in-deep analysis of predictive factors, tumor histology resulted as the strongest predictor of radiological response. Intrinsic pineal lesions, particularly pineocytomas, predicted local control while GCTs had higher odds of local failure and progression. Surprisingly, ataxia as presenting symptom strongly predicted progression and death. Although we observed that patients who underwent pre-GKSR VPS had higher chances of achieving CR compared to ETV, when overall local control was assessed (defined as CR, PR, or SD), both ETV and VPS did not show a robust predictive role. Treatment parameters did not significantly affect the efficacy or safety measures.

5 | CONCLUSIONS

These results support the efficacy and safety of primary GKSR treatment of PTs. Available data suggest that GKSR is a low-risk primary treatment option for pineal region lesions with biopsy only or without histological confirmation. Intrinsic pineal lesions and low-grade gliomas had the best outcomes, while high-grade gliomas and GCTs showed the worst OS and PFS rates. These results advise for multimodal treatments to be immediately considered in these latter cases, as primary GKSR alone may not be sufficient to achieve reasonable local control and survival advantage. Additional studies are needed to further validate these results, which highlight once more the importance of the initial presumptive diagnosis for choosing the best therapeutic strategy.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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