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Single fraction and hypofractionated radiosurgery for perioptic meningiomas - tumor control and visual outcomes: a systematic review and meta-analysis

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Abstract

Objective

Perioptic meningiomas, defined as those that are less than 3 mm from the optic apparatus, are challenging to treat with stereotactic radiosurgery (SRS). Tumor control must be weighed against the risk of radiation induced optic neuropathy (RION), as both tumor progression and RION can lead to visual decline. We performed a systematic review and meta-analysis of single fraction SRS and hypofractionated radiosurgery (hfRS) for perioptic meningiomas, evaluating tumor control and visual preservation rates.

Methods

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we reviewed articles published between 1968 and up to December 8^{-th}, 2022. We retained 6 studies reporting 1193 patients.

Results

For single fraction SRS, overall rate of tumor control was 93.4% (range 89.7-97, p<0.001); tumor progression was 8.1% (range 6.2-10.1, p<0.001). Overall rate of visual stability was 90.4% (range 88.1-92.7, p<0.001), including visual improvement in 29.4% (range 25.8-33, p<0.001); visual decline was 9.6% (range 7.3-11.9, p<0.001). For hfRS**,** overall rate of tumor control was 95.6% (range 92.1-99.1, p<0.001); tumor progression was 4.4% (range 0.9-7.9, p=0.01). Overall rate of visual stability was 94.9% (range 90.9-98.9, p<0.001), including visual improvement in 22.7% (range 5.0-40.3, p=0.01); visual decline was 5.1% (range 1.1-9.1, p=0.013).

Conclusions

SRS is an effective and safe treatment option for perioptic meningiomas. Hypofractionated regimens have similar rates of tumor control with better rates of visual preservation compared to single fraction SRS.

Introduction

Meningiomas are the most common primary brain tumors, accounting for one third of all primary brain tumors[1]. If these tumors are located ≤ 3 mm from the optic apparatus (usually sellar or parasellar), they are typically classified as perioptic meningiomas[2,3]. For perioptic meningiomas that are small and asymptomatic, some centers advocate for a "wait-and-scan" strategy. However, due to the intimate association with the optic apparatus, even minor growth can lead to visual deterioration or complete blindness[4,5]. Symptomatic tumors are classically treated by microsurgical and/or endoscopic resection[6] to ensure adequate, immediate decompression of the optic apparatus[7-9]. Maximal safe resection is the primary goal. This approach aims for a gross total resection to fully decompress the optic apparatus and reduce the risk of tumor recurrence but prioritizes preservation of visual function over complete resection[10-12]. Despite prioritizing functional preservation, microsurgery carries a risk of postoperative deficit between 2.6-13.7%[6,13].

Stereotactic radiosurgery (SRS) is a valuable therapeutic option for the treatment of small to medium sized, newly diagnosed or recurrent intracranial meningiomas[14-18], particularly those involving the skull-base[19]. One of the most radio-sensitive structures of the skull base and frequent obstacle for SRS is the optic nerve (ON)/optic apparatus (OA)[20]. Prior studies on OA dose tolerance suggest a cut-off between 8-12 Gy as the maximal delivered dose, above which the risk for radiation induced optic neuropathy (RION) becomes unacceptably high[21,22]. Due to this risk of RION, perioptic meningiomas, especially those in direct contact with the OA, often cannot be treated by single fraction since they do not have the separation needed to limit the dose to the OA. Hence, these cases need alternative therapeutic approaches.

Recently, the role of hypofractionated radiosurgery (hfRS) regimens has been rapidly expanding, especially for perioptic lesions. HfRS allows safer treatment of tumors near radiosensitive structures and for larger tumor volumes. For perioptic meningiomas, hfRS appears to have similar rates of high local tumor control as single fraction SRS, while potentially decreasing the risk of RION[23,24]. These techniques and fractionation schemes are derived from the linear quadratic model and its application to SRS and RT[25]. Tumor control must be weighed against the risk of RION, as both tumor progression and RION can lead to visual decline.

Here, we performed a systematic review and meta-analysis of the current knowledge related to the perioptic meningiomas, treated both with single fraction SRS and hfRS. We review local tumor control as well as visual outcomes.

Methods

Study guidelines

The study was performed in accordance with the published Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[26].

Eligibility criteria

Inclusion criteria: peer-reviewed articles of intracranial perioptic meningiomas treated either with single fraction or hypofractionated SRS, independently of the device; single center, multi-center, retrospective and prospective clinical studies or case series were included. Perioptic location was defined as intracranial meningiomas that were less than or equal to 3 mm from the optic nerve, optic chiasm, or optic tract.

Exclusion criteria: case reports, unpublished series, and series not published in English. Meningiomas of the orbit, optic nerve sheath within the optic canal, or series with a mixture of perioptic and other locations were excluded. Case series involving treatment of multiple pathologies were excluded if they did not report meningioma specific data separately from the other pathologies. If dose to the optic apparatus was not reported, the series was excluded.

Search strategy

Our information sources were Medline, Pubmed, Embase, Scopus and Web of Science databases. The following MESH terms or combination of those were used: “perioptic”, “anterior optic pathways”, “radiosurgery”, “stereotactic radiosurgery”, “meningioma”, “hypofractionated”. Two independent reviewers (DP, CT) have screened the content of all articles and abstracts published between 1968 and December 8^{-th} 2022. The corresponding PRISMA diagram can be found in figure 1.

Articles selection

Six papers met inclusion criteria, of whom 2 were mainly focusing on results after single fraction SRS[27,28] and 4 on hfRS[23,24,29,30]. We extracted clinical data related to patient demographics, prior treatments with surgery or radiation, tumor size, and dosimetric data (tables 1 and 2).

Primary and secondary outcome

Primary outcome was tumor control, defined as stable to decreased size of the tumor on follow up imaging. Secondary outcome was visual function after SRS or hfRS (table 3). The outcomes were sometimes reported using heterogenous scales, including Radiation Therapy Oncology Group central nervous system criteria[31] and Common Terminology Criteria of adverse events (CTCAE)[32].

Statistical analysis

OpenMeta (Analyst) from the Agency for Healthcare Research and Quality was used for statistical analysis. A binary random-effects model (DerSimonian-Laird method) was chosen. Weighted summary rates were identified, testing for heterogeneity was completed, and pooled estimates were attained for all the outcomes of interest.

Results

Single fraction radiosurgery

The funnel plots can be seen in figure 2.

The overall rate of prior radiation was 2.5% (range 1.4-3.6, standard error 0.006, $p<0.001$; Figure 2, a). The overall rate of prior surgery was 35.1% (range 31.7-38.5, standard error 0.017, $p<0.001$; Figure 2, b).

The overall rate of tumor control was 93.4% (range 89.7-97, standard error 0.019, $p<0.001$; Figure 2, c). The overall rate of tumor progression was 8.1% (range 6.2-10.1, standard error 0.01, $p<0.001$; Figure 2, d).

The overall rate of visual stability was 90.4% (range 88.1-92.7, standard error 0.012, $p<0.001$; Figure 2, e). Among those, the overall rate of visual improvement was 29.4% (range 25.8-33, standard error 0.018, $p<0.001$; Figure 2, f). The overall rate of visual decline was 9.6% (range 7.3-11.9, standard error 0.012, $p<0.001$; Figure 2, g).

Hypofractionated radiosurgery

The funnel plots can be seen in figure 3.

The overall rate of prior radiation was 5.6% (range 3.2-14.4, $I^2 = 80.52\%$, p heterogeneity= 0.02, $p=0.2$; Figure 3, a). The overall rate of prior surgery was 54.4% (range 40.9-67.8, $I^2 = 87.4\%$, p heterogeneity <0.001, $p<0.001$; Figure 3, b).

The overall rate of tumor control was 95.6% (range 92.1-99.1, $I^2 = 73.47\%$, p heterogeneity= 0.01, $p<0.001$; Figure 3, c). The overall rate of tumor progression was 4.4% (range 0.9-7.9, $I^2 = 73.47\%$, p heterogeneity= 0.01, $p=0.01$; Figure 3, d).

The overall rate of visual stability was 94.9% (range 90.9-98.9, I^2 = 77.05%, p heterogeneity= 0.004, p<0.001; Figure 3, e). Among those, the overall rate of visual improvement was 22.7% (range 5.0-40.3, I^2 = 95.94%, p heterogeneity< 0.001, p=0.01; Figure 3, f). The overall rate of visual decline was 5.1% (range 1.1-9.1, I^2 = 77.05%, p heterogeneity= 0.004, p=0.013; Figure 3, g).

Discussion

Our systematic review and meta-analysis show that for single fraction SRS, the overall rate of tumor control was 93.4% and of tumor progression was 8.1%. The overall rate of visual stability (patients who either improved or had no change in visual status after treatment) was 90.4%, with visual improvement of 29.4% and visual decline of 9.6%. For hfRS, the overall rate of tumor control was 95.6% and tumor progression was 4.4%. The overall rate of visual stability was 94.9%, with visual improvement of 22.7% and visual decline of 5.1%.

From a radiobiological point of view, meningiomas can be considered on the spectrum of late-responding normal tissue to normal brain tissue[33]. Hence, a high dose per fraction might improve local control[34]. Moreover, shorter treatment duration is associated with higher biologically effective dose (BED), leading to further improvement in local control[35-38]. Radiation-induced optic neuropathy (RION) may occur due to vascular occlusion, damage to the blood-brain barrier, free radical injury, DNA damage, demyelination[39]. The mechanism of damage may be different based on dosage, as cell response to different irradiation doses is not always the same[40,41].

Radiosurgery is a minimally invasive management approach for patients with skull-base meningiomas, particularly useful for lesions intimately involved with critical neurovascular structures, those that are difficult to access surgically, or in frail patients who are poor microsurgical candidates[42]. Commonly used dose regimens for WHO grade I, II and III meningiomas treated with single fraction SRS are 12-16 Gy, 16-20 Gy, and 18-24 Gy, respectively[43,44], but even with increased treatment dose, the long-term tumor control achieved is worse with increased WHO grade. Historical data[2] suggested that the maximal dose to the optic pathways should be kept below 8 Gy[45]. However, recent series suggested that such dose might be safer up to 12 Gy[20], with minimal risk for RION. Of note, RION is not necessarily immediate and can occur months and/or years after SRS, manifesting as painless visual loss, changes in color vision, and pupillary abnormalities[46]. Given that the acceptable dose limit to the optic apparatus is approximately 10-12 Gy[20-22], the gradients that

can be achieved with single-session photon SRS are usually challenging for the delivery of an adequate dose of radiation to the tumor while also keeping harmless doses to the optic nerve. Hence, perioptic meningiomas treated with single fraction SRS may receive smaller doses than typically used for meningiomas to accommodate this 10-12 Gy dose limit and reduce the risk of RION. This may lead to suboptimal tumor control, and visual deterioration may occur due to tumor progression.

Hypofractionated RS could be the best solution for perioptic meningiomas, balancing the risk of RION with reliable tumor control. The emergence of frameless, image-guided radiosurgery techniques[47] allows multisession stereotactic treatments, usually 2-5 fractions of 4-10 Gy each, comparable in terms of radiobiological effect to single fraction SRS, with lower toxicity to the optic apparatus[48]. Hypofractionation enables better chance of preservation of surrounding normal tissues and excellent tumor control[49,50]. The most used fractionation scheme in the analyzed data was 25 Gy in 5 fractions. Significant variability exists in the literature and there is currently no gold standard hypofractionated regimen.

The results of the present meta-analysis are in agreement with recent studies from Speckter et al., suggesting that there might be a benefit for hypofractionation with perioptic lesions, not only in benign but also in malignant tumors, due to the very low alpha/beta ratio of the optic system which is considered to be around 1.03[51].

Although fractionated external beam radiation therapy (EBRT) is a common treatment approach for perioptic meningiomas, the reported tumor controls rates are only 84%[52,53]. Such rates are not as good as SRS and complications are still possible[54]. The Quantec Project demonstrated that for conventional fractioned radiotherapy with fractionations of 1.8 to 2 Gy, the risk of RION increases (3-7%) when treatment dose is 55-60 Gy and goes even higher for doses above 60 Gy (7 – 20%)[55]. Another drawback of fractionated radiotherapy is the risk of neurocognitive dysfunction, including in patients treated for meningiomas[56].

Our meta-analysis has several inherent limitations. First, the treatment approaches and follow-up algorithm might be different from one intuition to another. Second, the timing of SRS or hfRS might be diverse. Third, except for one study[24], all reviewed retrospective data. In addition, prior radiotherapy and prior surgery might have influenced the reported outcomes. Another limitation comes from the histological grading, either unknown (as diagnosis based on MRI) or including a few rare cases of WHO grade II meningiomas (which have a different response to radiation in terms of tumor control). Lastly, treatment using single fraction SRS only included two studies, while hfRS included 4 studies.

Conclusions

For single fraction SRS, the overall rate of tumor control was 93.4% and tumor progression of 8.1%. The overall rate of visual stability was 90.4% and visual decline was 9.6%. For hfRS, the overall rate of tumor control was 95.6% with a small rate of tumor progression of 4.4%; the overall rate of visual stability was 94.9% and visual decline was 5.1%.

The authors of the present meta-analysis recommend prescribing at least 12 Gy for WHO I meningioma, while keeping the dose to the OA less than 10 Gy. Hypofractionated regimens rather than single fraction should be considered if the distance between the tumor and the OA and/or the treatment gradient cannot match these dosage recommendations.

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Figure and Table Legends

Table 1: Basic demographic data

Table 2 : Dosimetric data

Table 3: Visual outcomes and tumor control

Figure 1: PRISMA flowchart for article selection

Figure 2: Tumor control and visual status for single fraction SRS

Figure 3: Tumor control and visual status for hypofractionated radiosurgery

Figure 1. PRISMA flowchart for article selection

PRISMA flow diagram for new systematic reviews

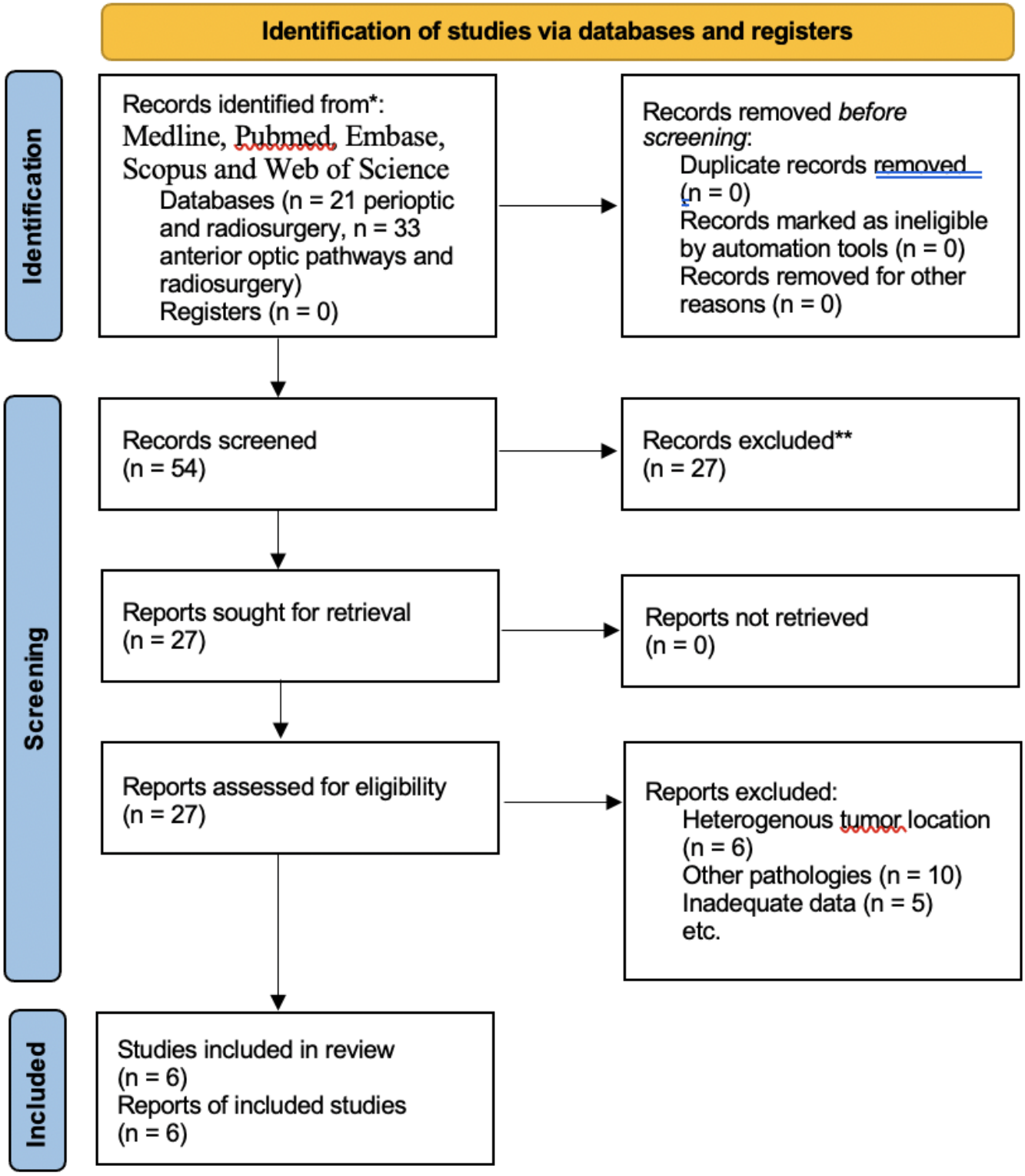
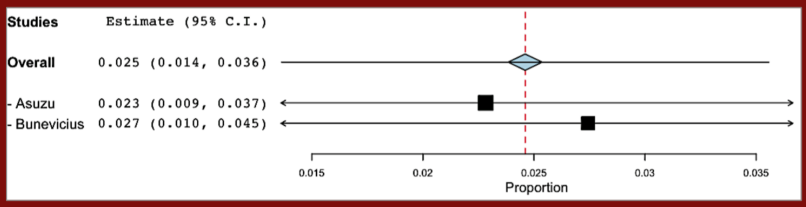


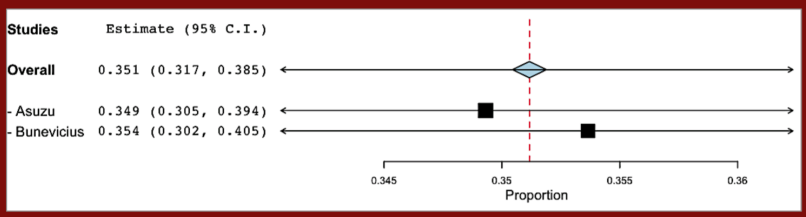
Figure 2. Tumor control and visual status for single fraction SRS

Figure 2: Single fraction SRS

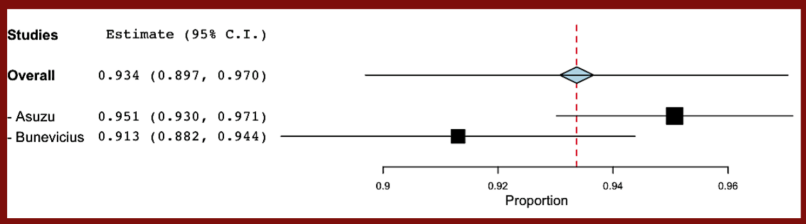
a. Prior radiation



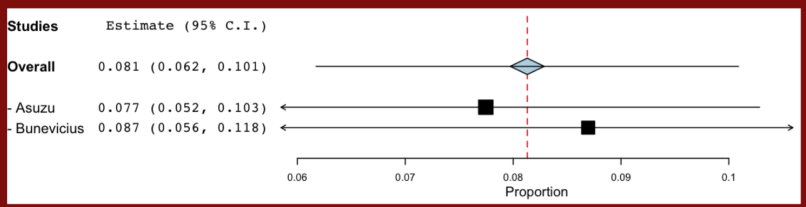
b. Prior surgery



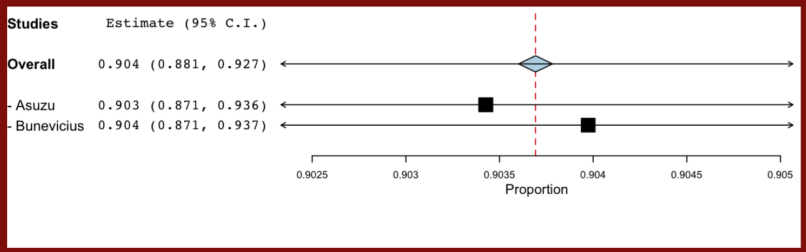
c. Tumor control (stability or decrease)



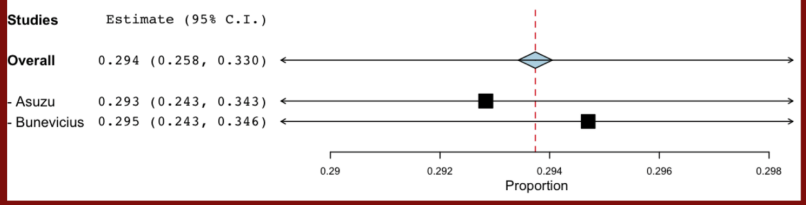
d. Tumor progression



e. Visual stability or improvement



f. Visual improvement



g. Visual decline

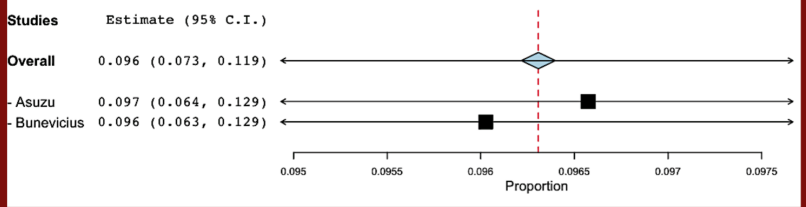
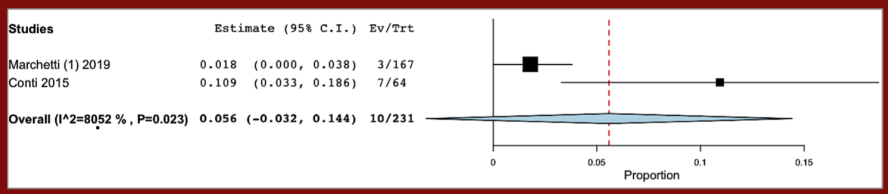


Figure 3. Tumor control and visual status for hypofractionated radiosurgery

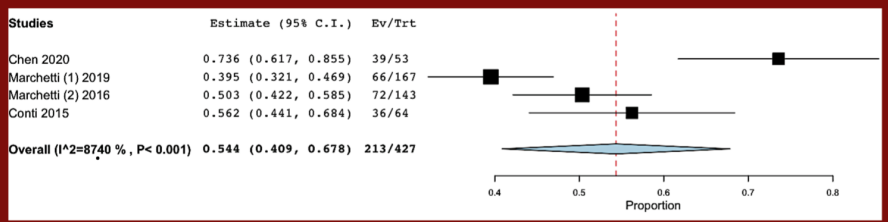
Figure 3

Figure 3: Hypofractionated radiosurgery

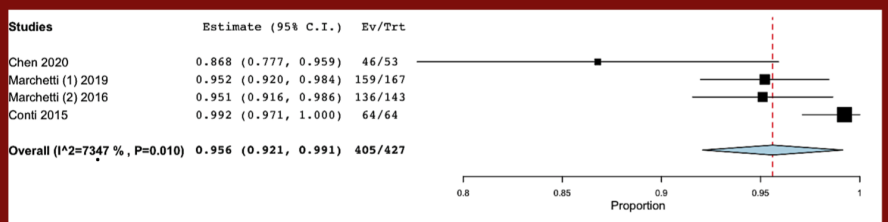
a. Prior radiation



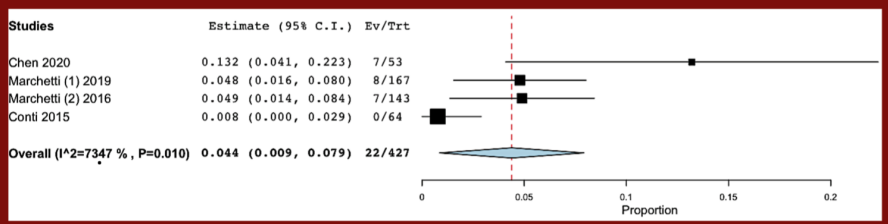
b. Prior surgery



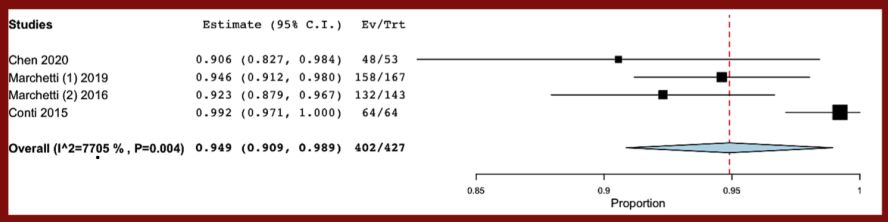
c. Tumor control (stability or decrease)



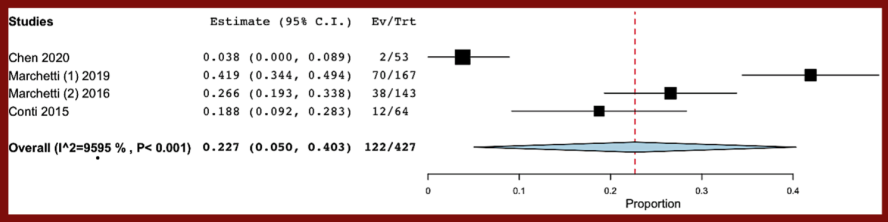
d. Tumor progression



e. Visual stability or improvement



f. Visual improvement



g. Visual decline

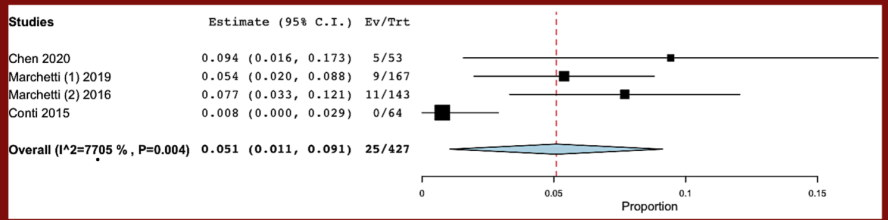


Table 1: Basic demographic data

	No	Follow-up	Age	Sex (F:M)	Prior surgery	Prior radiation	Symptom duration (months)	Location	KPS	WHO grade
Asuzu et al., 2022[27]	328	Median 56	Median 50.4+/-12.1	F (78.7%)	116/328, 35.4%	2.8%	20.1+/-30.8	Tuberculum (107/328, 32.6%) Clinoid (126/328, 38.4%) Cavernous sinus invasion (105/326, 32%)	85.7+/-14.4	
Bunevicius et al., 2021[28]	438	Median 55.6 (3.15-239)	Median 51 (15-83)	339:99	153/438 (35%)	10/438 (2%)	Median 10 (0-240)	Tuberculum: 136/438 (31%) Clinoid: 191/438 (44%) Sphenoid wing: 31/438 (7%)	Median 90 (50-100)	126/438 124/126 (WHO I) 2/126 (WHO II)
Chen et al., 2020[29]	53	Median 52 (6.8-156.3)	Median 41 (18 – 92)	35:18	39/53 (73.6%)	-	-	-	-	-
Marchetti et al., 2019[23]	167	Median 51 (36-129)	Median 53 (18-80)	134:33	66/167	3/167		Orbital: 36/167 Cavernous sinus: 54/167		167/167 WHO I
Marchetti et al., 2016[30]	143	Median 32 (12-113)	Median 52 (18-80)	114:29	72/143					72/143 WHO I
Conti et al., 2015[24]	64	Retrospective: Mean 60 +/- 12 (median 57.5) Prospective: Mean 17+/-10 (median 15)	Median 62 (23-84)	35/29	36/64	7/64	-	-	-	-

Table 2 : Dosimetric data

	Interval (surgery-SRS)	Device	Alpha/beta	Dose	Isodose	Single fraction	BED	Target volume	OAR distance	OAR doses	OAR BED
Asuzu et al., 2022[27]	-	GK	3			93%		0.174+/- 1.482 mL		mean maximal ON : 8.7 OC : 7.7 OT : 6.2	
Bunevicius et al., 2021[28]	Median 9 (1-246)	GK		Median 12 (7-18)		405/438 (93%)	Median 60 (23.3-101.3)	Median 8.01 (0.130-57.3) mL	Median 0 (0-2.3) 328/438 (75%) in contact	OA: median 8.5 (2-23) Maximal> 16 Gy-> hypofractionnation	Maximal 36 (5.3-101.3)
Chen et al., 2020[29]	-	Novalis, Brainscan, Mask	-	Mean: 6.8 (6-7) per fraction treated with 3 consecutive fractions		0/53	-	Median 6.95 Mean 9.69 (0.3-58.23)	Median 0 (0-3)	OA: median 6.3 mean 6.1 (3.64-7.3)	-
Marchetti et al., 2019[23]	-	Cyberknife	-	25 Gy 5 x 5 Gy 5 consecutive fractions	Median 79% (67-86)	0/167	-	Median 7.3 (0.1-76.8)	-	ON: median 23 (2.8-32.5) OC: median 20.2 (2-31.6)	-
Marchetti et al., 2016[30]	-	Cyberknife	-	3 fractions: Mean 17 (15-21) 4 fractions: 16-20 Gy 5 fractions: 25 Gy (20-25)	Median 80% (65-86)	0/143	-	Median 8 mL (0.1-126.3)	-	ON: median 25.5 Gy (2.8-34) OC: median 21.4 Gy (2.5-34)	-
Conti et al., 2015[24]		Cyberknife	2	Retrospective: Median 23 Gy 2-5 fractions 18 Gy in 2 18-21 Gy in 3 20-22 Gy in 4 23-25 Gy in 5 fractions Prospective: Median 25 Gy Mean 5 (3-15) 18 Gy in 2 18-21 Gy in 3 20-22 Gy in 4 25 Gy in 5 27.5 Gy in 6 30 Gy in 9 34 Gy in 10 40 Gy in 15 fractions	Retrospective:- Prospective: Median 75% (62-82)		Retrospective: Mean: 82.8 Gy_2 (median 87.5; 72-102) Prospective: Mean 91.3 Gy_2 (median 87.5, 60-120)	Retrospective: Median 4.95 mL (0.3-18.8) Prospective: Median 7.5 mL (1.2-44.1)		Retrospective: Maximal accepted dose to the: ON: 10 Gy in 2, 15 in 3, 20 in 4, 25 in 5 fractions Prospective: 10 Gy in 2 15 Gy in 3 20 Gy in 4 25 Gy in 5 30 Gy in 9 34 Gy in 10 40 Gy in 15	

Table 3: Visual outcomes and tumor control

	Visual stability/improved	Visual decline	Visual decline timing	Visual decline (statistics)	Tumor control detail	Tumor control	Tumor control (statistics)	Tumor progression
Asuzu et al., 2022[27]	273/302 (90.4%) Improvement: 89/302 (29.5%)	29/302 (9.6%) 12/29 (41.4%) tumor progression Blind: 4/302 (1.3)	Median 55 (0.2-193)	Lower pre-SRS KPS (p<0.01)	Stable <20% Regressed >20% decrease Progressed >=20% increase	294/322 (91.3%) Both stability and regression	preSRS symptom duration (p=0.02)	28/322 (8.7%) 13/28 (46%) repeat SRS
Bunevicius et al., 2021[28]	290/321 No change 196/321 (61%) Improved: 94/321 (29%) Time: 54.6 (3-151.7)	31/321 (10%) Actuarial rate: 5y: 9% 10y: 21% Blind: 4/321 (1%)	Median 52 months (0.2-133)	Maximal dose >10 Gy OA (p= 0.03) Tumor progression (p< 0.001)	Stable <20% Regressed >20% decrease Progressed >=20% increase	405/426 Actuarial rate: 5y: 96% 10y: 89%	Prescription dose >=12 Gy (p= 0.003) Single fraction (p= 0.002) Single: BED>=60 Gy (p= 0.005) Previous RTH (0.004) Lower risk	33/426 (8%) At median interval of 94 months (12-233)
Chen et al., 2020[29]	48/53 (90.6%) No change 46/53 (86.8%) Improved 2/53 (3.8%)	5/53 (9.4%) 3: tumor progression 2: cataracts 0: RION	Median 5 years (2-8 years)	-	Stable <20% Regressed >20% decrease Progressed >=20% increase	46/53 (86.8%) 1y: 98.1% 3y: 92.4% 5y: 89.3% 8y: 86.8% 13y: 86.8%	-	7/53 (13.2%)
Marchetti et al., 2019[23]	Improved: 70/167 (42%) of those with pre-deficit	9/164 (5.5%) 3/164 worse with tumor progression 6/164 (3.7%) without progression of the tumor		Preexisting deficit (p= 0.02) Tumor progression (p= 0.01)	CR: reduction of minimum 2 mm on 2 main axes on 2 consecutive MR scan PD: any increase in tumor size along any dimensions confirmed on 2 consecutive MR scans	159/167 (95.2%) Decrease 30/167 (18%) 3y: 98% 5y: 94% 8y: 90%		8/167 (4.8%)
Marchetti et al., 2016[30]	Improved: 38/143 (36%)	Worsened: 7.4% (5.1% when excluding patients with progressive disease) After a mean latency period of 25.5 (1-90) Only 1/143 with normal pre-SRS function had a visual worsening		Tumor progression (p< 0.01)		3y: 100% 5y: 93% 8y: 90%		7/143 (4.9%)
Conti et al., 2015[24]	Retrospective: Improved: 5/25 (20%) Prospective: 7/39 (18%)	Retrospective: 0/25 Prospective: 0/39				Retrospective: 25/25		