Long-Term Outcomes After Linac Radiosurgery for Benign Meningiomas

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Original Article

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Abstract

Aims: Although several studies on outcomes following stereotactic radiosurgery (SRS) for benign meningiomas have been reported, Linac-based SRS outcomes have not been as widely evaluated. The aim of this retrospective institutional single-centre study was to determine long-term outcomes of Linac-based SRS for benign intracranial meningiomas.
Materials and methods: From July 1996 to May 2011, 60 patients with 69 benign meningiomas were included. All patients were treated with single-fraction Linac-based SRS with four to five non-coplanar arcs, dynamic or not. The marginal dose prescribed for the periphery was 16 Gy. Prognostic factors associated with local control, progression-free survival (PFS) and overall survival were tested.
Results: The median follow-up was 128 months. No patient was lost to follow-up. The values observed at 1, 5 and 10 years were, respectively, 100%, 98.4% and 92.6% for local control, 94.9%, 93.2% and 78% for PFS and 100%, 94.7% and 92.7% for overall survival. In univariate analysis, local control after SRS was significantly higher for skull base and parasagittal meningiomas compared with convexity meningiomas ($P = 0.031$). Multivariate analyses showed significantly longer PFS when the minimum dose delivered to the tumour was greater than 10 Gy ($P = 0.0082$). No grade 5 toxicity was reported.
Conclusion: Our long-term results from a large sample size of benign meningiomas treated with Linac-based SRS confirmed excellent local control (>90%) and good safety, which is in line with published studies on Gamma Knife surgery. Above all, we showed significantly poorer PFS if the minimum dose to the tumour was under 10 Gy.

Key words: Efficacy, linac, meningiomas, radiosurgery, toxicity

Introduction (A head)

Meningiomas are the most common primary intracranial tumours, accounting for 30–44% of cases [1]. The 15 subtypes of tumour of meningothelial cells fall into three grades: benign or grade I, unpredictable, atypical or grade II meningioma and malignant, anaplasic or grade III

meningioma. In the current pathological classification, about 70–80% of all meningiomas are benign [2]. Despite their slow-growing and non-infiltrating natural history, they can become quite large, resulting in seizures or neurological deficits from mass effect syndrome or cranial nerve compression, depending on their location. Surgery remains a cornerstone of benign meningioma treatment, aiming to minimise functional risks, although the treatment may change according to tumour location, size, growth speed and grading, and also according to patient wishes and medical facilities.

Stereotactic radiosurgery (SRS) has been used for more than 30 years in the treatment of patients with intracranial meningiomas as an alternative to surgical resection [3]. Primary SRS for benign meningiomas provides excellent local control, generally >90% at 5–10 years. Santacroce *et al.* [4] reported 5- and 10-year progression-free survival (PFS) of 95.2% and 88.6%, respectively, with very low morbidity in more than 3700 meningiomas treated with Gamma Knife SRS. Pollock *et al.* [5] found no significant difference between SRS and gross tumour complete resection (GTR) for 7-year PFS (>95% in both cases). Adjuvant SRS is not needed after GTR of a benign meningioma, but SRS after subtotal resection could be as efficient as GTR [6–8]. SRS in case of recurrence is considered as a second-line treatment. The National Comprehensive Cancer Network recommends that recurrent meningiomas should be resected if possible, and adjuvant radiotherapy should be delivered.

Although several studies on SRS outcomes for benign meningiomas have been reported, Linac-based SRS outcomes for benign meningiomas have not been as widely evaluated. The aim of this retrospective institutional single-centre study was to determine the long-term outcomes of Linac-based SRS for benign intracranial meningiomas.

Materials and Methods (A head)

Population and Stereotactic Radiosurgery Characteristics (B Head)

Between July 1996 and May 2011, 60 patients treated consecutively with Linac-based SRS for 69 benign meningiomas were included. Inclusion was discontinued in May 2011 for the assessment of long-term outcomes for all treated patients. *De novo* meningiomas, residual meningiomas after subtotal resection and recurrent meningiomas were included in the analysis. Meningiomas were deemed benign if classified as World Health Organization grade I after anatomopathological examination or on the basis of clinical evolution and imagery characteristics. Patients with type II neurofibromatosis were excluded. Meningiomas with a diameter greater than 3 cm (i.e. volume ≤15 mm^3) were treated with fractionated radiotherapy and, thus, were not included in this study. In the first years (from 1996 to 2000), we used a 10 mm margin as an exclusion criterion for optic nerves and chiasm and 5 mm for brainstem. These margins were than reduced to 5 and 0 mm for optic nerves/chiasm and brainstem, respectively.

Between July 1996 and January 2011, SRS was carried out using a Varian® Clinac 2100C (Varian Medical Systems, Palo Alto, CA, USA) Linac, with cylindrical collimators (diameters: 6–24 mm) from 1996 to 2000 and with an additional micro multileaf collimator m3 Brainlab® (Brainlab, Feldkirchen, Germany) from 2000 to 2011. At this time, a Leksell stereotactic head frame was used. From January 2011, SRS was carried out with a Novalis Tx® (Varian Medical Systems) Linac with an integrated ExacTrac X-ray 6D system ®(Brainlab), which enables pretreatment positioning. A frameless mask without invasive procedure was used. Dose distributions were carried out with four to five non-coplanar conformal arcs from July 1996 to January 2002 and with four to five non-coplanar dynamic arcs after January 2002. Brainlab® TPS were used: BrainScan® and IplanRT®, respectively, before and after January 2011.

The gross tumour volume (GTV) was identified on the basis of 0.9 mm gadolinium-enhanced axial magnetic resonance imagery (MRI) fused with high-resolution (1.25 mm slice thickness) computed tomography images. All 69 meningiomas were treated with single-fraction SRS. No margin was added to the GTV to create the planning target volume (PTV). Concerning the prescribed dose, the median coverage prescribed dose was 16 Gy, with 18 Gy to the isocentre. Accepted coverage limits were that 95% of the PTV or more should receive at least the coverage prescribed dose (16 Gy) and 98% of the PTV or more should receive at least 14 Gy. Case by case, in case of nearby organs at risk (optic nerves, chiasm, brainstem or eloquent areas), the coverage prescribed dose was lowered so that 98% of the PTV or more should receive at least 12 Gy. So, the marginal dose sometimes had to be reduced, as shown in Table 1. All treatment schedules were reviewed and approved by the treating radiation oncologist, neurosurgeon and physician.

Table 1 here

Follow-up (B head)

Follow-up included MRI or computed tomography and a clinical examination at 6, 12, 24, 36, 60 months and then every 2 years after SRS. A complete response was defined as the disappearance of the meningioma. A partial response was defined as tumour shrinkage greater than 10% in at least one of the meningioma diameters without any local failure criteria. Local failure was defined as tumour enlargement greater than 10% in at least one of the meningioma diameters. Distant failure was defined as a new meningioma outside the initial SRS area appearing during follow-up on imagery. Stable meningioma was defined as neither sufficient shrinkage to qualify for a partial response nor sufficient enlargement to qualify for local failure. The cause of death was determined for all deceased patients. Clinical treatment-related toxicities were defined as new neurological deficits occurring after SRS. Clinical radiation-related toxicities were classified as temporary when they resolved spontaneously or after a short course of medical therapy, such as corticosteroids, and as permanent if they did not resolve. Radiological treatment-related toxicities, such as radionecrosis, oedema or haemorrhage, were determined on the basis of histological findings (among patients who underwent surgical resection) or were assessed on contrast-enhanced MRI and/or dynamic susceptibility weighted contrast-enhanced perfusion MRI.

Statistical Analysis (B Head)

Local control, PFS and overall survival were calculated using the Kaplan–Meier method. The time to local failure was defined as the period of time from SRS to the date of radiographic evidence of local failure at the treated site. The time to disease progression was defined as the period of time from the date of SRS to the date of radiographic evidence of a new meningioma outside the SRS field or the date of radiographic evidence of local failure. A comparison of survival curves was conducted using the Log-rank test and the Cox proportional hazards model was carried out to identify prognostic factors associated with local control, PFS and overall survival. A two-sided P value <0.05 was considered significant. The following factors were included in the analysis: tumour volume, SRS minimum dose, SRS maximum dose, SRS isocentre dose, SRS marginal dose, collimator type (cylindrical versus micro-multileaf), SRS indication, V100% (percentage of tumour volume receiving 100% of the prescribed marginal dose) and tumour location. Prognostic factors associated with a P value ≤ 0.1 in the univariate analysis were included in the multivariate analysis.

Results (A head)

Patient Characteristics and Dosimetric Data (B head)

All characteristics of the 60 patients at the time of SRS are reported in Table 1. The overall gender ratio was 5:1 (female:male). Most SRS procedures were conducted on *de novo* meningiomas (77%) and on growing or symptomatic meningiomas (93%). Meningioma localisations were equally distributed across the convexity, skull base and parasagittal areas. SRS characteristics are reported in Table 1. The mean tumour volume was 4.4 cm^3 (0.15–17.7 cm^3). The median marginal prescribed dose was 16 Gy. The median minimum dose delivered to the tumour was 12 Gy (6–15.5 Gy). The median follow-up from SRS was 128 months (range 48–247). No patient was lost to follow-up.

Local Control (B Head)

Following SRS, local control at 1, 5 and 10 years was, respectively, 100%, 98.4% (95% confidence interval 91.5–99.7) and 92.6% (95% confidence interval 82–97) (Figure 1). Results of the univariate and multivariate analyses of local control predictive factors are shown in Table 2. In univariate analysis, local control after SRS was significantly greater for skull base and parasagittal meningiomas than for convexity meningiomas ($P = 0.031$). Although not statistically significant, there was a trend towards efficacy of a minimum dose of 10 Gy delivered to the tumour ($P = 0.1$). After SRS, tumour shrinkage for 41 meningiomas (59%) and disease stability for 24 meningiomas (35%) were observed. There was local progression for four meningiomas (6%): three convexity meningiomas and one skull base meningioma. The mean time to recurrence was 64 months.

Figure 1 here
Table 2 here

Progression-free Survival (B head)

Following SRS, PFS at 1, 5 and 10 years was, respectively, 94.9% (95% confidence interval 86–98), 93.2% (95% confidence interval 84–97) and 78% (95% confidence interval 64–87) (Figure 1). The results of the univariate and multivariate analyses are shown in Table 2. In univariate analysis, PFS after SRS was significantly longer for skull base and parasagittal meningiomas than for convexity meningiomas ($P = 0.012$). Multivariate analyses showed a significantly longer PFS when the minimum dose delivered to the tumour was greater than 10 Gy ($P = 0.0082$). Two patients had local meningioma progression, 10 patients had distant progression and two patients had both local and distant meningioma progression.

Overall Survival and Causes of Death (B head)

Following SRS, overall survival at 1, 2, 5 and 10 years was, respectively, 100%, 98.3% (95% confidence interval 91–100), 94.7% (95% confidence interval 85–98) and 92.7% (95% confidence interval 82–97) (Figure 1). The results of the univariate and multivariate analyses are shown in Table 2. No statistically significant prognostic factor was found. During follow-up, we identified three deaths; 57 patients were still alive at the last follow-up. One patient may have died from both local and distant meningioma progression, but had concomitant melanoma brain metastases; the two other patients died from extra-neurological causes. No grade 5 toxicity was reported.

Clinical Follow-up and Toxicities (B head)

At the time of Linac-based SRS, 57% (n = 34/60) of our patients were symptomatic. Symptoms improved in 21 cases (62%), were unchanged in 10 cases (29%) and worsened in three cases (9%) after SRS. Overall, we found toxicities for six SRS procedures (9%). They are reported in Table 3. The median time to toxicity was 15 months (3–33). Five SRS procedures (7%) led to transient toxicities and only one SRS (2%) led to permanent toxicity. Clinical toxicity was associated with radiological toxicity (oedema) except for one meningioma.

Table 3 here

Concerning the only one permanent toxicity, it occurred in a patient with a 22 mm diameter parasagittal meningioma and a pre-existing oedema. The marginal prescribed dose was 16 Gy and 96% of the PTV received at least 16 Gy. The maximum received dose was 17.6 Gy. This SRS treatment was responsible for a permanent moderate oedema that induced permanent motor disability, despite the use of corticosteroids.

Discussion (A head)

To our knowledge, the present study is one of the first to date to report long-term outcomes, with a median follow-up of 128 months of a single-centre cohort of 69 meningiomas treated with Linac-based SRS. The results found in this study are consistent with previous large published studies on Gamma Knife SRS, which reported local control rates over 90% at 5 and 10 years with low morbidity [4,9–12]. The few Linac-based SRS results for meningiomas are reported in Table 4. Our major finding is that convexity locations for benign meningiomas were statistically predictive of poorer local control and shorter PFS after SRS. We also highlighted the fact that a minimum dose <10 Gy was predictive of a shorter PFS.

Table 4 here

We found 10-year local control and PFS of 92.6% and 78%, respectively, which are in agreement with previous published studies, between 87 and 95% and 74 and 80%, respectively [4,10,13–15]. Three predictive parameters of local control or PFS can be mentioned: location, volume and marginal received dose. Concerning location, the tumour location in our study was statistically predictive of local control and PFS. In univariate analysis, convexity meningiomas were significantly associated with poorer local control and PFS than parasagittal or skull base meningiomas. Similarly, Santacroce *et al.* [4] showed better local control rates for skull base meningiomas versus convexity meningiomas, with a 2.07 hazard ratio difference (P < 0.001). There may be some explanations for this: non-benign meningiomas are more commonly reported in the convexity or parasagittal regions, and benign convexity meningiomas could more frequently become non-benign meningioma [8]; alternatively, the delineation of convexity tumours may be more difficult (meningeal spread). In the same analysis, postoperative SRS was associated with poorer PFS than primary SRS (P = 0.015), which is also consistent with previous reports [4,15]. In fact, postoperative disease is harder to define than primary disease. Treating postoperative disease often means treating a recurrent disease, which is more likely to be aggressive. Concerning volume, the tumour volume was not statistically predictive of local control in our study, probably because of the homogeneity and the small size of the meningiomas treated (only five meningiomas larger

than 10 cm^3), whereas cut-offs of 5 and 10 cm^3 are described in the literature [16–19]. Concerning the marginal received dose, the minimum marginal dose commonly recommended until now has been 12 Gy, which equates to $EQ_{2Gy/2}$ 42 Gy [11,14,18,20]. However, the volume to be covered by the marginal dose was not specified in the trials cited. Our results are in favour of a minimum dose (Dmin) < 10 Gy delivered to the tumour, which could reduce local control. All patients treated with a Dmin <10 Gy were mostly treated with cylindrical collimators, with complex shaped meningiomas and [AQ1]close to organs at risk or eloquent areas. Enhancement of PTV coverage while sparing organs at risk has been widely improved in the last few years with the development of modern SRS platforms and micro-multileaf collimators. The Dmin reported here is not often reported in meningioma published series. It might not be the best dosimetric parameter to evaluate the quality of a treatment plan as it represents the dose in one pixel. Reporting, as an example, D98, as recommended in recent ICRU reports, could have been a better dosimetric parameter. However, many patients were treated before 2011 with BrainScan®, which is no longer available in our institution, and D98 could not be reported for these patients.

As far as efficacy is concerned, we noted a clinical improvement in 62% of cases and stability in 29% of cases among patients with symptomatic meningioma. This is consistent with a previous study that reported a clinical improvement rate of 60% and a stability rate of 33% [14]. Our results suggest the possibility of using SRS even for symptomatic meningiomas, while surgical treatment can lead to functional risks. This clinical improvement is probably linked to the shrinkage of 59% and stability of 35% in our study, which is also in agreement with the 59–66% and 28–48%, respectively, found in previous studies [10,11,14].

Finally, our results are also in agreement with previous studies for toxicity. We found 9% transient complications, of which only 2% were permanent. No margin was used here with a Linac-based SRS, [AQ2]which probably enabled to reduce V12Gy delivered to healthy brain parenchyma, without reducing local control. Permanent complications after SRS for meningiomas have been reported in 2–23% of cases with modern radiosurgery techniques [21]. Most reported complications are in the range of 8%, with about 5% being permanent and 3% transient. Deteriorating or *de novo* peritumoral oedemas occur in about 25% of patients undergoing SRS for meningiomas, with a peak period 6–8 months after treatment [22]. A linear association between tumour volume and toxicity has been described in the literature. Tumour volume > 10 cm^3 is often statistically associated with more complications [23,24] and a proportion of 23% complications was found for tumours > 17.5 cm^3 [19]. The other toxicity factor described in studies is tumour location. Zada *et al.* [23] showed that 66% of complications occurred in non-skull base meningiomas, whereas they only amounted to 25% of total tumours. In the same way, Patil *et al.* [22] found parasagittal location to be a risk factor for peritumoral oedema, with 29% symptomatic oedemas compared with 7.5% for other locations. In our study, we observed that toxicities only occurred for tumours with a maximum diameter > 20 mm and for parasagittal locations in half of the cases. The only one permanent toxicity occurred in a patient treated in 2002 for a 22 mm parasagittal meningioma, with pre-existing oedema.

In summary, our long-term results from a large sample size of 69 benign meningiomas treated with Linac-based SRS without patients lost to follow-up confirm published data on Gamma Knife studies. We found considerable efficacy, with 10-year local control > 90% and good safety (9% transient complications of which 2% were permanent) for benign meningiomas treated with Linac-based SRS with a marginal dose to the periphery of 16 Gy.

Conflict of interest

The authors report no conflicts of interest.

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Fig 1. (a) Probability of local control after stereotactic radiosurgery (SRS) for the 69 benign meningiomas, (b) probability of progression-free survival for the 60 patients receiving SRS for 69 meningiomas, (c) probability of overall survival for the 60 patients receiving SRS for 69 meningiomas.

Table 1
Patient characteristics

Characteristics	Number (%)
Total patients	60
Total meningiomas	69
Gender	
Male	9 (15)
Female	51 (85)
Age (years)	
Median	56
Range	27–76
KPS	
≤70	7 (11)
80	9 (14)
90–100	48 (75)
Tumour location	
Convexity	22 (30)
Skull base	24 (30)
Parasagittal	21 (37)
Intraventricular	2 (3)
Tumour volume	
Median	4.4
Range	0.15–17.7
SRS strategy	
Postoperative residue	2 (3)
Postoperative recurrence	14 (20)
De novo meningioma	53 (77)
SRS indication	
Symptomatic patient	34 (57)
Growing meningioma	43 (62)
Neither symptomatic patient nor growing meningioma	
Collimator type	
Cylindrical	22 (32)
Micro-multileaf	47 (68)
V100%	
<60%	4 (8)
60–85%	16 (34)
85–95%	13 (27)
>95%	15 (31)
Marginal prescribed dose (Gy)	
Median	16
Range	12–16
Maximum received dose (Gy)	

Median	18
Range	14.2–38.5
Minimum received dose (Gy)	
Median	12
Range	6–15.5

KPS, Karnofsky performance status; SRS, stereotactic radiosurgery.

Table 2
Results of univariate and multivariate analyses on local control, progression-free survival, overall survival and toxicity incidence

	Kaplan–Meier univariate analysis (*P*)				Multivariate analysis (*P*)		
	Local control	PFS	Overall survival	Toxicity	Local control	PFS	Overall survival
Age (>75 years)	0.7	0.5	0.1	0.7	–	–	–
Gender	0.9	0.6	0.5	0.6	–	–	–
Tumour volume (≥10 cm^3)	0.5	0.4	0.4	0.2	–	–	–
Minimum dose (≥10 Gy)	0.1	0.07	0.6	0.55	–	0.008	–
Maximum dose (≥20 Gy)	0.97	0.77	0.6	0.15	–	–	–
Marginal dose (≥16 Gy)	0.6	0.08	0.3	0.3	–	0.3	–
V100% (≥ 95%)	0.7	0.88	0.42	0.4	–	–	–
Collimator	0.9	0.9	0.9	0.7	–	–	–
Location (convexity versus others)	0.031	0.012	0.15	0.2	–	0.16	–
SRS indication (primary SRS versus postoperative SRS)	0.2	0.015	0.5	0.8	–	0.41	–

PFS, progression-free survival; SRS, stereotactic radiosurgery.

Table 3
Reported toxicities for the 60 patients receiving stereotactic radiosurgery for 69 meningiomas

	Toxicities	Location	Irradiated volume (cm^3)	Maximum diameter (mm)	Marginal dose (Gy)	Dmax (Gy)	V100% (%)
Case 1 (re-irradiation after oligodendroglioma-fractionated radiotherapy)	Moderate oedema Motor disability (temporary)	Parasagittal	6	27	12	14.3	95
Case 2	Moderate oedema Motor disability (permanent) Epilepsy (temporary)	Parasagittal	3	22	16	17.6	96
Case 3	Mild oedema Epilepsy (temporary)	Parasagittal	8.7	29	16	18.3	95
Case 4	Moderate oedema Motor disability (temporary)	Convexity	–	30	16	37	–
Case 5	Visual disability (temporary)	Cavernous sinus	6.2	20	16	–	–
Case 6	Mild oedema Motor disability (temporary)	Intraventricular	10.4	30	14	16.5	97

Table 4
Outcomes following Linac stereotactic radiosurgery for intracranial meningiomas

Reference	No. patients	Localisation	OMS grading (*n*)	Primary/adjuvant (%)	Median volume (cm^3)	Median marginal dose to tumour (Gy)	Median follow-up (months)	Local control (%)	Complications (%)
Spiegelmann *et al.* [15]	102	CS	I (33) or presumed (69)	68/32	7	13.5	67	98 (5 years)	5
El-Khatib *et al.* [14]	148	All (111 skull base)	I (72) or presumed (76)	51/49	4.7	12	151	93.6 (15 years)	7.8
Shafron *et al.*	70	All	I (32) or presumed (38)	54/46	10	12.7	23	100	2.8
Hadelsberg *et al.*	74	Parasagittal	I (61) or presumed (13)	18/82	6.9	13	49	90.6	6.7
Chuang *et al.*	43	Skull base	I (28) or presumed (14) II (1)	33/67	5.7	16	74.5	89.7 (7 years)	9.3

CS
OMS

Author queries

Table 4: please clarify CS, OMS
Also, please supply reference details for Shafron, Hadelsberg and Chuang

AQ1 'closed' has been changed to 'close'. Is this OK?
AQ2 Please clarify text

Figures

Figure 1: a) probability of local control after SRS for the 69 benign meningiomas, b) probability of progression-free survival for the 60 patients receiving SRS for 69 meningiomas, c) probability of overall survival for the 60 patients receiving SRS for 69 meningiomas