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Long-term stroke risk of single-fraction photon-based stereotactic radiosurgery for meningioma

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ABSTRACT

Objectives: A recent randomized study of fractionated radiation therapy (RT) examining 44 subtotally resected/recurrent benign meningioma patients revealed that at median follow-up of 17.1 years, the risk of stroke following proton-photon RT was 20.5%; the average stroke developed 5.6 years following RT completion (Sanford et al., 2017). This stroke risk is up to 10 times higher than the 2–6% rate expected for the general population of ages 40–79 (Mozaffarian et al., 2015). The stroke rate following single-fraction stereotactic radiosurgery (SRS) has not been previously studied in meningioma patients.

Patients and Methods: A PubMed database search for relevant articles examining SRS for meningioma with minimum mean/median follow-up of six years was undertaken. Stroke rate was assessed either from direct description in manuscripts, or from extrapolating post-SRS complications from reported clinical examinations (i.e. hemiparesis/weakness, pituitary dysfunction following treatment of cavernous sinus lesions). Results were then culled to determine an overall stroke rate.

Results: Fourteen studies met inclusion criteria; 1431 patients received photon-based SRS for meningioma with a sufficient long-term follow-up. Median/mean follow-up ranged from 75 to 144 months. Operative resection prior to SRS occurred in 769/1377 patients (55.8%) for whom surgical history was reported. Twenty-four patients suffered a stroke following SRS, yielding a rate of 1.7%.

Conclusions: The long-term stroke rate following single-fraction photon-based SRS for benign meningioma was 1.7%, more than twelve times lower than for fractionated proton-photon RT and comparable to that expected for the general population. The majority of patients underwent resection prior to SRS. These findings indicate that for patients with benign meningioma desiring to avoid the high stroke risk of fractionated proton-photon RT, SRS has a comparable stroke risk profile to observation. Such findings are pertinent for radiation oncology, neuro-oncology, and neurosurgery management of these patients.

1. Introduction

For subtotally resected benign residual/recurrent meningiomas, the primary modalities include operative re-resection, fractionated stereotactic radiotherapy (RT), stereotactic radiosurgery (SRS), and observation [1–4]. Given the anatomic considerations hindering a gross total resection for these lesions, radiation or observation have been the predominant treatment modalities. A recent randomized study from the Massachusetts General Hospital of proton-photon fractionated RT examining 44 subtotally resected/recurrent benign meningioma patients receiving a minimum total dose of 55.8 Gy revealed that at a median follow-up of 17.1 years, the risk of stroke following RT was 20.5% with the average stroke developing 5.6 years following RT completion [1]. Given that more than one in five subtotally resected/recurrent benign meningioma patients receiving proton-photon RT will develop a stroke based on this data, recent increased advocacy for observation as an alternative despite inferior local control to proton-photon RT has developed [2]. With two-thirds of untreated meningiomas not requiring intervention at more than 46 months of follow-up, the safety of radiation treatment as an alternative to observation is a significant concern [3]. While the stroke risk following proton-photon RT for subtotally resected/residual meningioma has been examined with long-term follow-up, the same cannot be said for patients receiving photon-based SRS. This study was performed to address this issue.

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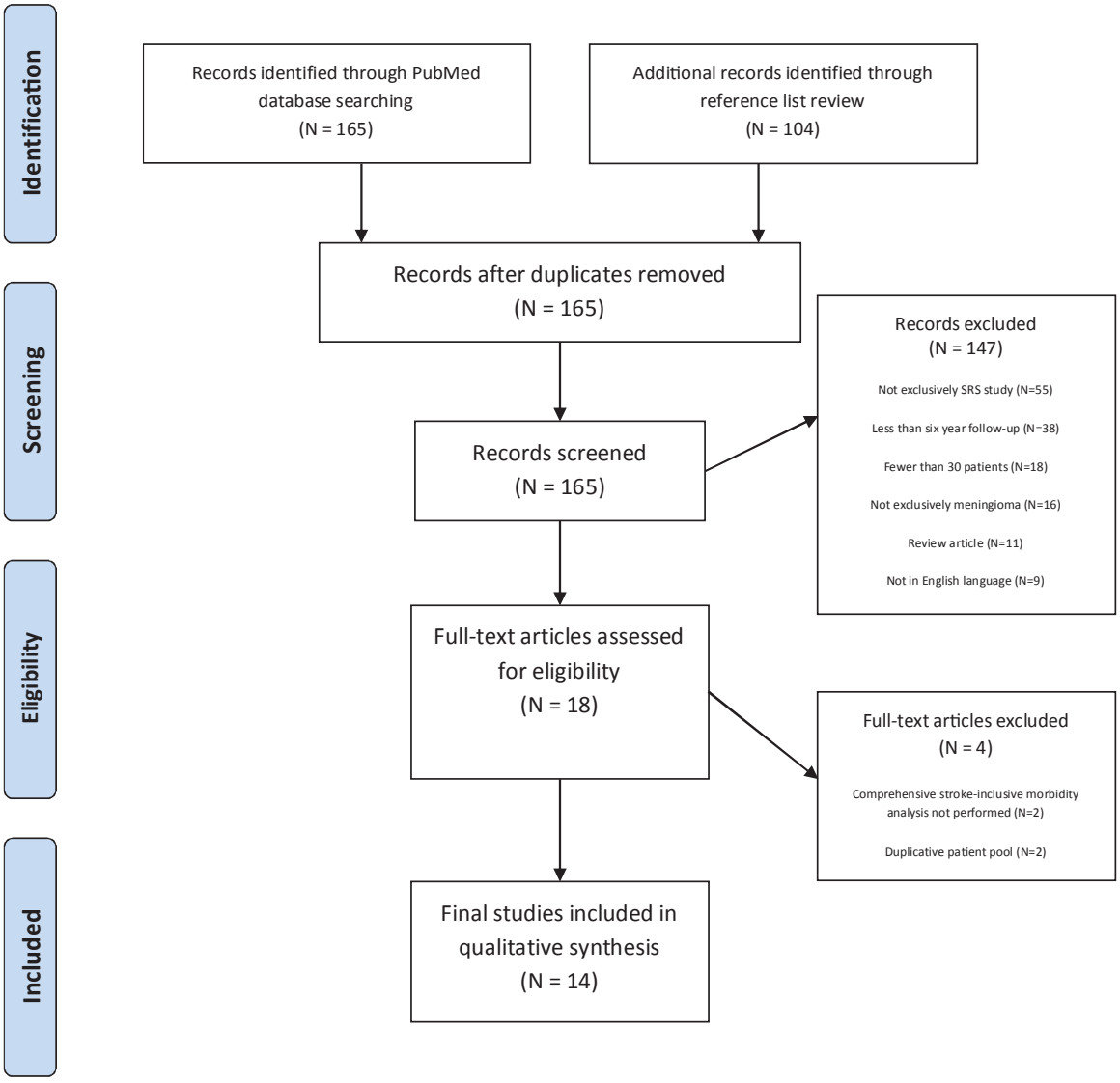

Fig. 1. PRISMA 2009 Flow Diagram.

Table 1
Studies meeting inclusion criteria (minimum clinical follow-up = 72 months) for long-term stroke evaluation following single-fraction stereotactic radiosurgery (SRS); N/A = not available.

Study	Number of patients	Follow-up (months)	Resection prior to SRS	SRS as primary treatment	Clinical evidence of stroke	Stroke incidence	SRS modality
Kobayashi et al. [4]	54	84 (median)	N/A	N/A	0	0%	Gamma Knife
Kreil et al. [6]	200	95 (median)	99	101	1	0.5%	Gamma Knife
Zachenhofer et al. [7]	36	103 (mean)	25	11	1	2.8%	Gamma Knife
Davidson et al. [8]	36	81 (median)	36	0	0	0%	Gamma Knife
Han et al. [9]	63	77 (mean)	20	43	1	1.6%	Gamma Knife
Iwai et al. [10]	108	86 (mean)	83	25	3	2.8%	Gamma Knife
Flannery et al. [11]	168	72 (median)	71	97	0	0%	Gamma Knife
Zada et al. [12]	116	75 (mean)	72	44	0	0%	Gamma Knife
Skeie et al. [13]	100	82 (mean)	60	40	3	3%	Gamma Knife
dos Santos et al. [14]	88	87 (mean)	41	47	0	0%	LINAC
Williams et al. [15]	138	76 (median)	84	54	0	0%	Gamma Knife
Gande et al. [16]	41	76 (median)	20	21	0	0%	Gamma Knife
[17]	148	144 (median)	72	76	0	0%	LINAC
Cohen-Inbar et al. [18]	135	103 (median)	86	49	15	11%	Gamma Knife
Total	1431		**769**	**608**	**24**	**1.7%**	

2. Material and methods

Studies examining single-fraction SRS for meningioma were assessed using an extensive search of the PubMed database and references from relevant articles. Search terms used were “long-term”, “radiosurgery”, and “meningioma”. In order to optimize the accuracy of studies being able to account for post-SRS stroke, only those with mean/median clinical follow-up of at least six years (72 months) were included in the final analysis. This was to ensure these studies exceeded the 5.6 year lag time between completion of RT and stroke development established by Sanford et al. [20]. Additional inclusion criteria were: a) minimum of 30 patients, b) English language, c) exclusive single-fraction SRS patient population, d) exclusive meningioma population, e) comprehensive post-SRS morbidity analysis, and f) non-duplicant patient pool.

Stroke rate was assessed either from being directly described in the manuscript, or extrapolating post-SRS complications from reported clinical examinations (i.e. hemiparesis/weakness, pituitary dysfunction following treatment of cavernous sinus lesions). Results were then culled to determine an overall stroke rate. This study met PRISMA criteria by clearly stating eligibility criteria, information sources, a full electronic search strategy, study selection process, data collection process, data items (including all assumptions/simplifications made), risk of bias in individual studies, and synthesis of results [5].

3. Results

A full PRISMA diagram of included studies is provided in Fig. 1. Fourteen studies examining SRS for meningioma with long-term follow-up met inclusion criteria, yielding a total of 1431 patients as shown in Table 1 [4,6–18]. Twelve of the 14 studies (85.7%) used Gamma Knife for SRS; the remaining two used a linear accelerator (LINAC) (Table 1). Median/mean follow-up ranged from 75 to 144 months. Operative meningioma resection prior to SRS occurred in 769/1377 patients (55.8%) for whom surgical history was reported. Twenty-four patients suffered a stroke following SRS, for a stroke rate of 1.7% (Table 1); the vast majority of these strokes were deduced from reported clinical manifestations, most predominantly hemiparesis not present prior to SRS.

4. Discussion

Traditionally the treatment of benign meningioma, particularly for patients with residual or recurrent disease after surgical resection, has involved radiation therapy over observation. The argument for radiation is that it provides excellent tumor control with morbidity comparable to “doing nothing” (observation). Among radiation therapies, fractionated RT has been traditionally preferred to SRS due to the perceived improved morbidity profile of multiple-fraction versus single-fraction treatment, particularly with regard to radiation-induced brain necrosis, which has been observed in a variety of conditions treated including brain metastases [19].

However, the recent results reported by Sanford et al. provide game-changing information, as their prospective trial indicates a stroke rate of more than 20% following fractionated proton-photon RT for subtotally resected/residual benign meningiomas. With such a high stroke rate, an honest clinical discussion with these patients can no longer presume that the toxicity of RT is comparable to observation. It is known from long-term natural history studies of meningioma that the mean doubling time of meningioma is 21.6 years, and that approximately 70% grow fewer than 1 cubic centimeter/year [20,21]. Therefore, it would be very reasonable, for example, for an otherwise healthy 65 year old woman with a 5 mm residual benign meningioma to choose observation (knowing that she would likely be at least 85 years old by the time it grew to 1 cm) over radiation, using the 20% stroke risk of fractionated RT as the deciding factor for her choice of observation. For such a patient, SRS potentially provides a degree of local tumor control unmatched by observation, but could a physician honestly tell her that the stroke profile of photon-based SRS is more comparable to that of observation versus fractionated proton-photon RT? Providing an answer to this question was the purpose of the current study.

Our results indicate that from the literature of benign meningioma patients with follow-up long enough to detect post-SRS stroke (5.6 years following RT according to Sanford et al., the stroke rate of single-fraction photon-based SRS is 1.7%. This result is more than twelve times less than that for fractionated proton-photon RT, and is comparable to the 2–6% stroke rate expected for the age 40–79 general population according to recent stroke statistics from the American Heart Association [22].

Limitations of this study include its retrospective nature, and the inability to determine the individual follow-up and tumor characteristics of the 24 patients who suffered post-SRS stroke. Furthermore, it is presumed but unclear the degree to which stroke was assessed for clinically post-SRS. It could be argued that regular follow-up with neurologists may have been more likely to detect stroke in these patients; however, this is a limitation of the Sanford et al. study as well. Another limitation is that a large minority of these patients did not undergo resection, while the entirety of the Sanford et al. study did. While no association between pre-SRS surgery and post-SRS stroke risk has been established, this fact does underscore a difference between the patient population in this study versus Sanford et al. [20]. Another limitation is that the histologic grade of meningioma was not specified in stroke cases; this leaves the speculative possibility of some of these lesions being higher grade than those not associated with stroke post-SRS. Finally, since studies failed to separate observed strokes by the presence versus absence of operative intervention, the current analysis is not able to address this important issue with the amount of detail it deserves.

In conclusion, a large sample size from the published literature with follow-up sufficient to adequately assess stroke development found that the stroke rate following single-fraction photon-based SRS for benign meningioma was 1.7%, more than twelve times lower than for fractionated proton-photon RT and comparable to that expected for the general population. The majority of these patients underwent resection prior to single-fraction SRS. These findings indicate that for patients with benign meningioma desiring to avoid the high stroke risk of fractionated proton-photon RT, single-fraction photon-based SRS has a comparable stroke risk profile to observation. Such findings are pertinent for radiation oncology, neuro-oncology, and neurosurgery management of this patient population. Future investigation will be required to determine whether the 20.5% stroke rate of fractionated proton-photon RT is applicable to fractionation conducted without protons.

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Conflict of interest statement

No author has any conflict of interest.

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