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ISRS Practice Guideline

Stereotactic radiosurgery for vestibular schwannoma: International Stereotactic Radiosurgery Society (ISRS) Practice Guideline

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DISCLAIMER

These guidelines should not be considered inclusive of all methods of care or exclusive of other methods or care reasonably directed to obtain similar results. The physician must make the ultimate judgment depending on characteristics and circumstances of individual patients. Adherence to this guideline will not ensure successful treatment in every situation. The authors of this guideline and the International Society of Stereotactic Radiosurgery assume no liability for the information, conclusions and recommendations contained in this report.

ABSTRACT

Objectives: The aim of this systematic review was to develop International Stereotactic Radiosurgery Society (ISRS) consensus guideline statements for vestibular schwannoma.

Methods: A systematic review of the literature was performed up to April 2015.

Results: A total of 55 full-text articles were included in the analysis. All studies were retrospective, except for 2 prospective quality of life studies. Five-year tumour control rates with Gamma Knife

radiosurgery (RS), single fraction linac RS, or fractionated (either hypofractionated or conventional fractionation) stereotactic radiation therapy (FSRT) were similar at 81-100%. The single fraction RS series (linac or Gamma Knife) with tumour marginal doses between 12 and 14 Gy revealed 5-year tumour control rates of 90-99%, hearing preservation rates of 41-79%, facial nerve preservation rates of 95-100% and trigeminal preservation rates of 79-99%.

There were 6 non-randomized studies comparing single fraction RS versus FSRT. There was no statistically significant difference in tumour control; HR=1.66 (95% CI 0.81, 3.42), p =0.17, facial nerve function; HR = 0.67 (95% CI 0.30, 1.49), p =0.33, trigeminal nerve function; HR = 0.80 (95% CI 0.41, 1.56), p =0.51, and hearing preservation; HR = 1.10 (95% CI 0.72, 1.68), p =0.65 comparing single fraction RS with FSRT.

Nine quality of life reports yielded conflicting results as to which modality (surgery, observation, or radiation) was associated with better quality of life outcomes.

Conclusions: There are no randomized trials to help guide management of patients with vestibular schwannoma. Within the limitations of the retrospective series, a number of consensus statements were made.

Keywords: vestibular, acoustic, schwannoma, neuroma, systematic review

INTRODUCTION

Epidemiology

Vestibular schwannoma arises from Schwann cells of the vestibulocochlear nerve (cranial nerve VIII). These benign lesions account for 5-10% of all intracranial tumours, representing 80% of tumours located in the cerebellopontine angle (1,2). Incidence rates range from 0.2-1.7 per 100 000 population (1–6). The majority of vestibular schwannmomas arise sporadically and occasionally they are associated with the genetic disorder Neurofibromatosis 2 (NF2). The reported incidence of vestibular schwannoma in NF2 patients is as high as 4 per 100 000 in the United Kingdom and 1.4 per 100 000 in Finland (6). Incidence rates for NF2 patients diagnosed at less than 20 years of age was found to be 0.1 per 100 000, rising to 0.6 per 100 000 for patients between 20-39 years of age (6).

Presentation and diagnosis

The most common symptoms associated with vestibular schwannoma are hearing loss and tinnitus (7). The diagnosis of vestibular schwannoma is made radiographically using contrast enhanced magnetic resonance imaging (MRI). Most vestibular schwannoma have an intracanalicular component, with widening of the porus acousticus, which is present in 90% of cases (8,9). As these tumours enlarge, extracanalicular extension occurs.

Koos, Gardner-Robertson and House-Brackmann grading

The following grading systems, namely Koos, Gardner-Robertson and House-Brackmann are useful for extent of tumour involvement, hearing and facial motor function classifications, respectively.

The Koos grading system (10) defines a grade 1 tumour as those involving only the internal auditory canal. A grade 2 tumour extends into the cerebellopontine angle, but does not encroach on the brainstem. A grade 3 tumour reaches the brainstem and may deform the brainstem but does not shift the 4th ventricle, whereas a grade 4 tumour deforms the brainstem and shifts the 4th ventricle.

The Gardner-Robertson grade defines the following hearing grades (11). Grade I refers to good to excellent hearing [pure-tone average (PTA) 0-30 dB, 70-100% speech (SD) discrimination score]. Grade II refers to serviceable hearing [PTA 31-50 dB, SD 50-69%]. Grade III is defined as non-serviceable hearing [PTA 51-90 dB, SD 5-49%]. Grade IV refers to poor hearing [PTA 91-maximum, SD 1-4%] and Grade V is defined as deafness [PTA not testable, SD 0%].

The House-Brackmann scale (12) defines the following facial nerve motor functions. Grade I is normal function, Grade II is mild dysfunction, Grade III is moderate dysfunction, Grade IV is moderately severe dysfunction, Grade V is severe dysfunction and Grade VI is total paralysis. Details regarding specific grade examples are available in the literature (12).

MANAGEMENT

Management options for newly diagnosed vestibular schwannoma include observation, surgery or radiation. To clarify the many radiation regimens used in the literature for vestibular schwannoma, we have used the terms single fraction radiosurgery (RS) or fractionated stereotactic radiation therapy (FSRT). Single fraction RS is given in one treatment session, whereas FSRT is given either hypofractionated in doses greater than 2.5 Gy per fraction or conventionally fractionated in 1.8 – 2.0 Gy per day.

Observation is a controversial option (13). However, the risk-to-benefit ratio for observation versus intervention may favour a strategy of observation for these benign tumours especially if the vestibular schwannoma does not grow significantly to negatively affect quality of life, or hearing, during a patient's remaining lifespan.

Surgical intervention includes varying degrees of resection from gross total resection to intentional subtotal resection depending on tumour size, location, risks of surgical morbidity and surgical expertise. There are a variety of surgical approaches including translabyrinthine, middle fossa and retrosigmoid, each with its own advantages, disadvantages and technical difficulties (14–19).

RS or FSRT is often used for small to moderate sized vestibular schwannoma (Koos grades I-III) with the intent to prevent tumour growth.

OBJECTIVES

1. The aims of this systematic review are:
2. To provide an objective summary on the published literature pertaining to vestibular schwannoma management

To develop consensus guideline recommendations

METHODS

A systematic review of the literature was performed using Medline (1946-April week 4, 2015), Pubmed and Cochrane databases (1991-April 30, 2015). The following search strategy was used:

1. Exp Radiosurgery/
2. (acoustic or schwannoma).mp
3. 1 and 2
4. Limit 3 to English language and adult

A total of 404 records were identified through Medline. There was one additional systematic review on stereotactic radiotherapy for vestibular schwannoma identified through the Cochrane library. A total of 405 articles were screened for eligibility.

Inclusion criteria were the following: any randomized trial, or if non-randomized then articles that met a minimum of 100 total cases. English language only articles were considered.

Only one randomized trial has been reported comparing radiation planning between the Gamma knife Perfexion (Elekta AB, Stockholm, Sweden) versus Gamma Knife 4C (Elekta AB, Stockholm, Sweden) (20,21). Radiation parameters were assessed, but no clinical outcomes were examined in this trial. As such, this trial was excluded.

Duplicate studies (22–41) were defined as those that included outcomes on the same patients. The latest publication containing the larger number of patients was included and earlier published results on the same but smaller number of patients were excluded. A total of 55 full-text articles are included in the analysis (Figure 1).

Recommendations have been summarized based on levels of evidence (Table 1). Then the 2014 ISRS Board (10 authors on this guideline) rated their agreement with each recommendation on a 5-point scale (strongly agree, agree, disagree, strongly disagree, or uncertain). A threshold of 80% or more (agree or strongly agree responses) represented strong consensus and 60-79% agreement represented moderate consensus.

RESULTS

Summary of literature search

Table 2 summarizes the included studies covering single fraction RS (Gamma Knife or linear accelerator), FSRT (conventional fractionation, hypofractionation), or surgery.

There were 6 non-randomized studies which compared single dose RS to FSRT (42–47). The Generic inverse variance method and fixed effects model in Review Manager (Cochrane Library RevMan 5.3) was used to pool data from these 6 non-randomized studies. The outcome measures used the log hazard ratio (lnHR) and its variance, which were estimated using the Hazard Ratio Meta-analysis Tool Box (48).

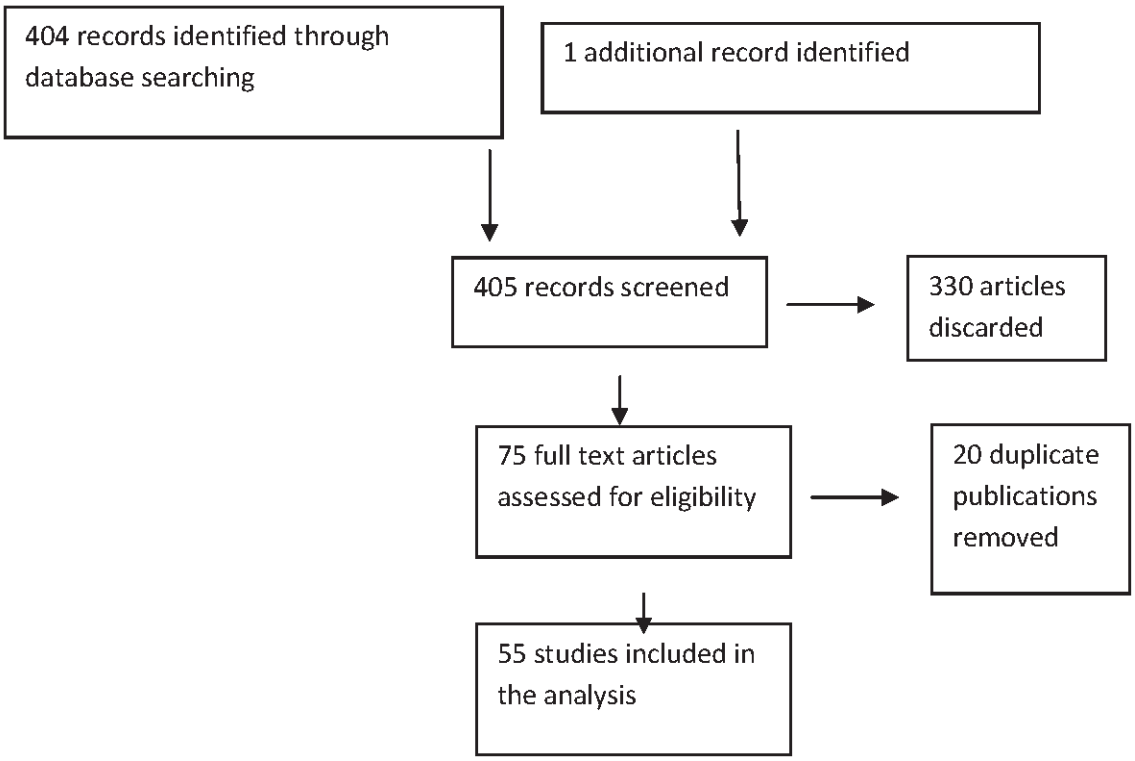


Figure 1. Study flow diagram

There were 4 non-randomized quality of life studies (49–52) comparing observation versus surgery versus radiation. Two studies (53,54) compared surgery with Gamma Knife RS. Two studies (55,56) reported quality of life in patients treated with Gamma Knife RS and one for patients treated with surgery (57)

Other studies which included more than 100 patients included 2 publications describing growth patterns (58,59) and 1 publication examining methods used to measure tumour size (60).

Radiosurgery dose and tumour control:

Series of patients treated with Gamma Knife RS included prescription doses from 6-25 Gy to the tumour margin. Single fraction linear accelerator RS doses ranged from 10-22.5 Gy to the tumour margin (Table 3).

Some of these publications included treatments given during the pioneering period of single fraction RS, when very high doses were sometimes given for benign disease (37). For the contemporary series, which included marginal doses of 12-14 Gy, the 5-year tumour control rates were 91-99% for the Gamma Knife series and 90% for single fraction linac RS. As such, there appears to be no compromise in tumour control rates for the currently used single fraction RS doses for vestibular schwannoma, ranging from 12-14 Gy (Table 5).

FSRT and tumour control:

FSRT regimens included conventional radiation therapy (eg. 50- 50.4 Gy in 1.8- 2.0 Gy daily fractions, 5 times per week) or hypofractionation (eg. 5 Gy daily x 5; 3 Gy daily x 10; 6 Gy daily x 3). Five-year tumour control rates were 81-98% with the conventional regimens and 96-100% with hypofractionation (Table 3).

Tumour control for RS compared to FSRT:

There were 6 non-randomized studies (42–47) comparing single fraction RS (9.7 – 16 Gy) versus FSRT (Table 4). None reported a difference in 5-year tumour control rates between single fraction RS versus FSRT (conventional or hypofractionated). When the 5-year tumour control rates were pooled from these 6 non-randomized studies, there was still no statistically significant difference, with a hazard ratio (HR) between single fraction RS versus FSRT of 1.66 (95% CI 0.81, 3.42), p =0.17 (Figure 2a).

Table 1. Levels of evidence (Oxford Centre for Evidence-based Medicine 2009):

Level 1 a: systematic reviews with homogeneity of randomized controlled trials
Level 1 b: individual randomized controlled trials (with narrow confidence intervals)
Level 1c: All or none case series (eg. all patients died before treatment became available, now none die of the disease on treatment or now some survive on treatment)
Level 2 a: systematic reviews (with homogeneity) of cohort studies
Level 2 b: individual cohort study including low quality randomized controlled trials (eg. < 80% follow-up)
Level 2 c: "outcomes" research
Level 3 a: systematic review with homogeneity of case-control studies
Level 3b: individual case-control study
Level 4: case-series (and poor quality cohort and case-control studies)
Level 5: expert opinion without explicit critical appraisal or based on physiology, bench research or "first principles"

TOXICITY

Hearing

Hearing preservation at 5-years was defined as preservation of Gardner-Robertson grades 1 or 2. Of note, hearing preservation rates for these single fraction RS series are difficult to compare due to the reduction in RS dose prescription over the years. In large series of patients treated with single fraction RS to a contemporary marginal dose of 12-14 Gy, the 5 year hearing preservation rate ranged from 41-79% (Table 5).

For the 6 series which directly compared the hearing outcomes of single fraction RS (9.7-16 Gy) versus FSRT, one study (42) reported statistically significant hearing preservation favouring the FSRT group over the single fraction RS group. However, this study has been criticized for the unusually low 5-year hearing preservation rate of 33% in the single fraction RS group as compared to the other series in Table 4. Four series (43–45,47) reported no statistically significant difference between single fraction RS and FSRT in terms of hearing preservation. One series (46) did not report statistical comparisons. When these 5-year hearing preservation rates were pooled, there was no statistically significant difference: HR = 1.10 (95% CI 0.72, 1.68), p =0.65 (Figure 2b).

Trigeminal sensation:

Valid comparisons between these large RS series (Gamma Knife versus linear accelerator) were not pos-

Table 2. Summary of included studies

Treatment	Number of studies	References	Type of study	Mean or median follow-up range
Gamma Knife	28	(62,65,66,71–95)	All retrospective	2 - 12.5 years
Linear accelerator single fraction RS	1	(96)	Retrospective	3.3 years
FSRT				
Conventional fractionation (1.8-2 Gy per day)	2	(64,97)	All retrospective	2.2 – 6 years
Hypofractionation (at least 2.5Gy per day)	2	(98,99)		
Surgery	4	(100–103)	All retrospective	At least 1 year to 10.2 years

RS = radiosurgery

FSRT = fractionated stereotactic radiation therapy

Comparisons	Number of studies	References	Type of studies	Mean or median follow-up range
Single fraction RS versus FSRT comparisons	6	(42–47)	All retrospective	2.2 – 7.7 years
Quality of life outcomes:				
Observation versus surgery versus radiation	4	(49–52)	Two prospective (the rest retrospective)	1.8 – 8.7 years
Surgery or Gamma Knife radiosurgery	2	(53,54)		
Gamma Knife	2	(55,56)		
Surgery	1	(57)		

Miscellaneous	Number of studies	References	Type of studies	Mean or median follow-up range
Growth patterns	2	(58,59)	All retrospective	2 – 2.7 years
Measuring size	1	(60)	All retrospective	Not applicable

RS = radiosurgery

FSRT = fractionated steretotactic radiation therapy

Table 3. Results

Category (references)	Dose to tumour margin	Prescription isodose line	5 year* tumour control	5 year* hearing preservation Ŧ	5 year* facial nerve preservation	5 year* trigeminal nerve preservation
Single fraction RS						
Gamma Knife (62,65,66,71–95)	6-25 Gy	20-95%	89-99%	41-92%	84-100%	74-99%
Linear accelerator (96)	10-22.5 Gy	70-80%	90%	Not evaluated	96%	96%
FSRT						
Conventional fractionation (64,97)	50-50.4 Gy in 1.8 Gy-2.0 Gy daily fractions (5 x per week)	Planning target volume	81-98%	54-56%	91-98%	89-97%
Hypofractionated (98, 99) stereotactic radiotherapy	5 Gy daily x 5; 3 Gy daily x10; 6 Gy daily x 3	At tumour margin or at planning target volume	96-100%	70-76%	100%	99-100%

RS = radiosurgery

FSRT = fractionated stereotactic radiation therapy

*Crude or actuarial

Ŧ preservation of Gardner Robertson Grades 1 or 2 hearing

Gy = Gray

Table 4. Studies which directly compare single fraction RS vs. FSRT

Study (reference)	Dose to tumour margin (number of patients)	5 year* tumour control	5 year* hearing preservation Ŧ	5 year* facial nerve preservation	5 year* trigeminal nerve preservation
Andrews et al (42)	**Single fraction RS:** 12 Gy in 1 fraction (n=69)	**Single fraction RS:** 98%	**Single fraction RS:** 33%	**Single fraction RS:** 98%	**Single fraction RS:** 95%
	FSRT: 50 Gy in 25 daily fractions (n=56)	**FSRT:** 97% (NS)	**FSRT:** 81% (p=0.02)	**FSRT:** 98% (NS)	**FSRT:** 93% (NS)
Collen et al (43)	**Single fraction RS:** 11-14 Gy in 1 fraction (n=78)	**Single fraction RS:** 95%	**Single fraction RS:** 82%	**Single fraction RS:** 83%	**Single fraction RS:** 96%
	FSRT: 30-40 Gy in 10 daily fractions (n=31)	**FSRT:** 95%	**FSRT:** 59%	**FSRT:** 97%	**FSRT:** 96%
	50 Gy in 25 daily fractions (n=10)	(NS)	(NS)	(p=0.047)	(NS)
Meijer et al (44)	**Single fraction RS:** 10 Gy in 1 fraction or 12.5 Gy in 1 fraction (n=49)	**Single fraction RS:** 100 %	**Single fraction RS:** 75%	**Single fraction RS:** 93%	**Single fraction RS:** 92%
	FSRT: 4 Gy daily x 5 or 5 Gy daily x 5 (n=80)	**FSRT:** 94% (NS)	**FSRT:** 61% (NS)	**FSRT:** 97% (NS)	**FSRT:** 98% (p=0.048)
Combs et al (45)	**Single fraction RS:** Median: 13 Gy in 1 fraction (range 10-20 Gy) (n=169)	**Single fraction RS:** 95%	**Single fraction RS:** 84%	**Single fraction RS:** 97%	**Single fraction RS:** 99%
	FSRT: 57.6 Gy in 1.8 Gy daily fractions (n=291)	**FSRT:** 95% (NS)	**FSRT:** 86% (NS)	**FSRT:** 99% (NS)	**FSRT:** 99% (NS)

Study (reference)	Dose to tumour margin (number of patients)	5 year* tumour control	5 year* hearing preservation Ŧ	5 year* facial nerve preservation	5 year* trigeminal nerve preservation
Kopp et al (46)	**Single fraction RS:** 12 Gy in 1 fraction (n= 68)	**Single fraction RS:** 99 %	**Single fraction RS:** 85%	**Single fraction RS:** 93%	**Single fraction RS:** 82%
	FSRT: 54 Gy in 1.8 Gy daily fractions (n= 47)	**FSRT:** 98% (statistical significance not reported)	**FSRT:** 79% (statistical significance not reported)	**FSRT:** 96% (statistical significance not reported)	**FSRT:** 87% (statistical significance not reported)
Anderson et al (47)	**Single fraction RS:** Median: 12 Gy in 1 fraction (range: 9.7-16 Gy in 1 fraction) (n=48)	**Single fraction RS:** 97%	**Single fraction RS:** 60%	**Single fraction RS:** 98%	**Single fraction RS:** 90%
	FSRT: 4 Gy x 5 weekly (n=37)	**FSRT:** 91%	**FSRT:** 63%	**FSRT:** 100%	**FSRT:** 75%
	50.4 Gy in 1.8 Gy daily fractions (n=19)	100% (NS)	44% (NS)	100% (NS)	95% (NS)

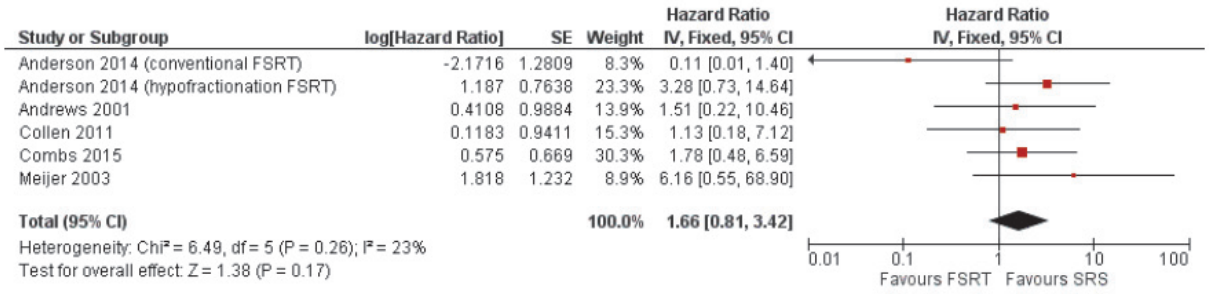
RS = radiosurgery
FSRT = fractionated stereotactic radiation therapy
*Crude or actuarial
Ŧ preservation of Gardner Robertson Grades 1 or 2 hearing
Gy = Gray
NS = not significant

Table 5. Single fraction RS series with marginal dose 12-14 Gy

Treatment (references)	5 year * tumour control	5 year* hearing preservation	5 year * facial nerve preservation	5 year * trigeminal nerve preservation
Gamma Knife RS (71,75,80,83,86,91, 104)	91-99%	41-79%	95-100%	79-99%
Linac RS (96)	90%	Not evaluated	96%	96%

RS = radiosurgery
Gy = Gray
* crude or actuarial
Ŧ preservation of Gardner Robertson Grades 1 or 2 hearing

sible, partly because the RS dose prescriptions decreased over the years. For the series of single fraction RS patients treated with a marginal dose of 12-14 Gy, the 5-year trigeminal nerve preservation rate was 79-99% (Table 5).



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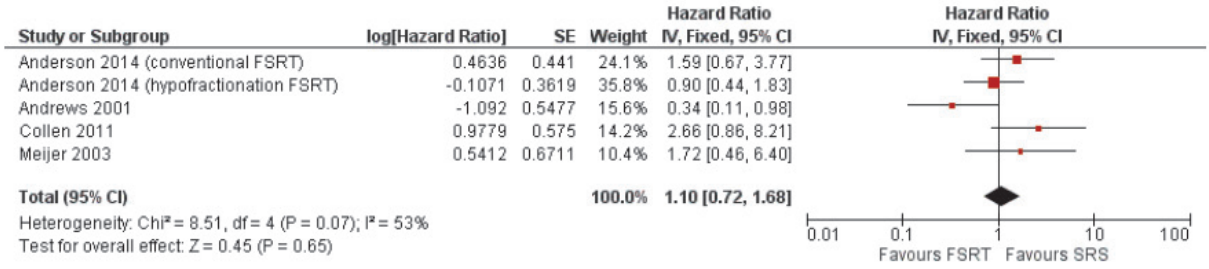

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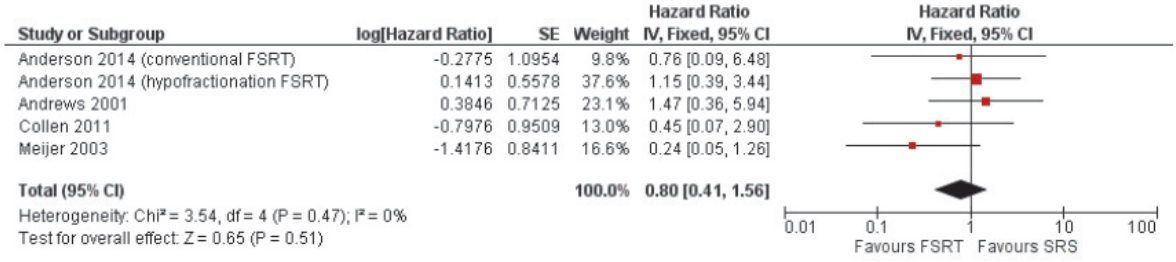

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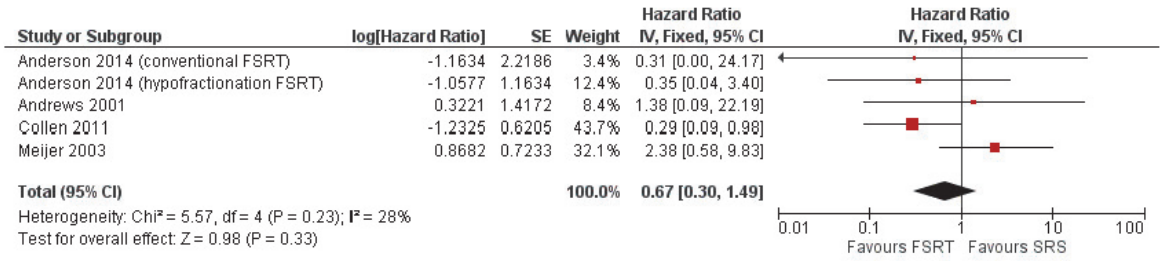

d)

Figure 2. Pooled retrospective results of studies which compare single fraction RS versus FSRT for vestibular schwannoma: a) 5 year tumour control; b) 5 year hearing preservation; c) 5 year trigeminal nerve preservation; d) 5 year facial nerve preservation

For the 6 large series which directly compare the trigeminal nerve preservation rate of single fraction RS (9.7-16 Gy) versus FSRT, only one study (44) reported statistically significant trigeminal nerve preservation rate favouring FSRT over single fraction RS. When these 5-year trigeminal function preservation rates were pooled, there was no statistically significant difference: HR = 0.80 (95% CI 0.41, 1.56), p =0.51 (Figure 2c).

Facial motor function

For the single fraction RS series with a marginal dose of 12-14 Gy, the 5-year facial nerve preservation rate ranged from 95-100% (Table 5).

For the 6 series which directly compare the facial preservation rate of single fraction RS (9.7-16 Gy) versus FSRT, no study reported statistically significant differences in facial preservation rate at 5 years. When these 5-year facial motor function results were pooled, there was no statistically significant difference: HR = 0.67 (95% CI 0.30, 1.49), p =0.33 (Figure 2d).

Quality of life (QOL)

One prospective study (49) examining QOL, using the 36-Item Short Form Health Survey (SF-36) at regular intervals, included a total of 229 vestibular schwannoma patients (47 patients were observed, 48 received single fraction RS or FSRT, and 134 patients underwent surgery). The mean follow-up was 31.8 months. There were no baseline QOL differences among the management groups. Overall, QOL remained unchanged for the three management groups throughout the follow-up period.

In contrast, another study (50) used a retrospective database of vestibular schwannoma patients either managed conservatively or treated with RS or surgery. The Glasgow Benefit Inventory (GBI) QOL questionnaire was sent by mail to these patients. Of the 165 patients who returned the completed questionnaire, the authors reported that QOL deteriorated after surgery, QOL did not change for patients managed conservatively and there was a trend toward poorer QOL after RS which did not reach statistical significance.

Carlson et al (51) reported on 144 patients treated with microsurgery, 247 treated with RS and 148 patients who were observed. QOL questionnaires were sent via mail using SF-36, the 10-item Patient-Reported Outcomes Measurement Information System short form (PROMIS-10), GBI, and the Penn Acoustic Neuroma QOL (PANQOL) scale. The authors reported that the differences in QOL were small among the three management categories, and that the diagnosis of vestibular schwannoma rather than treatment strategy most significantly affected QOL.

The PANQOL survey was also used in a total of 186 vestibular schwannoma patients reported by McLaughlin et al (52). Ninety-eight patients managed conservatively, 49 patients treated with Gamma Knife RS and 39 patients treated with surgery, completed the QOL survey during a follow-up visit (administered at different stages of treatment and follow-up). The general and total domain scores were similar for all treatment groups. However, hearing domain scores were better for the conservative group.

Myrseth et al (53) sent the SF-36 and GBI questionnaire by mail to 168 patients treated either with microsurgery or Gamma Knife RS. Questionnaires from 140 patients were received and analyzed. The mean observation time between treatment and QOL assessment was 6.7 years. The authors reported statistically significant worse deviations below norms for the categories of physical (p=0.026), role-physical (p =0.040) and role-emotional (p=0.003) functioning scores in the microsurgical group as compared to the Gamma Knife RS group.

Regis et al (54) reported upon functional side effects occurring during the first 2 years after single fraction RS. After 4 years of follow-up, the authors reported RS yielding better functional outcomes compared to microsurgery. The authors used a non-validated questionnaire which included symptoms such as facial weakness, vertigo but also QOL type questions such as social, family, sexual, professional and intellectual QOL aspects.

There were two studies (55,56) on QOL for Gamma Knife RS. One study (55) reported on high QOL scores using the European Quality of Life- 5 dimensions (EQ-5D) mailed to 109 patients treated with Gamma Knife RS. With a median follow-up time of 104 months, the mean QOL score was 0.77 and median 0.91 (QOL 1.0 represents best possible QOL). Another study (56) reported that SF-36 scores were similar to a normal Dutch population. In this group of vestibular schwannoma patients treated with Gamma Knife RS, a marginal decline in QOL was observed using GBI.

A prospective study by Turel (57) was published in which 100 patients with large vestibular schwannoma (3 cm or more) treated with surgery completed the SF-36 QOL questionnaire. These patients scored lower on all QOL domains at baseline preoperatively compared with the normative population. Approximately 60% of these patients reported improvement in QOL 1 year after surgery as compared to the baseline QOL obtained preoperatively. The authors reported that 1 year after surgery, QOL had improved to the level of the normative population in most domains. With additional follow-up, QOL scores were sustainable in all domains but also statistically significant improvements in physical role (p=0.01) and social functioning (p=0.03) scores compared with scores from the 1-year follow-up were noted.

In summary, the QOL studies are conflicting in terms of which modality (observation, surgery or radiation) has better QOL outcomes.

Growth patterns

Tumour growth was reported as the most significant factor for a change in management from observation to intervention (microsurgery or radiosurgery) in one study (58). Larger tumour size at diagnosis was also associated with higher odds of growth. Tinnitus at diagnosis also increased the odds of growth by almost 3-fold.

In another study (59), the average tumour growth rate was defined as the total increase in tumour size (in mm) divided by the total number of years of observation. Based on this definition, the authors concluded that the average growth of untreated acoustic neuromas was 0.7±1.4 mm per year. For this observed group, 82% grew less than 1 mm per year, 18 % grew 1 mm or more per year and 13% grew more than 2 mm per year. If growth is defined as more than 2 mm per year, 87% of observed acoustic neuromas did not grow with a mean follow-up of 38 months (range: 1-13 years). Although diagnostic imaging change in size is usually reported unidimensionally, it should be recognized, for example, that a 2 mm diameter change in a large tumour is a more significant absolute change in volume compared to a 2 mm diameter change in a small tumour.

Measuring size

Post gadolinium MR images from 139 vestibular schwannoma patients (60) were examined to determine the accuracy and reliability of volume estimates based on i) one single maximum diameter, ii) three orthogonal diameters or iii) the maximal slice area. The authors concluded that the three orthogonal diameters and maximal slice area methods were recommended. The single maximum diameter method was found to be the least reliable with the greatest retest errors. However, volumetric assessments, considered the gold standard, (105) were not examined in this study.

DISCUSSION

Diagnosis

Since the 1990's, all radiation (single fraction RS or fractionated radiation therapy) series have been based on the diagnosis of vestibular schwannoma on contrast enhanced MRI. In comparison to histopathological findings, a study from Bangladesh demonstrated that MRI has 96% sensitivity, 88% specificity, 92% positive predictive value, 94% negative predictive value and 93% accuracy for the diagnosis of acoustic neuroma (61).

TREATMENT CHOICE (OBSERVATION, RS, SURGERY, FSRT)

Observation

The two series of patients who were managed with observation provide some evidence that observation in patients with small vestibular schwannoma is safe (58,59). The average growth rate of untreated vestibular schwannoma was 0.7±1.4 mm per year (59). For this group of vestibular schwannomas on observation, 82% grew less than 1 mm per year, 18 % grew 1 mm or more per year and 13% grew more than 2 mm per year. Tumour growth was reported as the most significant factor for a change in management from observation to intervention (microsurgery or RS) in one study (58). However, a larger tumour seen at diagnosis was reported to be associated with higher odds of growth (58). Tinnitus at diagnosis also increased the odds of growth by almost 3-fold. Therefore, observation may be an option restricted to small asymptomatic vestibular schwannoma such as Koos Grade I tumours (especially in elderly patients with significant co-morbidities).

RS, surgery

Hasegawa and colleagues (24) reported on 246 patients (excluding NF2) who underwent RS. Tumours less than 15 cc [10 year progression free survival (PFS) 96%], did not compress the brainstem and did not deviate the 4th ventricle (10 year PFS 97%), had significantly better PFS as compared to large tumours more than 15 cc (10 year PFS 57%, $p < 0.001$) or compared to those where the 4th ventricle was deviated (10 year PFS 74%, $p = 0.008$), respectively.

A systematic review by Weil et al (63) reported that median tumour volume was negatively correlated with 5-year PFS ($r^2 = 0.74$, $p < 0.05$), and that for every 1 cc increase in tumour volume, 5-year PFS fell by 1.5% (95% CI, 1.11-1.93%).

Therefore, patients with small to moderate size vestibular schwannoma without significant brainstem compression, and those without significant deviation of the 4th ventricle (namely Koos Grades I- III) are good candidates for RS. Conversely, those that are large in volume with significant mass effect (Koos Grade IV) should be considered for surgery.

FSRT

The maximum volume in the series of patients treated with FSRT in this systematic review was 30.7 cc (corresponding to a sphere with a diameter of 39mm). Aoyama and colleagues (64) reported that worsening of trigeminal and facial nerve function was influenced by a tumor diameter of 30 mm or greater. Tumour expansion requiring surgical salvage was also statistically greater in those greater than 30 mm versus 30 mm or less, p=0.015. Within the limitations of these retrospective series, patients who are eligible for FSRT are those patients with small to moderate size vestibular schwannoma less than 30 mm in greatest dimension without significant mass effect (Koos Grades II-III).

For the 6 retrospective publications examining RS versus FSRT, there appears to be no difference in 5 year tumour control rates and facial nerve preservation rates between single dose RS and FSRT (42–47). It remains unclear whether hearing preservation rates and trigeminal preservation rates are better with FSRT or vice-versa. Whether there is a cut-off volume where FSRT may be favoured over SRS is unknown.

Due to the retrospective nature of reported comparisons (imbalance of tumour size and baseline hearing), it is also unclear as to whether RS, FSRT or observation results in better hearing preservation.

SRS dose, tumour delineation

Early Gamma Knife RS series in the 1980's used high tumour margin doses of 18-20 Gy (26,37,39). The toxicity of higher dose RS led to dose reduction to 16-18 Gy which resulted in a decrease in complication rates (63,104). Then in the 1990's the dose to the tumour margin dropped further to 14-16 Gy, and now more contemporary series of RS (Gamma Knife or linear accelerator) use doses between 12-14 Gy. In addition, Klijn S et al (66) reported on 420 patients treated with Gamma Knife RS with a median marginal dose of 11 Gy. The 5-year tumour control rate was 91.3% and the complication rates were similar to other contemporary series.

When the single fraction RS series of vestibular schwannoma patients treated with marginal doses of 12-14 Gy (Gamma Knife or linear accelerator) were analyzed (Table 5), the 5-year tumour control rates ranged from 90-99%. Five-year hearing, facial and trigeminal nerve preservation rates ranged from (41-79%, 95-100%, and 79-99%) respectively. In general, the length of follow-up in the published series is longer with single fraction RS as compared to FSRT. Of note, all the contemporary series use volumetric thin slice MRI for radiosurgery planning and the dose is prescribed to the tumour margin.

FSRT dose, target delineation

Conventional radiation therapy regimens for the majority of vestibular schwannoma patients included in this review ranged from 50.4 Gy to 57.6 Gy in 1.8 to 2.0 Gy daily fractions. Examples of hypofractionated regimens in this review included 5 Gy x 5 daily, 3 Gy x 10 daily and 6 Gy x 3. For relocatable frames, a PTV margin was added to the GTV to account for daily variation in set up (ranging from 0-2 mm in these studies).

Pseudoprogression

Transient enlargement of vestibular schwannomas, occurring within approximately the first 3 years after single fraction RS or FSRT due to treatment effects and not due to tumour growth has been reported in 20-30% of cases in the literature (28,67–69). For these patients who do not have progressive mass effect symptoms, observation is preferred rather than immediate surgical intervention.

Neurofibromatosis 2 (NF2)

Although many of the management series for vestibular schwannoma excluded NF2 patients, the options of observation, surgery, or radiation (single fraction RS or FSRT) also apply to patients with NF2. However, treatment control rates for patients with NF2 tend to be lower compared to sporadic vestibular schwannoma (70). These patients represent a challenge not only due to the different biologic behaviour but also due to the risk of bilateral hearing loss and propensity of multiple tumours, which may develop in the brain and spine. As such, the management and results for vestibular schwannoma patients with NF2 should be reported separately from the sporadic type.

Limitations

The limitations of this systematic review are that all except two of the included studies were retrospective in nature. These results suffer from reporting bias and selection bias. It is not clear how many patients were lost to follow-up. Furthermore, many patients did not have formal audiogram follow-up.

Direct and randomized comparisons for local control or hearing outcomes between single fraction RS and conventional or hypofractionated FSRT regimens are lacking. Furthermore, other outcomes such as eye complications (due to lacrimal gland deficits) and imbalance were missing from the large series. There is lack of evidence as to whether the risk of radiation induced carcinogenesis is different between single fraction RS versus FSRT.

The studies also included patients who were treated over many years. During this time, there may have been a shift in patient selection (such as smaller vestibular schwannomas treated with radiation), change in prescription doses and change in imaging for planning and follow-up. These factors confound results and make comparisons among centres and among treatment modalities difficult.

The consensus vote (Table 6) may have been biased as all 10 ISRS members are involved with single fraction RS. A minority also treat with FSRT, which worldwide, is a less common treatment modality.

CONCLUSIONS

There are no randomized trials to help guide management for patients with vestibular schwannomas. Within the limitations of the retrospective series published and the small voting pool (10 ISRS Board members), who all perform single fraction radiosurgery, the following consensus statements (based on strong or moderate agreement) were made (Table 6):

PATIENT SELECTION

In the absence of pathologic tissue, the diagnosis of vestibular schwannoma is based on MRI characteristics. All patients diagnosed radiographically should have the images reviewed with neuroradiology [strong consensus].

MANAGEMENT

1. For small newly diagnosed vestibular schwannoma without significant mass effect (Koos Grades I-III):
   - Observation is an option [strong consensus].
   - Single fraction RS is an option [strong consensus].
   - FSRT is an option [moderate consensus].
2. For growing vestibular schwannoma:
   - Surgery is recommended for vestibular schwannoma in surgically fit patients with significant mass effect (Koos Grade IV tumours) [strong consensus].
   - Single fraction RS is recommended for small to moderate size vestibular schwannoma without significant mass effect (Koos Grades I-III tumours) [strong consensus].
   - FSRT is recommended for small to moderate size vestibular schwannoma without significant mass effect (Koos Grades I-III tumours) [moderate consensus].

Imaging

Volumetric 3D (thin slice 1-1.5 mm) post gadolinium enhanced MRI is recommended for radiation planning, combined with T2 weighted images [strong consensus].

Target contours

For single fraction RS (Gamma Knife or linear accelerator) using a stereotactic head frame, no margin is added to the gross tumour volume (GTV) [strong consensus].

For FSRT using a relocatable frame, a formal quality assurance assessment of an appropriate planning target volume (PTV) should be done [moderate consensus].

Planning

A dedicated multidisciplinary team (radiation oncology, neurosurgery, radiation physics, radiation therapy) with a thorough quality assurance program should be in place for single fraction RS or FSRT planning and delivery [strong consensus].

Dose fractionation

Single fraction RS: 11-14 Gy to the GTV margin [strong consensus].

Hypofractionated radiation therapy options: Examples include 5 Gy x 5 daily, 3 Gy x 10 daily, 4Gy x 10, 6 Gy x 3, 4 Gy x 5 daily [moderate consensus].

FSRT (conventional): 50-57.6 Gy in 1.8-2.0 Gy per fraction to the PTV margin. Although these fractionated dose regimens did not reach consensus (40% agreement), these are commonly used fractionated regimens supported by series of studies with large patient numbers.

Table 6. Recommendations: Levels of evidence based on Oxford Centre for Evidence-based Medicine 2009

	Level of evidence	ISRS Board consensus level
Patient selection		
In the absence of pathologic tissue, the diagnosis of vestibular schwannoma is based on MRI characteristics. All patients diagnosed radiographically should have the images reviewed with neuroradiology.	1. Level 5	Strongly agree: 50% Agree: 30% Disagree: 0% Strongly disagree: 20% Uncertain: 0% Strong consensus reached with 80% of the ISRS Board members who strongly agreed or agreed.
Management		
2.For small newly diagnosed vestibular schwannoma without significant mass effect (Koos Grades I-III):		
2a. Observation is an option	2a. Level 4	2a. Strongly agree: 20% Agree: 60% Disagree: 10% Strongly disagree: 0% Uncertain: 10% Strong consensus reached with 80% of the ISRS Board members who strongly agreed or agreed.
2b. Surgery (in surgically fit patients) is an option	2b. Level 4	2b. Strongly agree: 10% Agree: 40% Disagree: 30% Strongly disagree: 20% Uncertain: 0% Consensus not reached.
2c. Single fraction RS is an option	2c. Level 4	2c. Strongly agree: 100% Agree: 0% Disagree: 0% Strongly disagree: 0% Uncertain: 0% Strong consensus reached with 100% of the ISRS Board members who strongly agreed.
2d. FSRT is an option	2d. Level 4	2d. Strongly agree: 0% Agree: 60% Disagree: 20% Strongly disagree: 20% Uncertain: 0% Moderate consensus reached with 60% of the ISRS Board members who agree.
3 For growing vestibular schwannoma:		
3a. Surgery is recommended for vestibular schwannoma in surgically fit patients with significant mass effect (Koos Grade IV tumours)	3a. Level 4	3a. Strongly agree: 40% Agree: 60% Disagree: 0% Strongly disagree: 0% Uncertain: 0% Strong consensus reached with 100% of the ISRS Board members who strongly agreed or agreed.

	Level of evidence	ISRS Board consensus level
3b. Surgery is recommended for small to moderate size vestibular schwannoma without significant mass effect (Koos Grades I-III tumours)	3b. Level 4	3b. Strongly agree: 0% Agree: 50% Disagree: 30% Strongly disagree: 20% Uncertain: 0% Consensus not reached.
3c. Single fraction RS is recommended for small to moderate size vestibular schwannoma without significant mass effect (Koos Grades I-III tumours).	3c. Level 4	3c. Strongly agree: 70% Agree: 30% Disagree: 0% Strongly disagree: 0% Uncertain: 0% Consensus reached with 100% of the ISRS Board members who strongly agreed or agreed.
3d. FSRT is an option for small to moderate size vestibular schwannoma without significant mass effect (Koos Grades I-III)	3d. Level 4	3d. Strongly agree: 0% Agree: 60% Disagree: 20% Strongly disagree: 20% Uncertain: 0% Moderate consensus reached with 60% of ISRS Board members who agreed.
Imaging		
Volumetric 3D (thin slice 1-1.5 mm) post gadolinium enhanced MRI is recommended for radiation planning, combined with T2 weighted images.	Level 5	Strongly agree: 70% Agree: 30% Disagree: 0% Strongly disagree: 0% Uncertain: 0% Strong consensus reached with 100% of the ISRS Board members who strongly agreed or agreed.
Target contours		
For single fraction RS (Gamma Knife or linear accelerator) using a fixed stereotactic frame with pins secured to the patient's skull, no margin is added to the gross tumour volume (GTV).	Level 5	1. Strongly agree: 70% Agree: 20% Disagree: 10% Strongly disagree: 0% Uncertain: 0% Strong consensus reached with 90% of ISRS Board members who strongly agreed or agreed.
For FSRT using a relocatable frame, a formal quality assurance assessment of an appropriate planning target volume (PTV) should be done	Level 5	2. Strongly agree: 20% Agree: 40% Disagree: 30% Strongly disagree: 0% Uncertain: 10% Moderate consensus with 60% ISRS Board members who strongly agreed or agreed.
Planning		
A dedicated multidisciplinary team (radiation oncology, neurosurgery, radiation physics, radiation therapy) with a thorough quality assurance program should be in place for single fraction RS or FSRT planning and delivery.	Level 5	Strongly agree: 70% Agree: 30% Disagree: 0% Strongly disagree: 0% Uncertain: 0% Strong consensus reached with 100% of ISRS Board members who strongly agreed or agreed.

	Level of evidence	ISRS Board consensus level
Dose fractionation		
1 Single fraction RS: 11-14 Gy to the GTV margin	Level 4	1. Strongly agree: 80% Agree: 10% Disagree: 0% Strongly disagree: 10% Uncertain: 0% Strong consensus reached with 90% of ISRS Board members who strongly agreed or agreed.
2 FSRT (conventional): 50-57.6 Gy in 1.8-2.0 Gy per fraction to the PTV margin	Level 4	2. Strongly agree: 10% Agree: 30% Disagree: 20% Strongly disagree: 30% Uncertain: 10% Consensus not reached.
3 Hypofractionated radiation therapy options: Examples include 5 Gy x 5 daily, 3 Gy x 10 daily, 4Gy x 10, 6 Gy x 3, 4 Gy x 5 daily	Level 4	3.Strongly agree: 10% Agree: 50% Disagree: 10% Strongly disagree: 10% Uncertain: 20% Moderate consensus reached with 60% ISRS Board members who strongly agreed or agreed.
Outcome measures		
1. Key elements for follow-up assessment of patients with vestibular schwannoma include radiographic follow-up (MRI brain), formal audiology, and neurologic examination. Examples of formal audiologic follow-up include use of the Gardner-Robertson grade, pure tone average, speech discrimination. Neurologic examinations should include an assessment of facial motor function (eg. House Brackmann scale), trigeminal nerve function (including any eye complications) and balance outcomes.	Level 5	1.Strongly agree: 80% Agree: 20% Disagree: 0% Strongly disagree: 0% Uncertain: 0% Strong consensus reached with 100% of ISRS Board members who strongly agreed or agreed.
2. Pseudoprogression is known to occur in vestibular schwannoma patients treated with radiation. For those patients with asymptomatic enlargement within 3 years of radiation (RS or FSRT), observation is favoured.	Level 4	2.Strongly agree: 60% Agree: 40% Disagree: 0% Strongly disagree: 0% Uncertain: 0% Strong consensus reached with 100% of ISRS Board members who strongly agreed or agreed.

Outcome measures

1. Key elements for follow-up assessment of patients with vestibular schwannoma include radiographic follow-up (MRI brain), formal audiology, and neurologic examination. Examples of formal audiologic follow-up include use of the Gardner-Robertson grade, pure tone average, speech discrimination. Neurologic examinations should include an assessment of facial motor function (eg. House Brackmann scale), trigeminal nerve function (including any eye complications) and balance outcomes [strong consensus].
2. Pseudoprogression is known to occur in vestibular schwannoma patients treated with radiation. For those patients with asymptomatic enlargement within 3 years of radiation (RS or FSRT), observation is favoured [strong consensus].

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Authors' disclosure of potential conflicts of interest
Lijun Ma reported patents with the Regents of the University of California specific to radiosurgery.
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