Gamma Knife radiosurgery for large vestibular schwannomas greater than 3 cm in diameter

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OBJECTIVE Stereotactic radiosurgery (SRS) is an important alternative management option for patients with small- and medium-sized vestibular schwannomas (VSs). Its use in the treatment of large tumors, however, is still being debated. The authors reviewed their recent experience to assess the potential role of SRS in larger-sized VSs.

METHODS Between 2000 and 2014, 35 patients with large VSs, defined as having both a single dimension > 3 cm and a volume > 10 cm³, underwent Gamma Knife radiosurgery (GKRS). Nine patients (25.7%) had previously undergone resection. The median total volume covered in this group of patients was 14.8 cm³ (range 10.3–24.5 cm³). The median tumor margin dose was 11 Gy (range 10–12 Gy).

RESULTS The median follow-up duration was 48 months (range 6–156 months). All 35 patients had regular MRI follow-up examinations. Twenty tumors (57.1%) had a volume reduction of greater than 50%, 5 (14.3%) had a volume reduction of 15%–50%, 5 (14.3%) were stable in size (volume change < 15%), and 5 (14.3%) had larger volumes (all of these lesions were eventually resected). Four patients (11.4%) underwent resection within 9 months to 6 years because of progressive symptoms. One patient (2.9%) had open surgery for new-onset intractable trigeminal neuralgia at 48 months after GKRS. Two patients (5.7%) who developed a symptomatic cyst underwent placement of a cystoperitoneal shunt. Eight (66%) of 12 patients with pre-GKRS trigeminal sensory dysfunction had hypoesthesia relief. One hemifacial spasm completely resolved 3 years after treatment. Seven patients with facial weakness experienced no deterioration after GKRS. Two of 3 patients with serviceable hearing before GKRS deteriorated while 1 patient retained the same level of hearing. Two patients improved from severe hearing loss to pure tone audiometry less than 50 dB.

The authors found borderline statistical significance for post-GKRS tumor enlargement for later resection ($p = 0.05$, HR 9.97, CI 0.99–100.00). A tumor volume ≥ 15 cm³ was a significant factor predictive of GKRS failure ($p = 0.005$). No difference in outcome was observed based on indication for GKRS ($p = 0.0761$).

CONCLUSIONS Although microsurgical resection remains the primary management choice in patients with VSs, most VSs that are defined as having both a single dimension > 3 cm and a volume > 10 cm³ and tolerable mass effect can be managed satisfactorily with GKRS. Tumor volume ≥ 15 cm³ is a significant factor predicting poor tumor control following GKRS.

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KEY WORDS Gamma Knife; stereotactic radiosurgery; vestibular schwannoma

THE goal in managing vestibular schwannomas (VSs) is to control their growth and preserve a patient's neurological function. With advances in microsurgical techniques, treatment outcome for small VSs has substantially improved with excellent long-term growth control and functional preservation. The alternative treatment of small- to medium-sized VSs with Gamma Knife radiosurgery (GKRS) is also an accepted treatment meth-

od that has a low incidence of trigeminal and facial neuropathy and high rates of hearing preservation and tumor control. Tumor control rates have been described as upwards of 95% in recent literature, and long-term actuarial resection-free control rates have been documented as high as 90%–98%.^{1,4,17,22}

Despite advancements in monitoring and surgical techniques, functional preservation of cranial nerves (CNs)

ABBREVIATIONS CN = cranial nerve; GKRS = Gamma Knife radiosurgery; HB = House-Brackmann; SRS = stereotactic radiosurgery; VS = vestibular schwannoma.

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in surgery for larger VSs remains a challenge, and good facial nerve function is reported in only 27%–58% of patients.^{2,13,14,25,28} Subtotal removal of large VSs, on the other hand, has been reported to preserve excellent facial nerve function and serviceable hearing. Some reports even consider subtotal removal followed by stereotactic radiosurgery (SRS) to be a reasonable treatment strategy to preserve CN function and achieve tumor control. With the combination of surgery and radiosurgery, clinical and radiological control has been documented at 92% and 90%, respectively, with high facial nerve preservation (House-Brackmann [HB] Grade I–II) ranging from 89% to 95%.^{7,11,18,26}

As for the use of SRS in the treatment of large VSs, there have been some preliminary reports of long-term tumor control ranging from 75% to 94% and reasonable maintenance of neurological function.^{5,15,27,29,30} Most authors have defined large VSs as lesions with one dimension > 3 cm, but the tumor volume has not yet been defined. This volume ranges widely, with means from 4.3 to 17.3 cm³ and an overall range from 1.34 to 25.2 cm³.^{5,15,27,29,30} We defined large VSs as having both a single dimension > 3 cm and a volume > 10 cm³. We reviewed our data to determine a possible role for GKRS, hypothesizing a possible option for GKRS in some patients. The end point of this study was loss of tumor control, defined as a lesion requiring resection.

Methods

Patient Population

We retrospectively reviewed a consecutive series of 35 patients with large VSs who underwent GKRS between 2000 and 2014. Large VSs were defined as having both one dimension > 3 cm and a volume > 10 cm³. Patients with neurofibromatosis Type 2 were also excluded. At least 2 years of data from regularly scheduled, follow-up visits were required. The study was approved by the institutional review board at our institution. MR images as well as trigeminal and facial nerve functions were routinely assessed on clinical consultation and graded using the House-Brackmann scale.⁹ Gardner-Robertson classes were derived from the posttreatment audiology reports.⁶ The mean age of patients harboring large VSs was 49.7 years, and there was a male predominance (57.1%) in this group. Microsurgical resection had been performed previously in 9 patients (25.7%). Three patients underwent volume-staged GKRS with the same 10-Gy margin dose at a 6- to 18-month interval. The demographic features of these 35 patients are summarized in Table 1. Preoperatively 3 people had serviceable hearing, while 32 had non-serviceable hearing. Twelve patients had isolated CN VIII involvement, 14 had CN V/VII involvement in addition to CN VIII involvement, and 9 patients had gait imbalance in addition to CN VIII involvement.

Radiosurgical Parameters

Treatment planning was achieved using MRI in all patients. The median isodose line was 50% (range 42%–55%). The median margin dose was 11 Gy (range 10–12 Gy), and the median maximal dose was 22 Gy (range 18.2–28.6 Gy). The median total volume covered was

TABLE 1. Demographic and radiosurgical features in 35 patients with large VSs

Characteristic	No. of Pts (range)
Laterality, rt/lt	18/17
Sex, M/F	20/15
Mean age (yrs)	49.7 (21–74)
Median FU period (mos)	48 (6–156)
No. of previous ops, 0/1/2/3	26/7/1/1
Median tumor vol (cm ³)	14.8 (10.3–24.5)
Median max dose (Gy)	22 (18.2–28.6)
Median margin dose (Gy)	11 (10–12)
Median isodose line (%)	50 (42–55)
Median no. of shots	17 (10–36)

FU = follow-up; Pts = patients.

14.8 cm³ (range 10.3–24.5 cm³), with a mean coverage of 96.2% (range 92%–100%). The median shot number was 17 (range 10–36). The radiosurgical features of these 35 patients are summarized in Table 1.

Follow-Up

Patients were followed up clinically and radiologically every 6 months for the first 2 years after GKRS, annually for the following 2 years, and then every 2 years thereafter. Imaging outcome was determined based on examination of the last available study. A change in tumor size was indicated by a minimum of 15% reduction in tumor volume, and an increase was defined by volumetric enlargement > 15%.²⁵ The tumor was defined as unchanged if it was within 15% of its volume at the time of GKRS. Tumor control was defined as an unchanged or decreased tumor volume. Failure was defined as loss of tumor control, defined as the need for resection.

Statistical Analysis

We analyzed the results by performing hazard ratios of risk factors based on a univariate Cox proportional hazards regression model for all possible factors in Table 2. Estimates of the tumor control rate were calculated using the log-rank test for tumor volume ≥ 15 cm³ and < 15 cm³ and also by indication as defined by those with only CN VIII involvement, more than one CN involvement in addition to CN VIII with no gait instability, and gait instability (regardless of CN involvement). For all tests, *p* values < 0.05 indicated statistical significance. All analyses were performed using SPSS 15.0 statistical software (SPSS, Inc.).

Results

Tumor Response

The median follow-up duration was 48 months (range 6–156 months). All 35 patients had regular MRI follow-up; 20 tumors (57.1%) had a volume reduction of more than 50%, 5 (14.3%) had a volume reduction of 15%–50%, 5 (14.3%) were stable in volume (volume change < 15%), and 5 (14.3%) had larger volumes (all of which were resected). Three patients who underwent volume-staged GKRS had marked volume reduction (Fig. 1). Among the 5 patients in

TABLE 2. Hazard ratios of risk factors based on univariate Cox proportional hazards regression model for clinical and radiological features

Characteristic	HR	95% CI for HR		p Value
		Lower	Upper	
Sex (M)	1.376	0.228	8.303	0.728
Age	0.985	0.927	1.047	0.628
Vol (cm ³)	1.135	0.981	1.313	0.088
Dose (Gy)	1.036	0.309	3.467	0.955
Isodose %	1.024	0.824	1.274	0.829
Shot	1.140	0.987	1.316	0.075
Pre-GKRS op	0.081	0.000	18.778	0.366
Necrosis	0.401	0.044	3.680	0.419
Cyst	1.593	0.261	9.70	0.614
Vol change				
↓ >75%	1			
↓ 50%–75%	0.000	0.000	—*	0.973
↓ 15%–50%	3.951	0.237	65.957	0.339
No change	0.000	0.000	—*	0.982
↑	9.972	0.994	99.998	0.051
CN V	1.995	0.330	12.047	0.452
CN VII	0.030	0.000	130.918	0.411
CN VIII	0.188	0.021	1.718	0.139
Gait	4.448	0.735	26.911	0.104

HR = hazard ratio; ↓ = volume decrease; ↑ = volume increase.

* Large upper limits generated because of large standard errors.

whom tumor volumes increased, 4 (11.4%) underwent resection (range 9 months to 6 years) because of progressive symptoms. One patient (2.9%) underwent open surgery due to new onset of intractable trigeminal neuralgia at 48 months after GKRS. Kaplan-Meier analysis of tumor control rate during follow-up after GKRS is shown in Fig. 2.

Clinical Outcomes and Complications of GKRS

There were no major complications after GKRS, although minor complications did occur. Two of 3 patients with serviceable hearing before GKRS deteriorated, and 1 retained the same level of hearing, but 2 patients improved from severe hearing loss to pure tone audiometry less than 50 dB (Fig. 3). Eight (66%) of 12 patients with pre-GKRS trigeminal dysfunction had hypoesthesia relief. One hemifacial spasm was completely resolved after 3 years. Seven patients with facial weakness experienced no deterioration after SRS. Two patients (5.7%) who developed a symptomatic cyst underwent placement of a cystoperitoneal shunt.

Risk Factors for GKRS Failure

Statistical analysis revealed no specific risk factors for GKRS failure or post-GKRS cranial neuropathy. This includes patient age, treatment volume, cystic tumor character, tumor margin dose, pre-GKRS trigeminal or facial neuropathy, and pre-GKRS hearing loss (Table 2). Univariate analysis showed borderline significance for patients with tumor enlargement after GKRS later requiring open resection ($p = 0.05$, HR 9.97, 95% CI 0.99–100.00). However, multivariate analysis failed to identify any significant univariate predictors. Tumor control rates were significantly different in patients with tumor volumes ≥ 15 cm³ and < 15 cm³ ($p = 0.005$) (Fig. 4). An ad hoc analysis for tumor control rates without the 3 patients who underwent

FIG. 1. Contrast-enhanced T1-weighted MR images showing a VS (22 cm³) treated with volume-staged GKRS in a 21-year-old woman. **A:** GammaPlan illustrating Stage I GKRS (GKSI) with a margin dose of 10 Gy to the anteromedial portion of tumor. **B:** Loss of central enhancement at 6 months. **C:** GammaPlan illustrating Stage II GKRS (GKSII) with a 10-Gy margin dose for the posterolateral portion of the tumor at 18 months. **D:** Loss of central enhancement at the previously treated portion after 2 years. **E–H:** Follow-up images demonstrating that the tumor gradually shrank 3, 5, 7, and 9 years after GKRS, respectively. M = months; Y = years. Figure is available in color online only.

FIG. 2. Kaplan-Meier plot showing tumor control rate in cases of large VSs plotted against follow-up time. Figure is available in color online only.

multiple treatments for the 2 groups remained statistically significant ($p = 0.0038$).

Tumor Control by Indication

Tumor response was also analyzed based on indication

and stratified by type of CN involvement (CN VIII only, multiple CN involvement, and gait instability) and showed no significance ($p = 0.0761$; Fig. 5). No single CN or gait instability showed significance in predicting outcome (Table 2).

FIG. 3. Contrast-enhanced axial MR images and audiograms obtained in a 31-year-old man with a large VS. **A:** Image showing a large 12.1-cm³ VS treated with GKRS at a margin dose of 11 Gy. **B:** Follow-up image demonstrating that the tumor volume shrank to 2.3 cm³ at 2 years after GKRS. **C:** Audiogram showing severe hearing loss before GKRS. **D:** Audiogram demonstrating serviceable hearing (Gardner-Robertson Class II) at 2 years follow-up. Figure is available in color online only.

Discussion

Typically, large VSs are defined by a maximal dimension > 3 cm and small VSs as < 3 cm. In the literature, however, most studies' measurements were obtained using less reliable 2D measurements ranging from > 2.5 cm to > 4 cm, and only 2 studies used volume measurements > 6 cm³ in one and > 8 cm³ in the other.^{3,27} One study defined size as a Koos Grade IV tumor.²¹ Most authors have defined large VSs as > 3 cm in maximal dimension, but no consensus on tumor volume has been determined. Currently there is a wide range, with mean volume from 4.3 to 17.3 cm³ and a range of 1.34–25.2 cm³.^{3,5,7,15,21,27,29–31} We defined large VSs as those with both a single dimension > 3 cm and a volume > 10 cm³, and we reviewed our data for a possible role for GKRS in treating large VSs.

Tumor Control

The tumor control rate in our patients with large VSs was 85.7%. Our findings are consistent with other recent reports of GKRS for large VSs. A limited number of studies on SRS as the primary treatment for large VSs have been conducted (Table 3). Tumor control rates vary from 82% to 94%.^{3,5,7,15,21,27,29–31} The University of Pittsburgh published data showing a long-term tumor control rate of 98% for VSs,¹² compared to 86.2% for large VSs in a subsequent study.³⁰

FIG. 4. Kaplan-Meier plot showing tumor control rate in large VSs after GKRS plotted against time in patients with tumor volumes < 15 and ≥ 15 cm³. p = 0.005, log-rank test. Figure is available in color online only.

Functional Outcome

No deterioration in facial nerve or trigeminal nerve function was noted. Other series of GKRS for large VSs have reported similar outcomes (Table 4). Obviously, facial nerve outcome following GKRS is superior to that associated with microsurgical removal of large VSs in which

good function (HB Grade I or II) is reported in 27%–58% of cases.^{2,24,27,28,32} Facial nerve outcome is comparable with those in studies featuring subtotal resection followed by GKRS.^{7,26} In a meta-analysis study of large VSs, Gurgel et al.⁷ showed a strong and significant association between extent of resection and outcome (p < 0.0001) in 471 pa-

FIG. 5. Kaplan-Meier plot showing tumor control rate in different clinical indications by CN involvement: 1) CN VIII only; 2) CN VIII + CN V or VII; 3) CN VIII + gait instability. p = 0.0761, log-rank test. Figure is available in color online only.

TABLE 3. Previous reports of radiosurgical experiences with large VSs

Authors & Year	No. of Pts	Type of SRS	Definition	Tumor Diam or Vol (range)	Tumor Control Rate (%)	Post-RS MS (no.)/Repeat RS/Obs	Median Mos of FU (range)
Chung et al., 2010	21	GKRS	>3 cm	Mean 17.3 cm ³ (12.7–25.2 cm ³)	90.5	9.5% (2)/1 GKRS	53 (12–155)
van de Langenberg et al., 2011 ²⁷	33	GKRS	>6 cm ³	Mean 3 cm (2.3–4 cm); mean 8.8 cm ³ (6.1–17.7 cm ³)	88	15% (5)	30 (12–72)
Yang et al., 2011	65	GKRS	3–4 cm	Median 9 cm ³ (5–22 cm ³)	86.2	10.8% (7)/1 GKRS	36 (1–146)
Milligan et al., 2012	22	GKRS	>2.5 cm	Median 2.8 cm (2.5–3.8 cm); median 9.4 cm ³ (5.3–19.1 cm ³)	82	9% (2)/0 of 2	66 (26–121)
Williams et al., 2013	24	GKRS	>3 cm	Median 9.5 cm ³ (3.1–24.7 cm ³)	75	12.5% (3)/3 GKRS	82.5 (7–222)
Zeiler et al., 2013	28	GKRS	>3 cm	Median 9.6 cm ³ (6.9–10.6 cm ³)	92	4% (1)	34.5 (6–99)
Casentini et al., 2015	33	CK	>8 cm ³	Median 9.4 cm ³ ; mean 11 cm ³ (8–24 cm ³)	94	6% (2)	48 (12–111)
Present series	35	GKRS	>3 cm & >10 cm ³	Median 14.8 cm ³ (10.3–24.5 cm ³)	85.7	14.3% (5)	48 (6–156)

CK = CyberKnife; Diam = diameter; MS = microsurgery; Obs = observation; RS = radiosurgery.

tients. Of the 80 patients receiving subtotal resections, 92.5% had good facial nerve outcomes compared with 74.6% (n = 55) and 47.3% (n = 336) in those who received near-total resections and gross-total resections, respectively.

In 2 of 3 patients with serviceable hearing before GKRS, deterioration occurred, while in 1 patient serviceable hearing was retained. Two patients improved from severe hearing loss to pure tone audiometry less than 50 dB. Hearing loss after GKRS is caused by the toxic effects of GKRS on the cochlea, which is nearly unavoidable when planning for GKRS. If possible, the treatment plan is modified to minimize the dosage to the cochlea. Other studies have documented serviceable hearing preservation from 30% to 82% after primary GKRS in cases of large VSs (Table 4). These results are superior to the published range of hearing preservation rates following complete microsurgical removal of large VS (0%–29%).^{20,23,24,26,32}

Resection for Failed Tumor Control

Five patients (14%) required resection of their large VSs for tumor progression after initial GKRS. This incidence

of tumor progression among large VSs ≥ 15 cm³ was significantly higher than it was for those with volumes < 15 cm³ (p = 0.005). In all cases requiring resection, the tumor volume was larger than 15 cm³. Hasegawa et al.⁸ analyzed a series of VSs of all sizes treated with GKRS (n = 317) and found that tumors “less than 15 cm³ in volume (10-yr PFS [progression-free survival], 96%; P < 0.001) or which did not compress the brainstem and deviate the fourth ventricle (10-yr PFS, 97%; P = 0.008) resulted in significantly better PFS rates.” Milligan et al.¹⁵ identified 2 major risk factors for tumor control failure: a tumor volume exceeding 15 cm³ (5-year progression-free survival 57%) and brainstem compression and/or displacement of the fourth ventricle (5-year progression-free survival 74%). Roche et al.²¹ also showed that tumor volume was correlated to GKRS failure in the univariate and multivariate models (p = 0.027). All the evidence demonstrates that larger tumor volume plays an important role in failed disease control, especially when the tumor volume is > 15 cm³.

In the studies of large VSs that we have reviewed, 17 patients required resection because of increased intracranial pressure or worsened symptoms, whereas 2 required resection for malignant change and 1 for cerebellar infarction (Table 5). As for the resection procedure itself, we rec-

TABLE 4. Previous reports of functional outcome in large VSs treated with GKRS

Authors & Year	No. of Pts	Outcome			
		CN V	CN VII	CN VIII	Gait
Chung et al., 2010	21	8 stable	100% (12/12) stable	1 worse	23% (5/23) worse
van de Langenberg et al., 2011 ²⁷	33	92% (11/12) imp	100% (33/33) stable	58% (7/12) stable	NA
Yang et al., 2011	65	94% stable, 6% worse	98% stable, 2% worse	82% stable	NA
Milligan et al., 2012	22	92% (19/22) stable, 8% (3/22) worse	90% (20/22) stable	30% (3/10) stable	NA
Williams et al., 2013	24	36% (4/11) imp, 28% (3/11) worse	70% (14/20) stable, 30% (6/20) worse	NA	NA
Zeiler et al., 2013	28	50% (6/12) imp	33% (3/9) imp, 3% (1) worse (HFS)	NA	NA
Present series	35	66% (8/12) imp	100% (7/7) stable	33% (1/3) stable, 6% (2/32) imp	11% (4/35) worse

HFS = hemifacial spasm; imp = improved; NA = not applicable.

TABLE 5. Previous reports of post-GKRS resection in large VSs

Authors & Year	No. of Pts	Post-RS MS	Reason for Resection	Mean Time to Failure in Mos (range)	Mean Tumor Vol in cm ³ (range)	No. of Post-GKRS VP Shunts
Chung et al., 2010	21	2 (9.5%)	1 ataxia, 1 malignant tumor	Ataxia: 72; tumor: 8	Ataxia: 7.0; tumor: 16.4	3
van de Langenberg et al., 2011 ²⁷	33	5 (15%)	5 regrowth	33 (12–50)	NA	
Yang et al., 2011	65	7 (10.8%)	5 symptom progression, 1 IICP, 1 IICP by cerebellar infarction	5 symptom progressions: 21 (4–50); IICP: 17; IICP by cerebellar infarction: 1	13.1 (8.1–21.6)	4
Milligan et al., 2012	22	2 (9%)	1 sarcoma, 1 IICP	Sarcoma: 90; IICP: 14	NA	3
Williams et al., 2013	24	3 (12.5%)	3 regrowth	NA	NA	
Zeiler et al., 2013	28	1 (4%)	1 ataxia (BS compression)	NA	NA	
Present series	35	5 (14.3%)	2 symptom progression by cyst, 1 trigeminal neuralgia, 2 IICP	30 (9–72)	18.6 (15–24.5)	2

BS = brainstem; IICP = increased intracranial pressure; VP = ventriculoperitoneal.

ommended subtotal resection of tumor using intracapsular decompression, hoping to attain better functional results. At the last follow-up, facial nerve function was preserved (HB Grade I–II) in all patients who required resection except one in whom near-total resection was performed. Iwai et al.¹⁰ reported that HB Grade I function was retained in 82% of their cases following salvage surgery for failed GKRS for VSs; the mean duration after GKRS of failed tumor control was 33 months in these patients. Previous studies revealed that most patients underwent resection between 2 and 4 years after GKRS (Table 5).

Staged GKRS for Transient Tumor Expansion

Three of our patients who underwent volume-staged GKRS had marked volume reduction during follow-up. In patients with larger tumors, transient tumor expansion after SRS can cause morbidity. One of our patients who required resection had symptom deterioration 9 months after GKRS, which was probably a case of transient tumor enlargement. Pollock,¹⁹ in a retrospective study of 208 patients with SRS-treated VSs, noted that 34 patients (14%) had tumors that enlarged at least 2 mm after SRS. The median volume increase was 75%, and 6 patients (20%) had new symptoms. The median time to tumor enlargement was 9 months.¹⁹ Mindermann and Schlegel¹⁶ reported transient tumor expansion that appeared at 6–18 months following GKRS. This is different from actual tumor growth, which was noted to occur at about 3–4 years. In some cases of large VSs, volume-staged GKRS may be feasible to ease transient tumor expansion to enhance successful disease control and ease clinical symptoms.

Challenges and Limitations

Despite not seeing any significance in outcome based on clinical indication, one must keep in mind that our sample size was 35 patients. When looking purely at percentages, those with only CN VIII involvement had a 0% treatment failure, whereas those with gait instability in addition to CN involvement had a 50% treatment failure (Fig. 5). Despite not reaching statistical significance, this discrepancy may be explained as such: patients with gait

instability tend to have worse mass effect, which would correlate with the findings in the study by Milligan et al.,¹⁵ who found that brainstem compression/fourth ventricle effacement is also an indicator for tumor control failure, as is a volume exceeding 15 cm³. A future study with additional cases may be warranted to validate this.

Conclusions

Gamma Knife radiosurgery for the treatment of large VSs—those with a diameter of > 3 cm and a volume of > 10 cm³—offers acceptable tumor control rates and good hearing and facial nerve preservation rates while also yielding a low permanent complication rate. Tumor volume ≥ 15 cm³ was a significant factor for GKRS failure. To prevent negative outcomes associated with transient tumor expansion, careful symptom evaluation and monitoring in follow-up is required.

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Disclosures

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Author Contributions

Conception and design: CF Huang. Acquisition of data: CW Huang, Tu. Analysis and interpretation of data: Lee. Critically revising the article: CW Huang, Chuang. Reviewed submitted version of manuscript: Chang, Lee. Statistical analysis: Chou.

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