Outcome of Intracerebral Cavernoma Treated by Gamma Knife Radiosurgery Based on a Double-blind Assessment of Treatment Indication

Chiung-Chyi Shen
Taichung Veterans General Hospital
Ming-Hsi Sun
Taichung Veterans General Hospital
Men-Yin Yang
Taichung Veterans General Hospital
Weir Chiang You
Taichung Veterans General Hospital
Meei-Ling Sheu
Taichung Veterans General Hospital
Yen–Ju Chen
Taichung Veterans General Hospital
Ying-Ju Chen
Providence University
Jason Sheehan
University of Virginia Health System: UVA Health
Hung-Chuan Pan (hcpan2003@yahoo.com.tw)
Taichgung Veterans General Hospital https://orcid.org/0000-0003-3021-7676

Research

Keywords: Intracerebral cavernoma (CM), Gamma Knife radiosurgery, double-blind assessment, treatment, benefit

Posted Date: July 7th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-550603/v2

Abstract

Background: The benefit and the risk profile of Gamma Knife radiosurgery for intracerebral cavernoma remains incompletely defined in part due to the natural history of low incidence of bleeding and spontaneous regression of this vascular malformation. In this study, we retrieved cases from a prospectively collected database to assess the outcome of intracerebral cavernoma treated with Gamma Knife using a double blinded review process for treatment.

Methods: From 2003 to 2018, there were 94 cases of cavernoma treated by Gamma Knife radiosurgery doubly blinded assessed by two experienced neurological and approved for Gamma Knife treatment. All the patients received Gamma Knife radiosurgery with margin dose of 11-12 Gy and afterwards were assessed for neurological outcome, radiologic response, and quality of life.

Results: The median age of the patients was 48(15-85) years with median follow up of 77(26-180) months post SRS. The mean treated volume was 1.93±3.45cc. In those who has pre-SRS epilepsy, 7 of 16(43.7%) achieved seizure freedom (Engel I/II) and 9 of 16 (56.3%) achieved decreased seizures (Engel III) after SRS. Rebleeding occurred in 2 cases (2.1%) at 13 and 52 months post SRS. The radiologic assessment demonstrated 20 (21.3%) cases of decreased cavernoma volume, 69(73.4%) were stable, and 5 (7.3%) increased size. Eight-seven of 94 (92.5%) cases at the last follow up achieve improvement in their quality of life, but 7 cases (7.4%) showed a deterioration. In statistical analysis, the effective seizure control class (Engel I/II) was highly correlated with patient harboring a single lesion ($p<0.05$) and deep seated location of the cavernoma ($p<0.01$). New neurological deficits were highly correlated with decreased mental ($p<0.001$) and physical ($p<0.05$) components of quality of life testing, KPS ($p<0.001$), deep seated location ($p<0.01$), and increased nidus volume ($p<0.05$). Quality of life deterioration either in physical component ($p<0.01$), mental component ($p<0.01$), and KPS ($p<0.05$) was highly correlated with increased cavernoma volume.

Conclusion: Low margin dose Gamma Knife radiosurgery for intracerebral cavernoma offers reasonable seizure control and improved quality of life while conferring a low risk of treatment complications including adverse radiation effect.

Background:

Intracerebral cavernoma (CM) are uncommon in the general population, with a prevalence ranging from 0.3–0.6% based on large autopsy series and prospective cohort studies. The increasing incidence of cavernoma is largely due to diagnostic advances with widespread use of magnetic resonance imaging (MRI) in clinical practice (prevalence 0.4–0.9%) [1–4].Individuals with CMs can present with seizures (23–50% of cases), headaches (6–52%), focal neurological deficits (20–45%), or hemorrhages (9–56%) [1, 5–10]. The extent of permanent neurological deficits highly correlates with the number of recurrent hemorrhages, and re-bleeding episodes tend to occur at progressively shorter time intervals [11]. In patients with a symptomatic cavernoma, microsurgery is the best treatment for CM, especially given

advances in microsurgical techniques and neuronavigation-guided approaches [12]. For patients with deeper seated or eloquently situated cavernomas, Gamma Knife radiosurgery (GKRS) is considered as an alternative [13–15].

The use of radiosurgery for cavernoma remains controversial especially for the primary goal of reducing the bleeding rate. Some authors have favored radiosurgery for intracranial cavernoma, due to a reduced risk of hemorrhages after a latency period of 2–3 years [16–18]. But others are less convinces about the benefits of SRS for cavernomas for a variety of reasons. First, the hemorrhage rate, particularly for retrospective series, is not simple to calculate due to the appearance of cavernoma in de novo and referral and treatment biases [19]. Second, the high-risk CM patients are usually selected to undergo surgery after SRS and thus deflate the post-SRS hemorrhage rates with time [20]. Ironically, in some reports, SRS itself can also induce de novo CM development [21–23]. Furthermore, the risk of a CM rebleeding is typically high for 2–3 years after the initial hemorrhage and, thereafter, cavernoma re-hemorrhage after SRS appears to be reduced after this period of time [24]. The temporal clustering of hemorrhagic events might give a false impression of how aggressive a lesion will be in the long term. The decline in hemorrhagic events observed after treating CMs with SRS could, therefore, be a reflection of the natural history of the lesions rather than the result of radiosurgery [20, 25, 26]. Finally, cavernous malformations are dynamic lesions that may exhibit enlargement, regression, or even de novo formation [10, 27, 28]. Hence, the beneficial effect of SRS in altering the natural history of cavernoma continues to be questioned.

The risk of seizures was estimated to be 1.34% per person-year for solitary CMs and 2.48% per person-year for multiple lesions [29]. The assessment of gamma knife on the seizure control rate based on the different study design achieved the seizure free rate from 31–53% and decreased seizure frequency from 45–66%, but without any treatment-related death [14, 18, 30–32]. Thus, it seems that GKRS seems to be a rationale approach for improving seizure frequency associated with a cavernoma.

The outcome of radiosurgery on the intracerebral cavernoma remains controversial. One way to verify the actual effect of GKRS is by clinical observation during a longer follow-up period. In addition, one could study the effects of GKRS on quality of life and seizures in cavernoma treatment patients. In this study, we prospectively evaluated the outcomes of GKRS in cavernoma patients who were blindly approved by two independent neurosurgeons.

Methods:

Patient population

From 2003 to 2018, there were 121 cases of intracranial cavernoma blindly approved by the two independent neurosurgeons excluding the in-charge neurosurgeon for the GKRS based on the patients' medical records and imaging findings at the Central Bureau of Health Insurance, Taichung, Taiwan, to determine whether GKRS was the appropriate treatment. The approval criteria was based on the consensus of Taiwan Neurosurgical Society on for GKRS including one or more of the following:

recurrence of cavernoma after craniotomy, nidus volume less than 20cc or maximum diameter less than 3.5cm, vulnerable location for the nidus removal, severe illness inappropriate for general anesthesia, or KPS>70. Finally, there were 105 of 121 (86.7%) cases approved for Gamma Knife treatment. There were 11 cases lost to follow up, and, as such, 94 (89.5%) cases were included in this study. The study was approved by the ethical committee of Taichung Veterans General Hospital on record No. CG 18080

Radiosurgical Technique

After the patient had received a local anesthetic agent, the Leksell G head frame was affixed to the head, and the patient was monitored for blood pressure, oxygenation, and electrocardiography. All patients were treated with a Leksell Gamma Knife model D (Elekta AB) by a team consisting of a neurosurgeon, neuroradiologist, radiation oncology, and medical physicist. All patients underwent GKRS with low margin dosage of 11-12 Gy prescribed to nidus at the isodose line of 50% to 60%. Radiosurgery dose plans, with single or multiple isocenters, were created, and the targeted margin of the cavernoma was considered to be the region characterized by mixed signal change within the T2-weighted signal-defined hemosiderin ring [33].

Imaging Technique

The target lesions were typically imaged using a 1.5-T MR imaging unit (GE Medical Systems). Target localization was performed using T1-weighted, fast-spin-echo T2-weighted, spoiled-gradient recalled, and time-off light imaging. Additional T1-weighted, spoiled-gradient recalled, and time-of-flight sequences were also obtained after administration of g*adolinium (*Gd). The axial volume acquisition of 256 × 256 matrices was divided into 1-mm thickness without a gap. All patients gave informed consent to receive a Gd injection in accordance with Taiwan guidelines concerning Gd administration during MR imaging examinations.

Clinical follow up and assessment of Life quality

The patients received regular follow up at 3-6 month intervals after GKRS including neurological examination and record of frequency, intensity and drug dosage in patients with a seizure history. SF-36 is a well-validated instrument for measuring quality of life (QOL) [34]. It covers 8 domains including physical function (PF), role limitation due to a physical problem (RP), bodily pain (BP), general health (GH), vitality, social functioning (SF), role limitation due to an emotional problem (RE), and mental health (MH). In this study, BP was specifically limited to headache and facial pain, and these were clearly described for the participants. In general, the physical component summary covered PF, RP, BP, and GH, whereas the mental component summary included vitality, SF, RE, and MH. Scores on the SF-36 scale range from 0 to 100, with higher scores indicating better condition. The QOL data were collected prior to GKRS and at last out-patient follow-up. The Karnofsky Performance Score (KPS) spans from 100 to 0, where 100 is "perfect" health and 0 is death [35]. KPS was also collected by the clinical team before GKRS and at last follow up.

Imaging Follow-Up

All patients underwent routine MR imaging examinations 6–12 months after GKRS. More specifically, T1-weighted images were obtained with or without administration of Gd, and T2-weighted images were obtained to evaluate whether there were any adverse treatment effects. If patients experienced new neurological deficits (increased seizure frequency, impairment sensory of motor function), they underwent additional imaging examinations at the time of newly neurological deficits to evaluate for radiologic changes associated with these clinical changes. The assessment of volume alteration was based on our previous investigation with volume enlargement by 20% defined as increase, volume reduction by 20 % defined as decrease, and volume changes of less than 20% from baseline defined as stable [36].

Statistical Analysis

Descriptive statistics were computed using standard methods to calculate mean± standard deviation or median values with ranges. Factors contributing to seizure frequency, imaging alteration, neurological outcome, and quality of life that were assessed by the Mann-Whitney test, Chi-Square test, and Fisher's Exact test. Logistical regression testing was used for the assessment of risk factors related to control of seizure, new neurological deficits and improvement in QOL. A p value < 0.05 was considered significant.

Results:

Patient demographics and Treatment parameters

The median age of the patients was 48 year old at the time of GKRS, and there was a male/female ratio of 55 to 39. The clinical diagnosis included 78 cases with hemorrhage and 16 with seizure. Forty one cases presented with pre-existing neurological deficits included motor weakness of 21, sensory impairment of 15, and gait imbalance of 5. Cavernoma locations include 20 cases in the brainstem, 36 in deep seated location and 38 in the sub-cortical region. The mean treated volume was 1.93 ± 3.45 cc. The median margin dose was 12 Gy (11–12). The scores of pre- GKRS KPS were 66.1 ± 7.4. Pre GKRS scores of SF-36 included general health (34.4 ± 15.2), pain (headache) (34.5 ± 21.2), social function (25.5 ± 16.6), emotional well being (35.6 ± 16.9), energy/fatigue (34.2 ± 14.2), role limitation by emotional health (15.6 ± 18.1), role limitation by physical health (28.7 ± 19.1), physical role (33.4 ± 9.4) (Table 1). Patient demographics stratified by the pre-GKRS indications of intracranial bleeding and seizure are shown in Table 2.

Table 1
Demography of the patient (n = 94)

Age		**48**	**(15–85)**
Sex	Female	55	(58.51%)
	Male	39	(41.49%)
Etiology	ICH / Craniotomy	78/6	(82.98%/6.3%)
	Seizure	16	(17.02%)
Interval from diagnosis to GKRS		3	1–24
Pre-existing neurological deficits		41	(43.62%)
Familial Hx		6	(6.38%)
Multiple lesions		28	(29.79%)
Location	Brain stem	20	(21.28%)
	Deep seated	36	(38.30%)
	Subcortex	38	(40.43%)
Venous abnormality		15	(15.96%)
Tumor volume (TV)		1.93 ± 3.45	
Margin Dose		12	(11–12)
Physical component		131.01 ± 34.30	
Mental component		118.04 ± 48.29	
KPS		66.06 ± 7.36	
Continuous data were expressed mean ± SD			
Categorical data were expressed number and percentage			

Table 2
Demography of the patients stratified by etiology

		ICH(n = 78)	Seizure (n = 16)	P values
Age		49(15–18)	39(18–73)	0.146
Sex	Female	44	11	0.526
	Male	34	5	
Craniotomy		3	3	0.06
Interval from diagnosis to GKRS		3(1–24)	5 (1–24)	0.038
Pre-existing neurological deficits		41	0	< 0.001
Familial Hx		3	3	0.059
Multiple lesions		21	7	0.231
Location	Brain stem	20	0	0.017
	Deep seated	31	5	
	Subcortex	27	11	
Venous abnormality		14	1	0.454
Tumor volume (TV)		1.89 ± 3.64	2.11 ± 2.41	0.577
Margin Dose		12(11–12)	12(11–12)	0.392
Physical component		126.12 ± 33.60	154.84 ± 27.73	0.001
Mental component		345.08 ± 77.92	382.50 ± 12.45	0.001
KPS		64.97 ± 7.34	71.88 ± 4.03	0.01
Mann-Whitney test. [C]Chi-Square test. Fisher's Exact test.*$p < 0.05$, **$p < 0.01$.				
Continuous data were expressed mean ± SD.				
Categorical data were expressed number and percentage				

Clinical and imaging outcome

The median follow up period was 77 months. The imaging analysis demonstrated 20 (21.3%) cases of decreased nidus (Fig. 1), 67(73.4%) stable (Fig. 2), 5 (7.3%) with increased size (Fig. 3 and Fig. 4)), and 2 cases with rebleeding (Fig. 5).

Mean post- GKRS KPS were 92.8 ± 11.4. Post GK scores of SF-36 included general health (88.8 ± 18.1), pain (headache) (88.7 ± 20.6), social function (84.9 ± 20.2), emotional well bening (88.5 ± 17.9),

energy/fatigue (86.2 ± 19.3), role limitation by emotional health (80.5 ± 24.2), role limitation by physical health (87.2 ± 24.8), physical role (86.7 ± 17.4). There were significant differences of life quality after GKRS in all patients (Fig. 6a) and also in those stratified by pre-GKRS indications of cavernoma hemorrhage and seizures (Fig. 6b).

Following GKRS, seven cases demonstrated new neurological deficits including 2 cases (2.1%) with re-bleeding at time point of 13 and 52 months following radiosurgery, and 5 cases with deficits associated with increased nidus volume at time point of 24, 52, 80, 96, 108, and 134 months, respectively. The predictive factors for new neurological deficits were shown in Table 3 and Table 4 including brainstem location ($p < 0.01$), venous abnormality ($p < 0.01$), nidus increased after GKRS ($p < 0.001$), post GKRS KPS ($p < 0.01$), post GKRS physical component ($p < 0.05$), and post GKRS mental component ($p < 0.01$). Those patients who developed new neurological deficits also showed no improvement in life quality as illustrated in Fig. 7.

Table 3
Demography of the patients with new neurological deficits

	No (n = 87)	Yes(n = 7)	P value
Age	46.8 ± 15.8	40.8 ± 15.8	0.376
Sex ration (F/M)	1.35	2.25	0.695
ICH history	71	7	0.599
Seizure History	16	0	0.512
Time to GKRS	4.95 ± 5.23	4.86 ± 5.11	0.913
Pre-existing Neurological deficits	37(42.5%)	4(57.5%)	0.695
TV (cc)	2.0 ± 3.56	0.98 ± 1.29	0.264
Familial Hx	6	0	1
Multiple lesion	27	1	0.670
Brain stem Location	15(17.2%)	5(71.4%)	P < 0.01
Venous abnormality	11(12.64%)	4(57.15%)	P < 0.01
Nidus Increased post GKRS	1(1.14%)	4(87.1%)	P < 0.001
Post-GKRS KPS	95.40 ± 5.67	60.0 ± 14.14	P < 0.01
Post GKRS Physical component	113.38 ± 47.08	79.3 ± 45.79	P < 0.05
Post GKRS Mental component	357.14 ± 36.01	129.30 ± 95.67	P < 0.001
Mann-Whitney test. [C]Chi-Square test. Fisher's Exact test.*$p < 0.05$, **$p < 0.01$.			
Continuous data were expressed mean ± SD.			
Categorical data were expressed number and percentage			

Table 4
Risk factors for the new neurological deficits

	Simple model		Multiple model	
	HR (95%CI)	*p* value	HR (95%CI)	*p* value
Age	1.00 (0.95–1.04)	0.909		
Sex				
Female	ref.			
Male	0.73 (0.13–4.07)	0.715		
Time from diagnosis to GKRS (months)	0.95 (0.78–1.14)	0.565		
Neurological deficits	3.29 (0.58–18.61)	0.179		
TV(cc)	0.91 (0.58–1.43)	0.693		
Margin dose (Gy)	1.33 (0.67–2.63)	0.419		
Multiple lesions	0.63 (0.07–5.62)	0.678		
at GKRS				
Physical component	0.95 (0.92–0.99)	0.019*	0.96 (0.91–1.01)	0.147
Mental component	0.97 (0.95–0.996)	0.019*	0.97 (0.94-1.00)	0.086
Location				
brain stem + deep seated	ref.			
subcortical	0.33 (0.04–2.89)	0.319		
Venous abnormality	5.36 (1.02–28.06)	0.047*	0.20 (0.00-10.54)	0.430
Post GKRS volume				
decrease + stable	ref.		ref.	
increase	16.42 (3.09–87.30)	0.001**	85.70 (1.56-4701.01)	0.029*
Cox regression. *$p < 0.05$, **$p < 0.01$.				

In 16 cases with pre GKRS seizure, 7 cases reach the Engel I –II and 9 cases of Engel III at last follow up. There was no case of Engel IV. The prognostic factors for seizure control are shown in Table 5 and

Table 6. The predictive factors for effective seizure control (Engel I/II) included post GK mental component ($p < 0.004$) and a single lesion ($p < 0.05$).

Table 5
Demography of the patients in the seizure control

	Engel 1–2 (n = 7)	Engel 3 (n = 9)	*p* value
Age	49.86 ± 20.23	33.89 ± 13.27	0.119
Sex (F/M)	5/2	6/3	1
Hx of Craniotomy	1	2	1
Interval from diagnosis to GKRS	8.00 ± 8.77	6.22 ± 3.49	0.898
Physical component at GKRS	162.14 ± 28.15	149.17 ± 27.64	0.303
Mental component at GKRS	384.29 ± 13.28	381.11 ± 12.38	0.639
KPS at GKRS	72.86 ± 4.88	71.11 ± 3.33	0.55
Physical component after GKRS	141.27 ± 18.94	142.76 ± 30.83	0.938
Mental component after GKRS	397.29 ± 3.86	377.59 ± 15.43	0.004
KPS after GKRS	98.57 ± 3.78	97.78 ± 4.41	1
TV (cc)	1.83 ± 2.04	2.33 ± 2.76	0.123
Multiple lesions	1	6	0.04
Location (subcortical region)	3	8	0.106
Post GKRS volume (increase)	0	1	0.652
Mann-Whitney test. [C]Chi-Square test. Fisher's Exact test.*$p < 0.05$, **$p < 0.01$.			
Continuous data were expressed mean ± SD.			
Categorical data were expressed number and percentage			

Table 6

Risk factors in good seizure control (Engel I/II)

	Simple model	
	OR (95%CI)	*p* value
Age	0.94 (0.88-1.01)	0.092
Sex		
Female	ref.	
Male	1.25 (0.15-10.70)	0.839
Past Hx of craniotomy	1.71 (0.12-23.94)	0.689
Time from diagnosis to GKRS (months)	0.95 (0.80-1.13)	0.562
TV(cc)	1.10 (0.71-1.70)	0.670
Margin dose (Gy)	0.56 (0.24-1.32)	0.186
Multiple Lesions	12.00 (0.96-150.69)	0.054
Location		
deep seated	ref.	
subcortical	10.67 (0.82-138.22)	0.070
Logistic regression. *p<0.05, **p<0.01.		

In the logistical regression analysis, QOL deterioration either in physical component or mental component and a decline in KPS were highly correlated to increased volume of nidus (Table 7–9).

Table 7
Risk factors in improvement of physical component in SF-36

	Simple model		Multiple model	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Age	1.06 (0.99–1.14)	0.070		
Sex				
Female	ref.			
Male	2.98 (0.32–27.75)	0.337		
Time from diagnosis to GKRS (months)	0.98 (0.84–1.14)	0.769		
Neurological deficits	0.50 (0.08–3.12)	0.456		
TV(cc)	1.48 (0.59–3.67)	0.401		
Margin dose (Gy)	0.73 (0.34–1.54)	0.406		
Multiple Lesions	1.74 (0.19–16.32)	0.627		
Venous abnormality	0.04 (0.004–0.34)	0.004**	0.14 (0.01–3.04)	0.210
Post GKRS volume				
decrease + stable	ref.		ref.	
increase	0.003 (0.0001-0.05)	< 0.001**	0.01 (0.0003-0.15)	0.002**
Logistic regression. *$p < 0.05$, **$p < 0.01$.				

Table 8
Risk factors in improvement of mental component in SF-36

	Simple model		Multiple model	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Age	1.08 (0.99–1.17)	0.070		
Sex				
Female	ref.			
Male	2.19 (0.22–21.90)	0.504		
Time from diagnosis to GKRS (months)	0.95 (0.82–1.11)	0.543		
Neurological deficits	0.76 (0.10–5.67)	0.793		
TV(cc)	1.28 (0.58–2.80)	0.537		
Margin dose (Gy)	0.59 (0.25–1.38)	0.221		
Multiple Lesions	1.29 (0.13–12.92)	0.831		
Venous abnormality	0.05 (0.005–0.53)	0.013*	0.26 (0.01–5.85)	0.400
Post GKRS volume				
decrease + stable	ref.		ref.	
increase	0.01 (0.001–0.11)	< 0.001**	0.02 (0.001–0.35)	0.008**
Logistic regression. *$p < 0.05$, **$p < 0.01$.				

Table 9
Risk factors in improvement of KPS

	Simple model		Multiple model	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Age	1.04 (0.98–1.11)	0.191		
Sex				
Female	ref.			
Male	2.98 (0.32–27.75)	0.337		
Time from diagnosis to GKRS (months)	1.16 (0.81–1.65)	0.417		
Neurological deficits	1.17 (0.19–7.35)	0.867		
TV(cc)	1.12 (0.70–1.77)	0.642		
Margin dose (Gy)	0.63 (0.29–1.35)	0.231		
Multiple Lesions	1.74 (0.19–16.32)	0.627		
Location				
brain stem + deep seated	ref.			
subcortical	2.85 (0.31–26.51)	0.358		
Venous abnormality	0.04 (0.004–0.34)	0.004**	0.14 (0.01–3.04)	0.210
Post GKRS volume				
decrease + stable	ref.		ref.	
increase	0.003 (0.0001-0.05)	< 0.001**	0.01 (0.0003-0.15)	0.002**
Logistic regression. *$p < 0.05$, **$p < 0.01$.				

Discussion:

The assessment of intracranial cavernoma outcomes after GKRS is confounded by the ill-defined incidence of bleeding rate, fluctuation of nidus volume, de-novo growth, and temporal hemorrhage clustering. Aside from the difficulty in the assessment of response in bleeding tendency, we found that the decreased seizure frequency and improved life quality were major contributors for the beneficial effects of GKRS on intracranial cavernoma patients.

There were some arguments in the assessment of a decreased cavernoma bleeding rate following GKRS. First, the long latency period of 2–3 years after GKRS to demonstrate a beneficial effect may simply

reflect the natural history of cavernomas after a prior hemorrhage [16–18]. Second, in calculating the hemorrhage rate, most of published studies are retrospective and influenced by selection and treatment biases [19]. The high-risk patients with complication usually were allocated to resection after SRS and reduce the post-SRS hemorrhage rates with time. [20]. The temporal clustering of hemorrhagic events may only reflect the natural history of the lesions rather than a meaningful alteration of that natural history by GKRS [20, 25, 26]. Also, in some reports, SRS itself can also induce de novo CM development [21–23]. Cavernous malformations are dynamic lesions that may exhibit enlargement, regression, or even de novo formation [10, 27, 28]. In this study, there were only two cases experiencing hemorrhage during the follow up at 13 and 52 months post-GKRS. Due to the low incidence of bleeding and the difficulty in defining the hemorrhage episode before GKRS, the factors subjected to analysis did demonstrate significant relationships to the development of rebleeding.

QOL improvement was a useful tool for the assessment of intracranial lesions treated by the GKRS [37, 38]. In general, the SF-36, BCM-20 and KPS were used for the assessment of life quality after GKRS. In the QOL assessment, the parameters obtained should ideally be assessed in a periodic and continuous fashion [34, 35, 37, 38]. In this study, the SF-36 and KPS data were only obtained at the time point of GKRS and the last outpatient follow up. Thus, the power of the assessment was decreased.

The effect of gamma knife on cavernoma related to seizure control was various due to the different approach in the study design. In one series, seizure control following Gamma Knife was achieved in 53% of patients with Engel Grade I or II, and there was no treatment-related death [18]. In another large series including 291 patients enrolled, 31% were reported to be seizure free and 35% exhibited a decreased seizure frequency [31]. In 18 of 28 patients whose chief complaint was seizures, there was a decrease in seizure frequency [32]. In the 65 patients, seizures were controlled without anticonvulsant medication in 81.8% [14]. In 112 patients, 45% exhibited improvement of their seizures [30]. Thus based upon published findings, GKRS seems to be a rationale approach for improving seizure frequency associated with a cavernoma.

There is still a debate concerning the optimal radiosurgical dose for cavernoma treatment to achieve a beneficial response and minimize side effects. Doses exceeding 15–16 Gy have previously demonstrated significant radiation edema [32, 39]. In lesions located at in the brainstem even with a margin dose of 13Gy, there is substantial increase in radiation induced complication [40], and it seem that 13 Gy is the upper margin dose without significant risk of adverse effects for radiosurgically treated cavernomas [33]. In some anecdotal report, a margin dose of as low as 10 Gy has significant effect in cavernoma shrinkage [41]. In this study, a margin dosage of 11–12 Gy afforded recognizable nidus shrinkage or stability without appreciable adverse effect. Thus the optimal dose and threshold for radiation-related complication for CMs have not been defined until now. It seems that there is a need to explore the issue further particularly for specific sites such as the brainstem.

The effects of GKRS on intracerebral cavernoma are confounded by many factors which are difficult to control, and, therefore, the role of GKRS for cavernomas remains controversial. The only way to verify a

beneficial effect of the treatment is to demonstrate no increased annual risk of re-bleeding and no appreciable complications from the treatment itself. Based on the above assumption, we applied a low margin dose of 11–12 Gy to treat the cavernoma and found that most patients demonstrated decreased seizure frequency, stabilization of the cavernoma, and improvement in QOL. Also, there were no definite adverse effects associated with GKRS. Therefore, a low margin dose of 11–12 Gy in the treatment of cavernoma seems to be a reasonable approach.

Conclusion:

Low margin dose GKRS for intracerebral cavernoma seems to be a reasonable approach which reduces seizure frequency and improves quality of life in the majority of patients. This treatment appears to be without appreciable risk of adverse radiation effects.

Abbreviations:

GKRS: Gamma Knife Radiosurgery; SRS: Stereotactic Radiosurgery; Gy: Gray; MRI: magnetic resonance imaging; Gd: *Gadolinium;* CM: Intracerebral cavernoma; KPS: Karnofsky Performance Score; QQL**:** quality of life; PF: physical function; RP: role limitation due to a physical problem; BP: bodily pain; GH: general health: SF: social functioning; RE: role limitation due to an emotional problem; MH: mental health (MH):

Declarations:

Acknowledgement:

The authors would like to thanks all assistant and Biostatistics Task Force of Taichung Veterans General Hospital for their kind assistances in the manuscript preparation and statistical analysis.

Funding:

The funding (TCVGH-1107306C and TCVGH-PU11068106) was received from Taichung Veterans General Hospital, Taichung, Taiwan

Availability of data and material:

All data generated or analyzed during this study are included in this published article and its additional files.

Author contribution:

SCC and SML collected the data and wrote the manuscript. YMY, YWC and CYJ collected the data of imaging and clinical data for analysis. CYJ and SML helped in statistical analysis. SJ helped to design this study and edit the manuscript. PHC conducted the study design and collected the data and edited the manuscript.

Competing interests:

There was no conflict of interest

Consent for publication:

Not applicable

Ethical approval and consent to participate:

Approval by ethical committee of Taichung Veterans General Hospital is on record No. CG 18080

References:

1. Del Curling O, Jr., Kelly DL, Jr., Elster AD, Craven TE. An analysis of the natural history of cavernous angiomas. Journal of neurosurgery. 1991;75:702-8.
2. Kim DS, Park YG, Choi JU, Chung SS, Lee KC. An analysis of the natural history of cavernous malformations. Surgical neurology. 1997;48:9-17.
3. Robinson JR, Awad IA, Little JR. Natural history of the cavernous angioma. Journal of neurosurgery. 1991;75:709-14.
4. Sarwar M, McCormick WF. Intracerebral venous angioma. Case report and review. Archives of neurology. 1978;35:323-5.
5. Aiba T, Tanaka R, Koike T, Kameyama S, Takeda N, Komata T. Natural history of intracranial cavernous malformations. Journal of neurosurgery. 1995;83:56-9.
6. Al-Shahi Salman R, Berg MJ, Morrison L, Awad IA. Hemorrhage from cavernous malformations of the brain: definition and reporting standards. Angioma Alliance Scientific Advisory Board. Stroke. 2008;39:3222-30.
7. Kondziolka D, Lunsford LD, Kestle JR. The natural history of cerebral cavernous malformations. Journal of neurosurgery. 1995;83:820-4.
8. Porter PJ, Willinsky RA, Harper W, Wallace MC. Cerebral cavernous malformations: natural history and prognosis after clinical deterioration with or without hemorrhage. Journal of neurosurgery. 1997;87:190-7.
9. Robinson JR, Jr., Awad IA, Magdinec M, Paranandi L. Factors predisposing to clinical disability in patients with cavernous malformations of the brain. Neurosurgery. 1993;32:730-5.
10. Zabramski JM, Wascher TM, Spetzler RF, Johnson B, Golfinos J, Drayer BP, et al. The natural history of familial cavernous malformations: results of an ongoing study. Journal of neurosurgery. 1994;80:422-32.
11. Porter RW, Detwiler PW, Spetzler RF, Lawton MT, Baskin JJ, Derksen PT, et al. Cavernous malformations of the brainstem: experience with 100 patients. Journal of neurosurgery. 1999;90:50-8.

12. Attar A, Ugur HC, Savas A, Yüceer N, Egemen N. Surgical treatment of intracranial cavernous angiomas. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2001;8:235-9.
13. Huang YC, Tseng CK, Chang CN, Wei KC, Liao CC, Hsu PW. LINAC radiosurgery for intracranial cavernous malformation: 10-year experience. Clinical neurology and neurosurgery. 2006;108:750-6.
14. Kim MS, Pyo SY, Jeong YG, Lee SI, Jung YT, Sim JH. Gamma knife surgery for intracranial cavernous hemangioma. Journal of neurosurgery. 2005;102 Suppl:102-6.
15. Régis J, Bartolomei F, Kida Y, Kobayashi T, Vladyka V, Liscàk R, et al. Radiosurgery for epilepsy associated with cavernous malformation: retrospective study in 49 patients. Neurosurgery. 2000;47:1091-7.
16. Gross BA, Batjer HH, Awad IA, Bendok BR. Brainstem cavernous malformations. Neurosurgery. 2009;64:E805-18.
17. Hasegawa T, McInerney J, Kondziolka D, Lee JY, Flickinger JC, Lunsford LD. Long-term results after stereotactic radiosurgery for patients with cavernous malformations. Neurosurgery. 2002;50:1190-7.
18. Liu KD, Chung WY, Wu HM, Shiau CY, Wang LW, Guo WY, et al. Gamma knife surgery for cavernous hemangiomas: an analysis of 125 patients. Journal of neurosurgery. 2005;102 Suppl:81-6.
19. Abla AA, Lekovic GP, Turner JD, de Oliveira JG, Porter R, Spetzler RF. Advances in the treatment and outcome of brainstem cavernous malformation surgery: a single-center case series of 300 surgically treated patients. Neurosurgery. 2011;68:403-14.
20. Barker FG, 2nd, Amin-Hanjani S, Butler WE, Lyons S, Ojemann RG, Chapman PH, et al. Temporal clustering of hemorrhages from untreated cavernous malformations of the central nervous system. Neurosurgery. 2001;49:15-24
21. Nagy G, Razak A, Rowe JG, Hodgson TJ, Coley SC, Radatz MW, et al. Stereotactic radiosurgery for deep-seated cavernous malformations: a move toward more active, early intervention. Clinical article. Journal of neurosurgery. 2010;113:691-9.
22. Nimjee SM, Powers CJ, Bulsara KR. Review of the literature on de novo formation of cavernous malformations of the central nervous system after radiation therapy. Neurosurgical focus. 2006;21:e4.
23. Yeon JY, Suh YL, Kim JH, Lee JI. Development of de novo cavernous hemangioma after radiosurgery for cavernous hemangioma. Journal of Korean Neurosurgical Society. 2010;48:532-3.
24. Duffau H, Capelle L, Sichez JP, Faillot T, Bitar A, Arthuis F, et al. Early radiologically proven rebleeding from intracranial cavernous angiomas: report of 6 cases and review of the literature. Acta neurochirurgica. 1997;139:914-22.
25. Gross BA, Batjer HH, Awad IA, Bendok BR. Cavernous malformations of the basal ganglia and thalamus. Neurosurgery. 2009;65:7-18.
26. Kim DG, Choe WJ, Paek SH, Chung HT, Kim IH, Han DH. Radiosurgery of intracranial cavernous malformations. Acta neurochirurgica. 2002;144:869-78

27. Clatterbuck RE, Moriarity JL, Elmaci I, Lee RR, Breiter SN, Rigamonti D. Dynamic nature of cavernous malformations: a prospective magnetic resonance imaging study with volumetric analysis. Journal of neurosurgery. 2000;93:981-6.
28. Raychaudhuri R, Batjer HH, Awad IA. Intracranial cavernous angioma: a practical review of clinical and biological aspects. Surgical neurology. 2005;63:319-28.
29. Pham M, Gross BA, Bendok BR, Awad IA, Batjer HH. Radiosurgery for angiographically occult vascular malformations. Neurosurgical focus. 2009;26:E16.
30. Liscák R, Vladyka V, Simonová G, Vymazal J, Novotny J, Jr. Gamma knife surgery of brain cavernous hemangiomas. Journal of neurosurgery. 2005;102 Suppl:207-13.
31. Lunsford LD, Niranjan A, Kano H, Kondziolka D. The technical evolution of gamma knife radiosurgery for arteriovenous malformations. Progress in neurological surgery. 2013;27:22-34.
32. Zhang N, Pan L, Wang BJ, Wang EM, Dai JZ, Cai PW. Gamma knife radiosurgery for cavernous hemangiomas. Journal of neurosurgery. 2000;93 Suppl 3:74-7.
33. Kim BS, Yeon JY, Kim JS, Hong SC, Lee JI. Gamma knife radiosurgery of the symptomatic brain stem cavernous angioma with low marginal dose. Clinical neurology and neurosurgery. 2014;126:110-4.
34. Motamed N, Ayatollahi AR, Zare N, Sadeghi-Hassanabadi A. Validity and reliability of the Persian translation of the SF-36 version 2 questionnaire. Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit. 2005;11:349-57.
35. Mendelsohn J. Blockade of receptors for growth factors: an anticancer therapy--the fourth annual Joseph H Burchenal American Association of Cancer Research Clinical Research Award Lecture. Clinical cancer research : an official journal of the American Association for Cancer Research. 2000;6:747-53.
36. Pan SY, Liu SA, Sun MH, Tsou HK, Lee SD, Chen YJ, et al. Outcome of hearing preservation related to tumor morphologic analysis in acoustic neuromas treated by gamma knife radiosurgery. Radiation oncology (London, England). 2017;12:134.
37. Pan HC, Sheehan J, Huang CF, Sheu ML, Yang DY, Chiu WT. Quality-of-life outcomes after Gamma Knife surgery for trigeminal neuralgia. Journal of neurosurgery. 2010;113 Suppl:191-8.
38. Pan HC, Sun MH, Chen CC, Chen CJ, Lee CH, Sheehan J. Neuroimaging and quality-of-life outcomes in patients with brain metastasis and peritumoral edema who undergo Gamma Knife surgery. Journal of neurosurgery. 2008;109 Suppl:90-8.
39. Liscák R, Vladyka V, Simonová G, Vymazal J, Novotny J, Jr. Gamma knife radiosurgery of the brain stem cavernomas. Minimally invasive neurosurgery : MIN. 2000;43:201-7.
40. Amin-Hanjani S, Ogilvy CS, Candia GJ, Lyons S, Chapman PH. Stereotactic radiosurgery for cavernous malformations: Kjellberg's experience with proton beam therapy in 98 cases at the Harvard Cyclotron. Neurosurgery. 1998;42:1229-36.
41. Ivanov P, Chernov M, Hayashi M, Nakaya K, Izawa M, Murata N, et al. Low-dose gamma knife radiosurgery for cavernous sinus hemangioma: report of 3 cases and literature review. Minimally invasive neurosurgery : MIN. 2008;51:140-6.

Figures

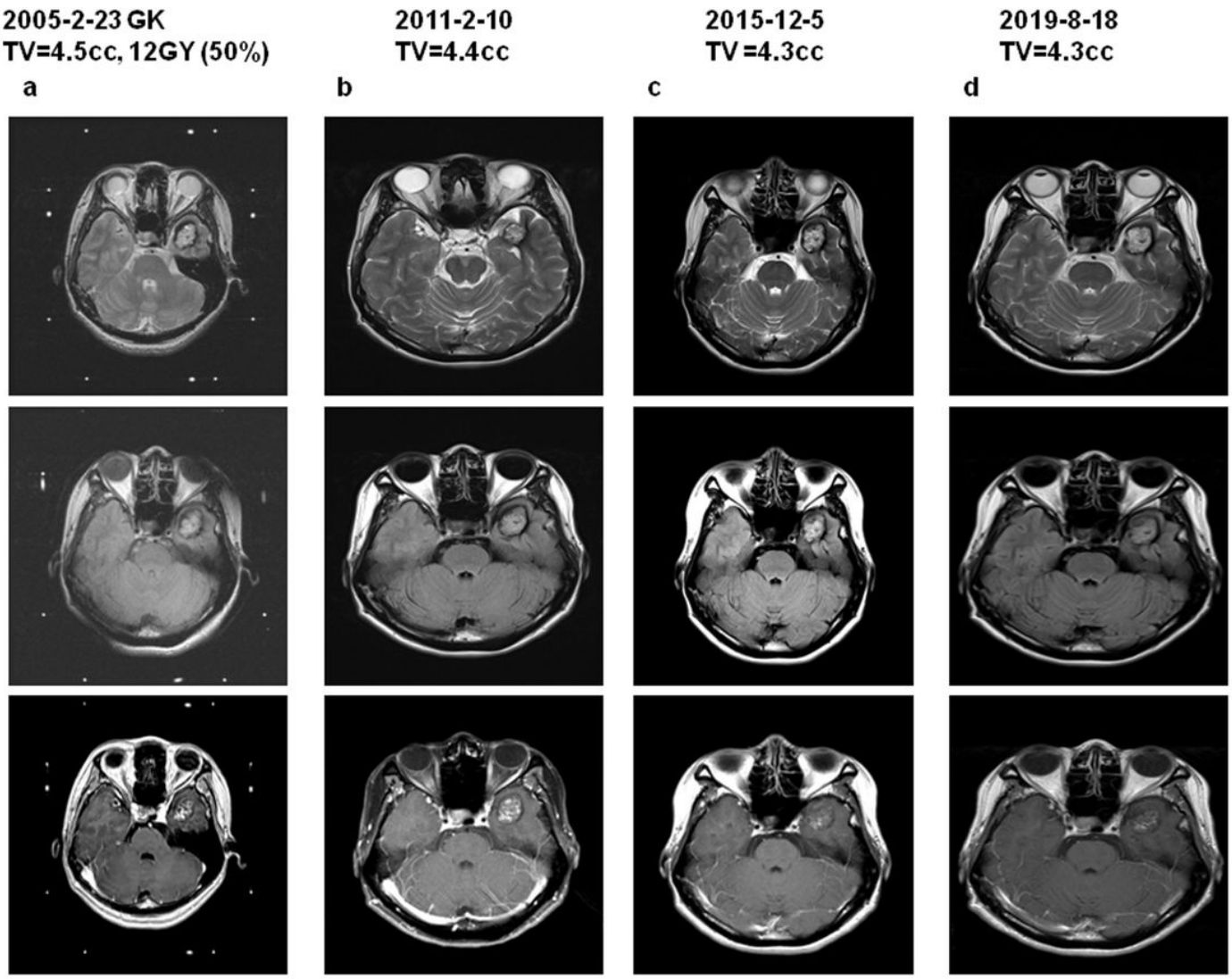

Figure 1

Cavernoma treated with GKRS with decreased size. A 13 year old girl suffered right side limb weakness with muscle power of grade IV and received GKRS with the regression of nidus. (a) MRI imaging of T2, Flair at the time of GKRS with radiation volume of 1.2 cc with 12 Gy in 50% line (b) MRI imaging of T2 and Flair 6 years after GKRS with nidus volume of 0.41 cc (c) MRI imaging of T2 and Flair 10 years after GKRS with nidus volume of 0.35 cc (d) MRI imaging of T2 and Flair 16 years after GKRS with nidus volume of 0.34 cc

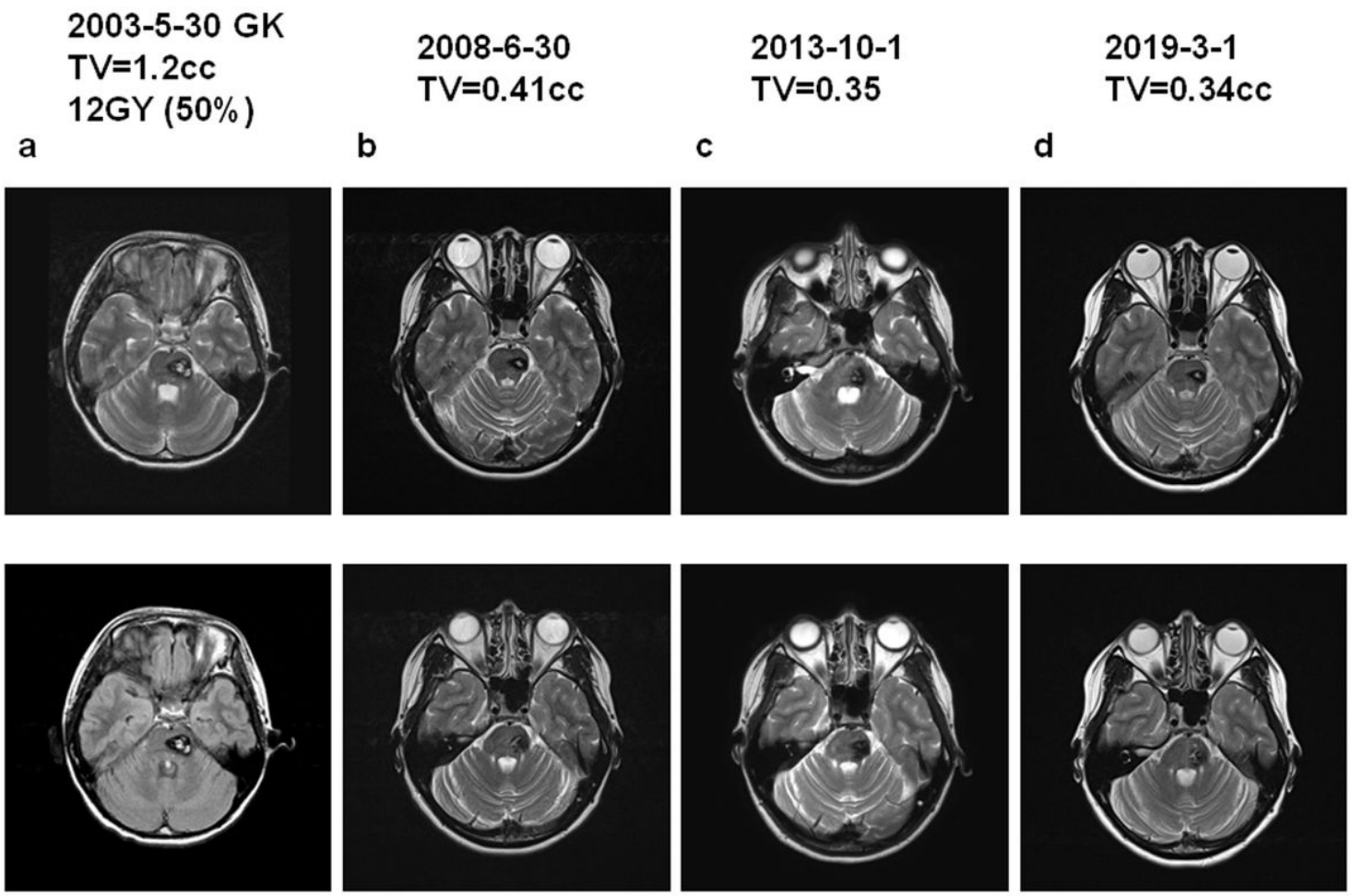

Figure 2

Cavernoma treated with GKRS and achieving stable size. A 30 year old female presented with tonic-clonic seizure treated with Gamma Knife radiosurgery with stable size of nidus and seizure control of Engel II. (a) MRI imaging of T2, Flair and T1 with contrast at the time of GKRS with radiation volume of 4.5 cc with 12 Gy in 50% line.(b) MRI imaging of T2, Flair and T1 with contrast 6 years after GKRS with nidus volume of 4.4cc (c) MRI imaging of T2, Flair and T1 with contrast 10 years after gamma knife treatment with nidus volume of 4.3cc (d) MRI imaging of T2, Flair and T1 with contrast 14 years after GKRS with nidus volume of 4.3cc

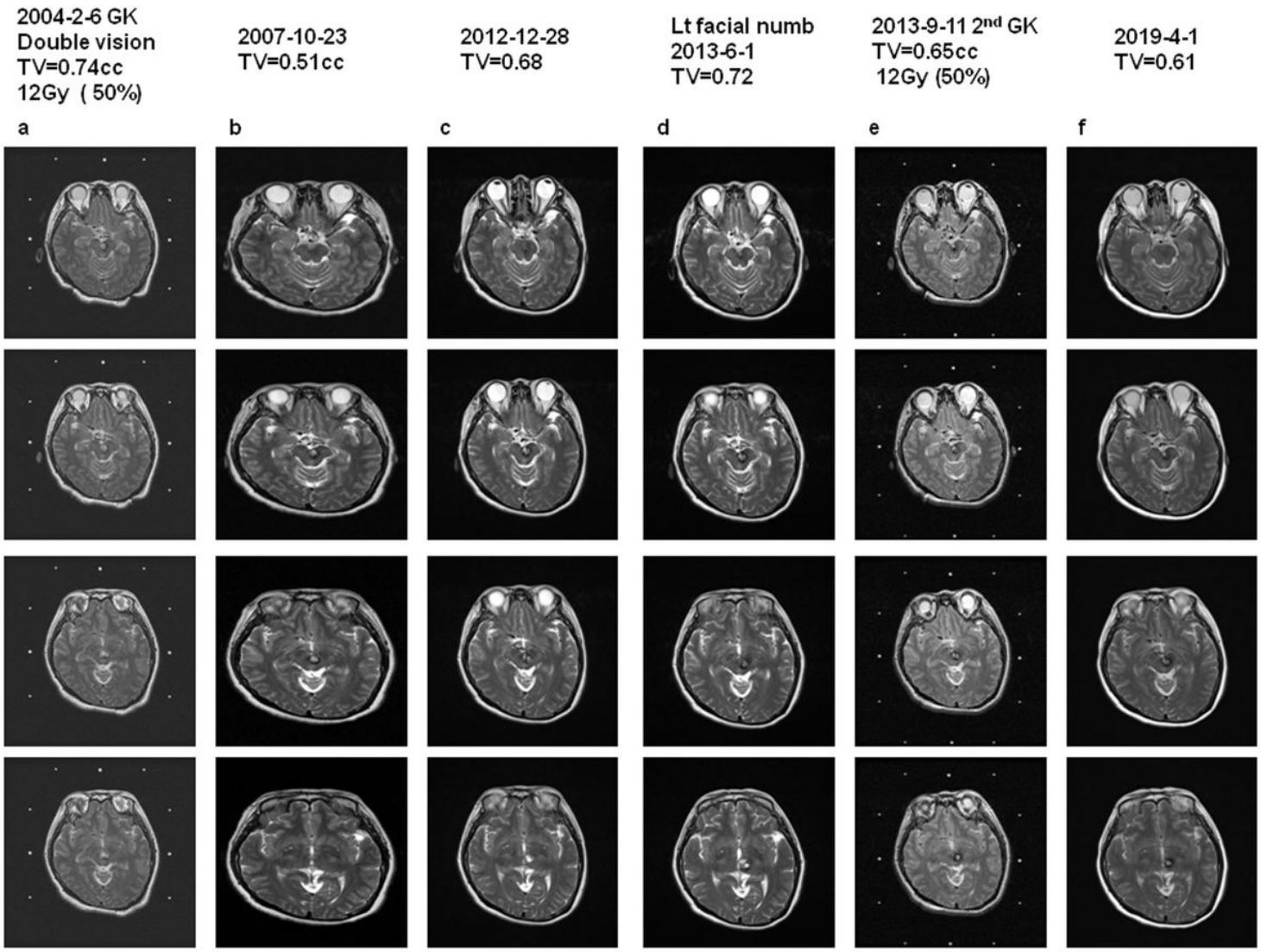

Figure 3

Cavernoma treated with nidus progression followed by second GKRS. A 39 year old female suffered double vision treated with GKRS and underwent a second GKRS due to increased volume of the nidus with associated symptom of facial numbness (a) MRI imaging of T2 at the time of GKRS with treatment volume of 0.74 cc with 12 Gy in 50% line (b) MRI imaging of T2 3 years after GKRS with nidus volume of 0.51 cc (c) MRI imaging of T2 weighted 8 years after GKRS with nidus volume of 0.68 cc (d) MRI imaging of T2 9 years after GKRS with nidus volume of 0.72cc (e) MRI imaging of T2 at the time of the second GKRS with radiation volume of 0.65 cc with 12 Gy in 50% line (f)MRI imaging of T2 15 years after GKRS with a nidus volume of 0.61cc

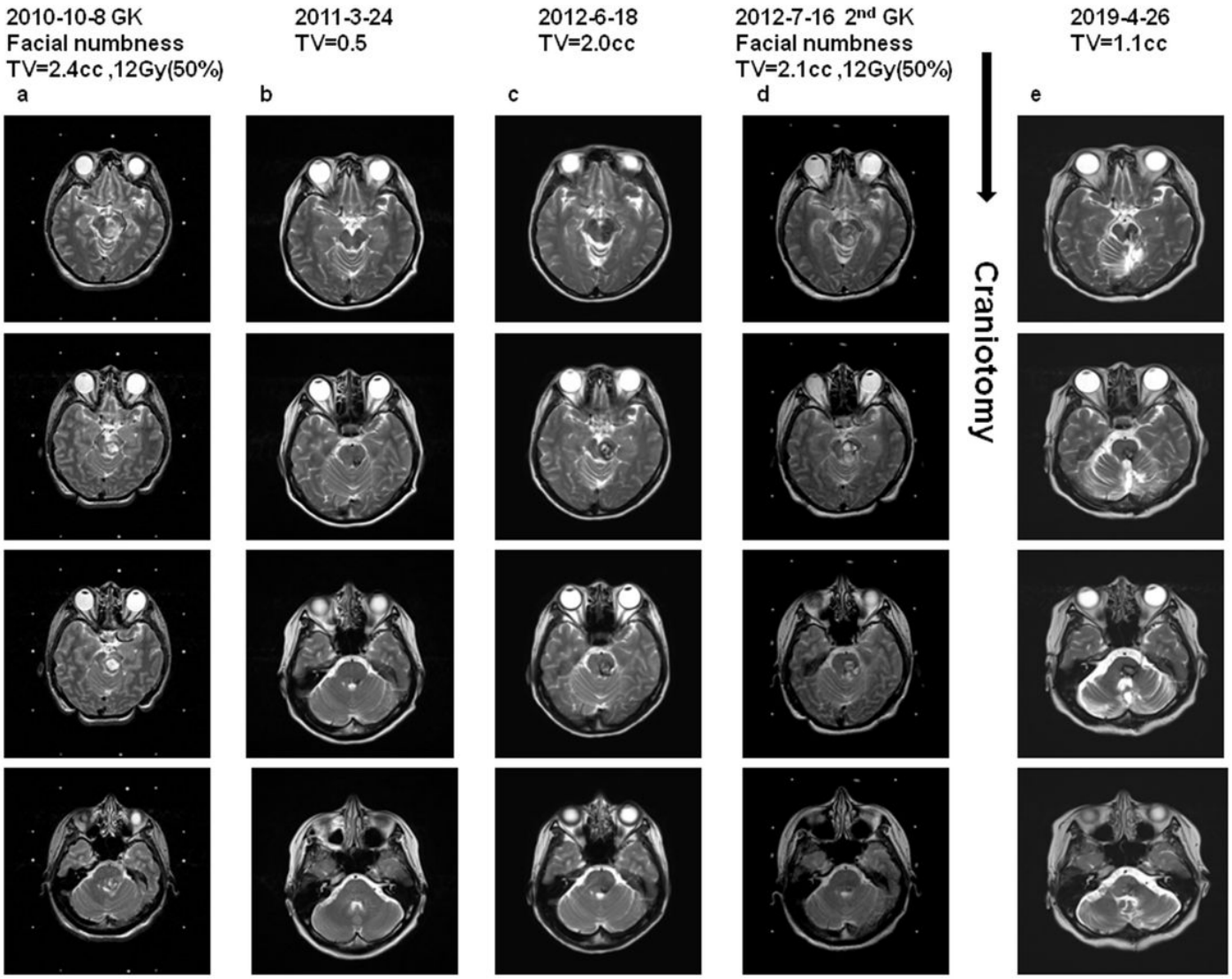

Figure 4

Cavernoma treated with nidus progression followed by second GKRS and craniotomy. A 29 year old female suffered facial numbness treated with GKRS and received a second GKRS due to increased volume of nidus with the recurrent symptom of facial numbness. The patient underwent a craniotomy due to intractable facial numbness and the surgery was associated with postoperative neurological deficits (a) MRI imaging of T2 at the time of GKRS with radiation volume of 2.4 cc with 12 Gy in 50% line (b) MRI imaging of T2 one year after GKRS with nidus volume of 0.5 cc (c) MRI imaging of T2 weighted 2 years after GKRS with nidus volume of 2.0 cc (d) MRI imaging of T2 at the time of second GKRS with radiation volume of 2.1 cc with 12 Gy in 50% line (e) MRI imaging of T2 9 years after a second GKRS and craniotomy with nidus volume of 1.1cc

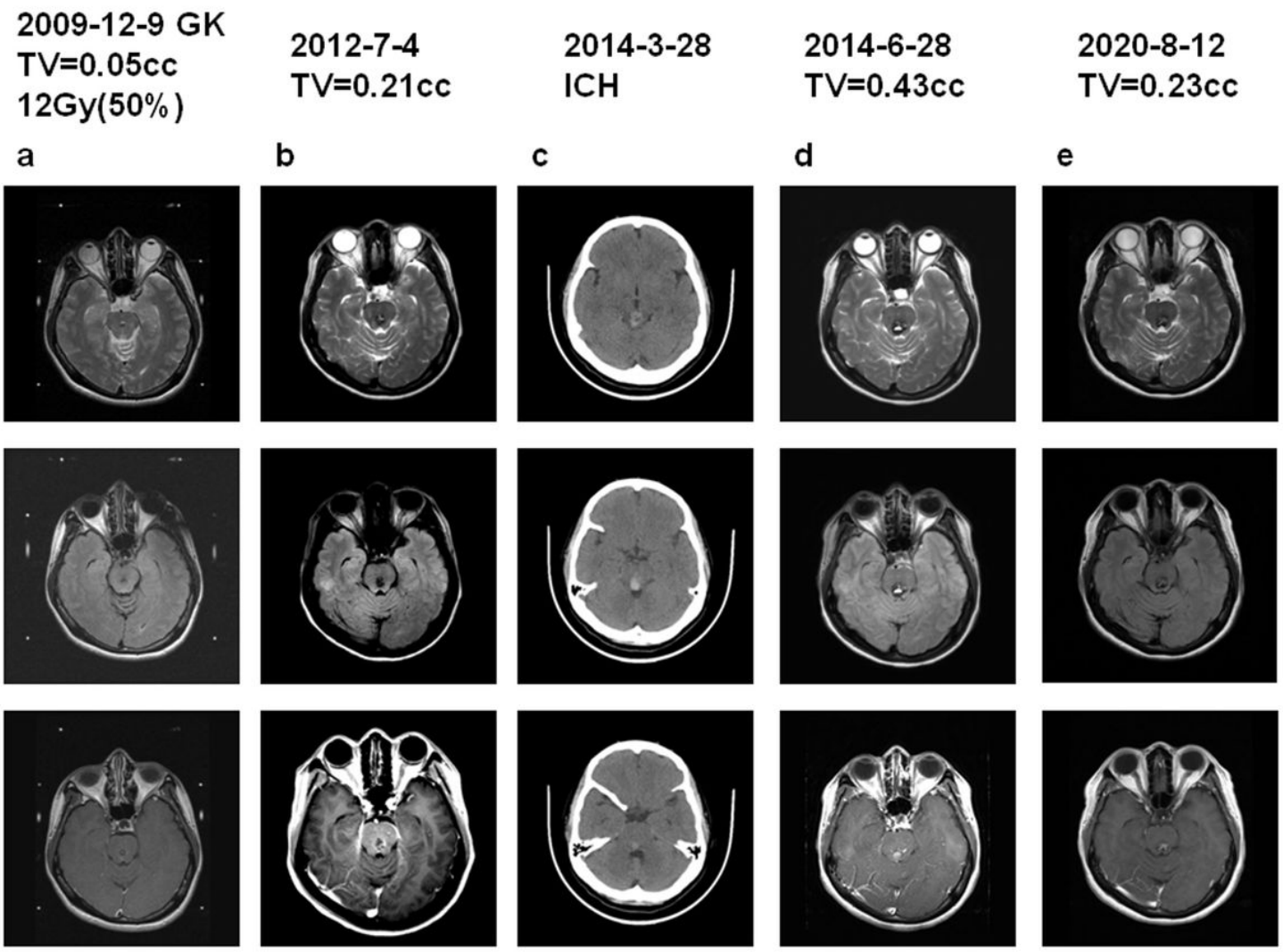

Figure 5

Cavernoma treated with GKRS and demonstrating nidus progression and hemorrhage. A 41 year old female suffered facial numbness treated with GKRS and suffered the repeated bleedings (a) MRI imaging of T2, Flair and T1 with contrast at the time of gamma knife treatment with radiation volume of 0.1cc with 12 Gy in 50% line (b) MRI imaging of T2, Flair ,and T1 with contrast three year after GKRS with nidus volume of 0.21 cc (c) CT imaging 5 years after GKRS with intracerebral hemorrhage (d) MRI imaging of T2, Flair ,and T1 with contrast 5 years after GKRS with a nidus volume of 0.023 cc (e) MRI imaging of T2, FLAIR, and T1 with contrast 11 years after GKRS with a nidus volume of 0.021cc

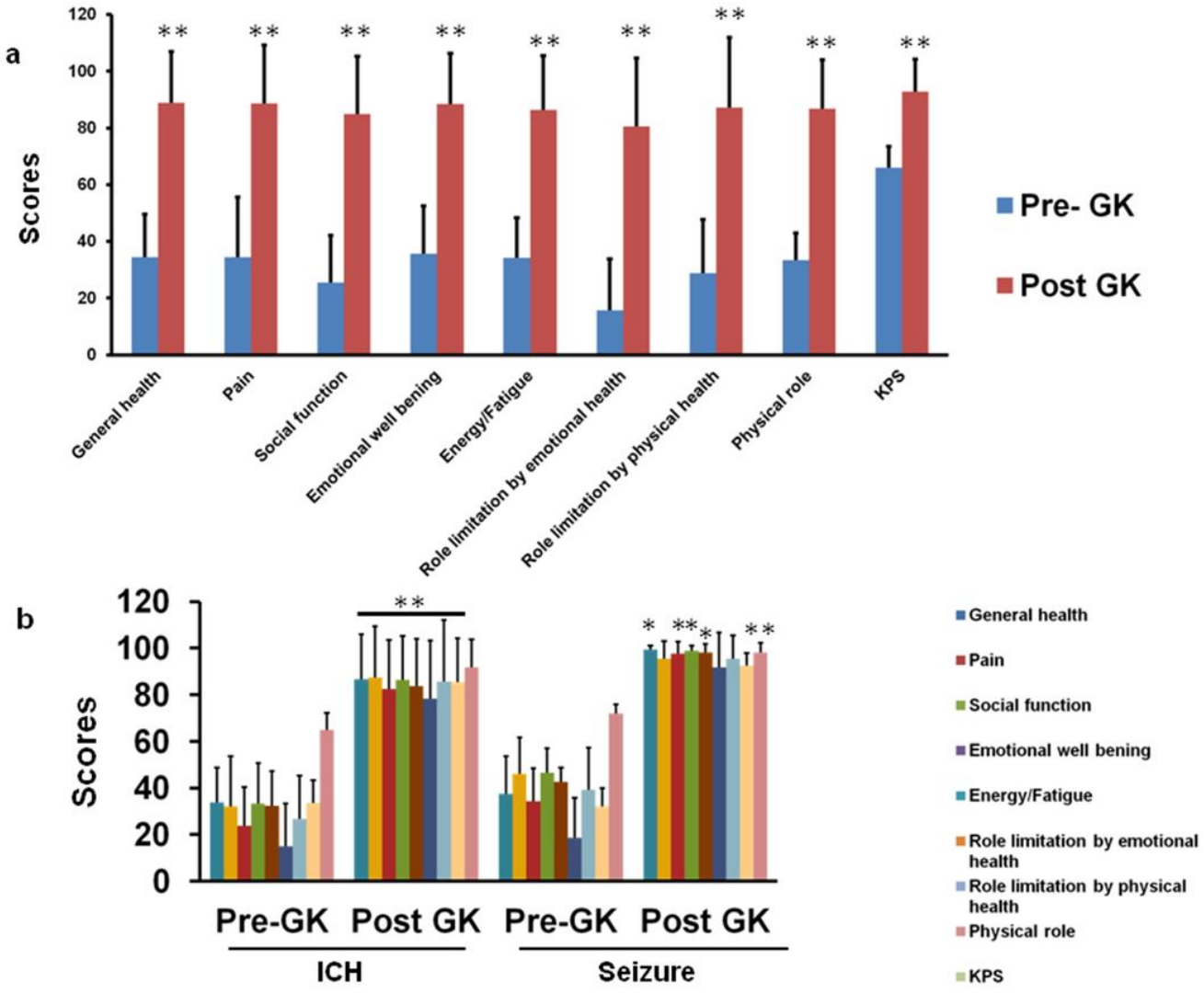

Figure 6

Plot of life quality before and after GKRS. (a) Plot of life quality including SF-36 and KPS before and after GKRS. (b) Plot of life quality of SF-36 and KPS stratified by the etiologies of intracerebral hemorrhage and seizure. *: $p<0.05$; **:$p<0.01$

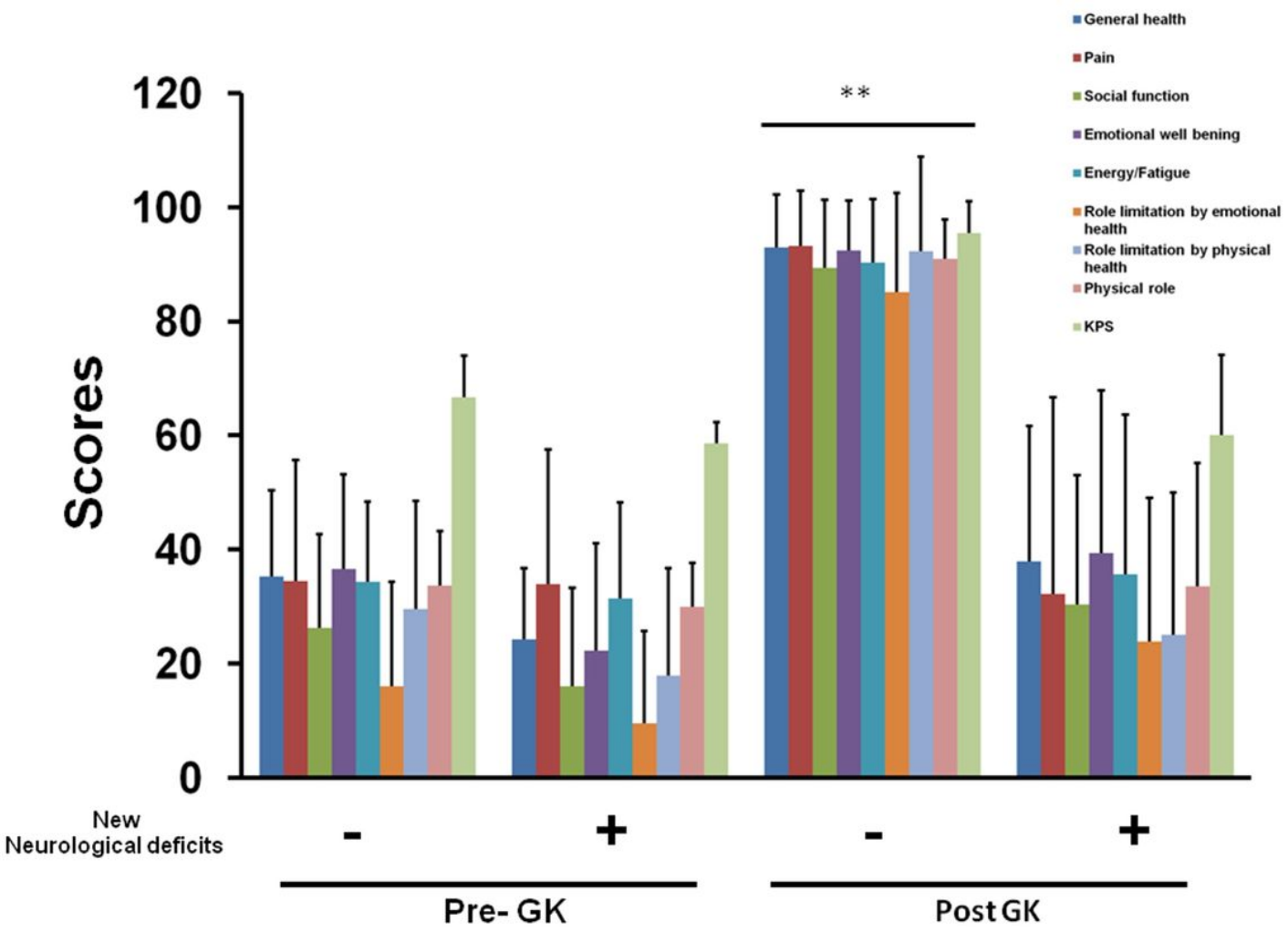

Figure 7

Plots of life quality of SF-36 and KPS in the patients either with or without development of new neurological deficits. **: p<0.01