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Visual field defects after radiosurgery versus temporal lobectomy for mesial temporal lobe epilepsy: findings of the ROSE Trial

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Author Contributions

NB and MQ contributed to the conception and design of the study, acquisition and analysis of data, and the drafting of the manuscript and figures. All authors contributed to concept and design of the study and review of final manuscript version.

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Abstract

Purpose: Stereotactic radiosurgery (SRS) may be an alternative to anterior temporal lobectomy (ATL) for mesial temporal lobe epilepsy (MTLE). Visual field defects (VFD) occur in 9 – 100% of patients following open surgery for MTLE. Postoperative VFD after minimally invasive versus open surgery may differ.

Methods: This prospective trial randomized patients with unilateral hippocampal sclerosis and concordant video-EEG findings to SRS versus ATL. Humphries perimetry was obtained at 24m after surgery. VFD ratios (VFDR = proportion of missing homonymous hemifield with 0 = no VFD, 0.5 = complete superior quadrantanopsia) quantified VFD. Regressions of VFDR were evaluated against treatment arm and covariates. MRI evaluated effects of volume changes on VFDR. The relationships of VFDR with seizure remission and driving status 3 years after surgery were evaluated.

Results: No patients reported visual changes or had abnormal bedside examinations, but 49 of 54 (91%) of patients experienced VFD on formal perimetry. Neither incidence nor severity of VFDR differed significantly by treatment arm. VFDR severity was not associated with seizure remission or driving status.

Conclusion: The nature of VFD was consistent with lesions of the optic radiations. Effective surgery (defined by seizure remission) of the mesial temporal lobe results in about a 90% incidence of typical VFD regardless of method.

Keywords

Visual field defects; gamma knife; radiosurgery; mesial temporal lobe epilepsy; epilepsy surgery; partial seizures; randomized controlled trial

Introduction

Visual field defects (VFD), typically homonymous superior quadrantanopsias, commonly occur after temporal lobe resections for patients with medically intractable mesial temporal lobe epilepsy (MTLE). The frequency of VFD after open resection ranges from 9 – 100% [1–3]. Techniques that may limit surgical volumes may prevent VFD. Nilsson et al. found that more restricted resections that spared the superior-most aspect of the superior temporal gyrus yielded less VFD [4]. Mengesha et al. found that the horizontal meridian of visual fields tended to be spared with selective amygdalohippocampectomy compared to standard anterior temporal lobectomy (ATL) [5]. Schmeiser et al. reported that the rate of VFD after limited subtemporal resections was 9% rate and after standard ATL was 35% [3].

Stereotactic radiosurgery (SRS) has undergone a series of single- and multicenter trials with the goal of offering a “minimally invasive” alternative to ATL with the hope that the technique would provide seizure remission while offering outpatient rather than inpatient procedures and less morbidity such as VFD. Our U.S. Multicenter Pilot Study [6] demonstrated that the severity of VFD was similar to historical reports from ATL [7]. Those patients with greater VFD (approaching the classic quadrant defect) were more likely to be seizure free; the findings supported the hypothesis that the mechanism of SRS involved some degree of tissue damage and was not produced entirely by functional changes via neuromodulation.

A recent randomized controlled comparison of SRS to ATL (Radiosurgery or Open Surgery for Epilepsy, the ROSE Trial) observed the trend that ATL offered earlier and higher rates of seizure remission than SRS, but that the incidence of seizure-freedom improved with time in the SRS group [8].

In this study, we compared the incidence and severity of VFD in patients who underwent treatment by SRS versus ATL. We evaluated three questions. 1. Do VFD vary by treatment arm? 2. Does the volume of resection (for ATL) or postsurgical atrophy (for SRS) correlate with the extent of VFD? 3. Are outcomes – seizure freedom after epilepsy surgery and the visually-dependent outcome of driving – dependent on the extent of VFD?

Methods

Participants

Study design, protocols, and demographics are discussed elsewhere [8]. Patients randomized to either SRS or ATL were ≥ 18 years old, had pharmaco-resistant unilateral MTLE, and

were eligible for resective epilepsy surgery. The study was approved by the institutional review boards at each center located in the US, UK, and India (we note the US Multicenter Pilot Study was confined to the US).

Treatment protocols and outcomes

The SRS protocol [6, 8] consisted of a single session of a 24 Gy dose delivered to a 50% isodose volume between 5.5–7.5 cc comprising the amygdala, anterior 2cm of hippocampus, and parahippocampal gyrus. No limit was specified for the number of isocenters. Safety factors limited dose to a maximum of 10 Gy to the brainstem and 8 Gy to the optic nerves and chiasm.

All ATL used a standard protocol [9] and consisted of resection of 1–2 cm of the anterior superior temporal gyrus and 3cm of the anterior middle and inferior temporal gyri, the temporal portion of the amygdala, the anterior 2–3 cm of the hippocampus, and adjacent entorhinal cortex.

We defined seizure remission as the absence of seizures that caused impairment of consciousness between months 25–36; thus, seizure remission is analogous to at least an Engel Class 1B.

Driving status (yes/no) was determined during the 36 month interview with the treatment site neurologists blinded by arm; patients were asked if they were driving with the approval of a physician.

Visual field measurements

Bedside visual examinations (performed by treatment site neurologists blinded to treatment arm) and automated visual field perimetry (Humphrey: including 24–2, 30–2 and 120 full field) was performed prior to treatment (patients were excluded from the study if there were abnormalities in the pre-treatment visual field assessment) and at the 24-month follow-up visit. Twenty-four month postoperative perimetry testing was evaluated in this study.

All perimetry results were reviewed by a neuroophthalmologist (S.A.N.) blinded to outcomes. Findings were assigned the following interpretations: 1) normal; 2) incomplete superior homonymous quadrantanopsia (the “pie in the sky” pattern typical for temporal lesions) without extension into the macula, 3) superior homonymous quadrantanopsia with macular involvement. Macular involvement was defined by one or more of the paracentral points in both the right and left hemifield on the appropriate side tested at < 0.5. If no points adjacent to fixation were identified as abnormal or if only one eye demonstrated depression (< 0.5), the field was considered to have macular sparing.

To quantify VFD, we calculated a quantitative measure of visual field loss validated in our earlier study [7]. We defined the visual field defect ratio (VFDR) as the proportional area of defect on the hemi-visual field contralateral to surgery:

$$\text{VFDR} = (\text{area defect OS} + \text{OD}) / (\text{total hemifield area OS} + \text{OD})$$

A complete homonymous superior quadrantanopsia (a visual field defect comprising 90° from the vertical to horizontal meridian with macular involvement) will have a VFDR = 0.5; a full homonymous hemifield loss will equal 1. Test points in Humphry perimetry with standard <v0.5% coefficients of reliability were deemed normal.

MRI measurements

All patients had pre-operative MRIs that showed some degree of mesial temporal sclerosis as rated by a central neuroradiologist (C.P.H.) MRI volume measurements were performed by a physician blinded to clinical outcomes (S.M.). In SRS patients the posttreatment images were acquired at 36 months after Gamma Knife treatment (well after onset and resolution of SRS-induced changes [10]) and in ATL patients 3 months after surgery. Each subject's pre-treatment T1 image was resampled to a 1×1×1 mm resolution (T1_resample) with FreeSurfer 5.6 (http://surfer.nmr.mgh.harvard.edu). The original T1 images were co-registered to the T1_resample and segmented into gray, white, and CSF regions using the "new segmentation" as implemented in SPM12 (www.fil.ion.ucl.ac.uk/spm/). The grey matter map (probability of tissue > 0.5) was coregistered to a template on which the left and right temporal lobes had been marked and the resulting transformations applied to all regions-of-interest (ROI) and previously segmented maps to restrict all measurements to the temporal lobe. The results were visually edited for accuracy (S.M.). After quality control, the labels were used to extract all gray and white matter volumes. The lesion volume, i.e., pre-treatment white and gray matter regions that had CSF intensity after treatment, was calculated by subtracting post- from pre-treatment temporal lobe brain tissue maps. The peri-lesion volume, i.e., white matter regions bordering the lesion region that had typical white matter intensity in the pre-treatment image but became hypo-intense in the post-treatment image, was calculated by subtracting the post-treatment temporal white matter volume from the pre-treatment white matter volume.

This process yielded the following variables:

1. HV = pre-treatment hippocampal volume adjusted to intracranial volume;
2. GMV = changes from preoperative baseline to postoperative imaging in the volumes temporal gray matter;
3. WMV = temporal white matter changes
4. PLV = temporal peri-lesional tissue changes
5. TV = total volume change = (GMV+WMV+PLV).

In addition to 36 month images, T2-weighted images obtained at 12 months after SRS were processed as above focusing on the volume of edema, or radiation-induced changes, around the surgical target. Segmentation was semi-automated by bracketing the edema value between the lower intensity threshold above contralateral temporal and amygdala gray matter and the upper threshold below sulcal and ventricular CSF. All voxels within this range of the treated temporal lobe were labeled as edema.

Data Analysis

Preliminary work evaluated variables as functions of present or absent VFD, but the low numbers of those with normal visual fields led us to concentrate analyses with VFDR. We examined univariate associations between VFDR and treatment arm along with potential covariates of sex, age at surgery, age at diagnosis, duration of epilepsy before surgery, and language dominance of surgery (dichotomous variables using Mann-Whitney U tests and continuous variables using Spearman's correlations). Subsequent linear regressions were used to obtain a difference in mean VFDR between the two arms with and without adjusting for the covariates identified at $P \leq 0.10$ during univariate analyses. Fisher's exact test was used to test the difference in proportion of patients with presence of VFD between the two arms.

Relationships between VFDR and MRI measurements within each arm were evaluated with Spearman correlations. Differences in MRI measurements between presence and absence of VFD were also examined using Mann-Whitney U tests.

Finally, we examined the relationships of VFDR with seizure remission status and driving status using logistic regression in which seizure remission status or driving status was the dependent variable while controlling for treatment arm. The model for driving status also included seizure remission status as an independent variable. P values of 0.05 or less were deemed statistically significant.

Results

58 patients were treated (SRS = 31, ATL = 27) with 29 SRS patients (94%) and 25 ATL patients (92%) completing VF testing; those not tested either dropped from the trial or refused testing.

Effect of treatment arm

Blinded perimetry interpretation: No patients had visual abnormalities noted during bedside confrontation testing, but 49 of 54 (91%) of patients experienced some VFD on formal perimetry (Table 1). Most patients in either treatment arm experienced homonymous superior quadrant defects that spared macular vision. The proportion of those with abnormal perimetry did not differ significantly by treatment arm. No patient experienced a complete homonymous hemianopsia.

VFDR: Mean VFDR was similar across the two arms (Figure 1). Those patients with VFDR > 0.5 implying defects below the horizontal meridian had interpretations of involvement of macular vision; therefore, "missing" vision below the meridian was likely to be attentional rather than arising from true field defects, but absent of other clinical findings, these choices could not be resolved.

On univariate analyses, the severity of VFDR did not correlate significantly with sex, age at surgery, duration of epilepsy, or side of surgery (dominant vs non-dominant) (Table 2). The covariate of younger age at diagnosis of epilepsy correlated with worse VFDR; the significance was stronger in the SRS arm than the ATL arm (regression P = 0.04 and 0.20).

Multivariable regression of VFDR as a function of treatment arm and the significant covariate confirmed that VFDR did not differ significantly by treatment arm (Table 3) even taking into account the effect of age of diagnosis.

Effect of volume change and edema

Post-surgical decreases in volumes from baseline were more obvious in the resections of ATL compared to the atrophic tissue after SRS (Figure 2).

In the case of SRS, smaller hippocampal targets at baseline (i.e. pre-treatment atrophy) predicted more severe VFDR after SRS (Table 4).

In patients who underwent ATL, the volumes of gray matter changes (cc = 0.601, P=0.018) and the total volume changes (cc = 0.556 P= 0.031) correlated with significantly worse VFDR (Table 4).

In SRS patients, radiation-induced edema at 12 months ranged from non-detectable to 121 cc. Edema, measured by the volume of T2-weighted changes at 12 months, did not correlate with severity of subsequent VFDR (Table 4).

Relationship between VFDR and seizure / driving outcomes

The proportion of those who self-reported driving after surgery did not differ significantly by presence or absence of interpreted VFD (Supplemental Table 1). Mean VFDR did not differ significantly according to seizure remission status (seizurefree = 0.30±0.22 vs. not seizure free = 0.22±0.16, P = 0.33 Mann-Whitney U test), although the seizure-free group tended to have more extensive VFDR. Even after adjusting for treatment arm, VFDR was not significantly associated with the odds of seizure remission (odds ratio = 10.6 [95% CI 0.43 – 259.4], P = 0.15). Similarly, mean VFDR did not differ by driving status (driving = 0.28±0.24 vs. not driving = 0.26±0.18, P = 0.94 Mann-Whitney U test). VFDR was not significantly associated with driving status after adjusting for treatment arm and seizure remission (odds ratio = 1.00 [95% CI 0.053 – 18.502], P = 1.00].

Discussion

The main finding was that the severity of visual field defects after temporal lobe surgery for epilepsy did not vary by treatment arm. As seen in our pilot study [6], our randomized controlled trial [11] showed that the SRS protocol with defined limits of dose-volume and protections to the optic nerve, optic chiasm and brain stem were effective in preventing excessive morbidity to the visual system even when the dose to the optic tract was not constrained. Neuroimaging demonstrated that the smaller preoperative hippocampal volumes were significantly associated with more extensive visual field defects in the radiosurgery arm; we speculate that the smaller volume of tissue receiving the same dose is a possible risk. Losses in gray matter and total volume predicted the severity of VFD in those who underwent open surgery. Finally, no definite relationships were present between VFD and outcomes of seizure remission or driving status. We conclude that effective surgery (defined by seizure remission) of the mesial temporal lobe results in about a 90% incidence of typical VFD regardless of surgical method.

One surprising finding was that an earlier age at epilepsy diagnosis was associated with worse post-treatment visual field defects in the SRS arm (as well as a similar trend in the ATL arm). This information was not available for the pilot study [6]. Younger patients have been noted to be more susceptible to radiation-induced changes [12], but no information is available by which to compare the present study's finding of temporal sensitivity. Given the small sample, the association could be spurious.

Our incidence of VFD after temporal lobe epilepsy surgery was 90%, within the range of 9 – 100% [1] [2] reported in previous open surgery studies and higher than the 62.5% reported from our pilot study of SRS. [7] Patients in the ATL group demonstrated a positive trend in correlation between the volume resected and the severity of VFD, supporting earlier open surgery studies that reported an association between amount of tissue resection and size of VFD [4, 5]. This relationship with "resected" volume was not present in the SRS group, probably reflecting the different nature of the radiation-induced lesion and the difficulty of MRI in defining whether tissue is truly functional [13]. The severities of VFD were similar by treatment arm. We anticipated that SRS patients may have less severe VFD because SRS is a form of "minimally invasive" epilepsy surgery. One implication of our findings is on the possible mechanisms of SRS in epilepsy surgery. Experimental models of epilepsy and limited human data suggest that the mechanism of action of SRS is due to a neuromodulatory effect [13]. Our pilot study [7] and the present study suggests that the anti-epileptic effects of SRS require a certain degree of tissue destruction. Similarly, the similar degree of visual field change suggests that both SRS and ATL result in tissue destruction with "collateral damage" to the optic radiations within the temporal lobe. However, the SRS protocol only constrained the dose to the optic nerve and chiasm; it remains to be tested if a SRS treatment plan that limits the dose to the optic tract to 8–10 Gy would lessen the risk of VFD. In addition, advances in neuro-imaging that better define the optic radiations within the temporal lobe might offer a way to avoid VFD for any destructive form of treatment.[14]

The severity of VFD after epilepsy surgery, regardless of surgical technique, is important given that VFD may independently limit the ability to drive. In the present study, the severity of VFD did not associate with self-reported driving status. Although vision criteria for driving are present in all countries and states, requirements vary widely. European Union regulations require 120° of intact vision across the 180° hemifield, with no encroachment of vision within 20–30° of the horizontal meridian. The majority of U.S. states define limits of 110–140° [15]. Only one study specifically evaluated driving eligibility related to postsurgical VFD [16]. Of a sample of 24 patients, 11–13 patients (depending on perimetry technique) had "failing" VFDs according to the European standard after temporal lobectomy; 3 (approximately 30%) of those patients could not drive despite seizure-freedom [16]. Although we lack records of patients denied driving privileges because of VFD in the present study, it would be unlikely since no patients had bedside confrontation examinations that demonstrated visual abnormalities. The international make-up of our cohort possibly affects driving status because of other socioeconomic barriers beyond visual or seizure outcomes. Since driving status was selfreported, patient bias and differing physician standards (nationally and internationally) could affect results. The most conservative interpretation of the lack of relationship between visual field defects and driving status is

that the lack of uniformity among states and countries allows patients and local physicians to place other factors above vision changes in considering driver eligibility.

Regarding other limitations, as in our pilot study [6, 7], the most severe visual field defect score (VFDR > 0.5) could be due to inattention on the Humphrey resulting in invalid data. Alternatively, these severe defects could represent lesions of the visual pathway outside of Meyer's loop. In either case, VFDR correlates strongly with expert interpretations of perimetry, as demonstrated in our initial validation[7]. We note that greater availability of diffusion tractography – not uniformly available among treatment centers – could have helped in defining optic radiations as a part of pre-operative assessments [17].

Neuroimaging was obtained at different timepoints from visual field perimetry for practical reasons centered on patient retention and clinical time. We did not obtain closely-spaced interval MRIs to catch the peak points of edema for each patient. We acknowledge that VF exams may not exactly correlate with MRI volumetry given the 12 month lag between perimetry and final MRI. But, the time course of development of the radiosurgical lesion is well-established, with the peak development of reactive edema occurring before 15 months and resolving by the second year [6, 11, 18]. This time course of latency and resolution was the main reason final seizure outcome was determined between postoperative months 25–36. Finally, our volumetry protocol could not distinguish between edema and necrosis. We note that MR spectroscopy obtained in our US Multicenter Pilot Study determined that within the radiosurgical target a core of necrosis is present surrounded by reactive edema [10].

Conclusions

The nature of VFD was consistent with lesions of the optic radiations in both open surgery and in minimally invasive surgery via SRS. Effective surgery (defined by seizure remission) of the mesial temporal lobe results in about a 90% incidence of typical VFD regardless of surgical method.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ATL	anterior temporal lobectomy
MTLE	mesial temporal lobe epilepsy
ROI	region of interest

ROSE	Radiosurgery or Open Surgery for Epilepsy Trial
SRS	stereotactic radiosurgery
VFD	visual field defects
VFDR	visual field defect ratio

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Highlights

- Patients with lesional mesial temporal epilepsy were randomized by surgical technique.
- VF defects were compared after temporal lobe SRS versus open epilepsy surgery.
- VFD incidence and severity did not differ significantly by treatment arm.
- VFD severity was not associated with seizure remission or driving status.
- VFD occurs in about 90% of patients regardless of surgical method.

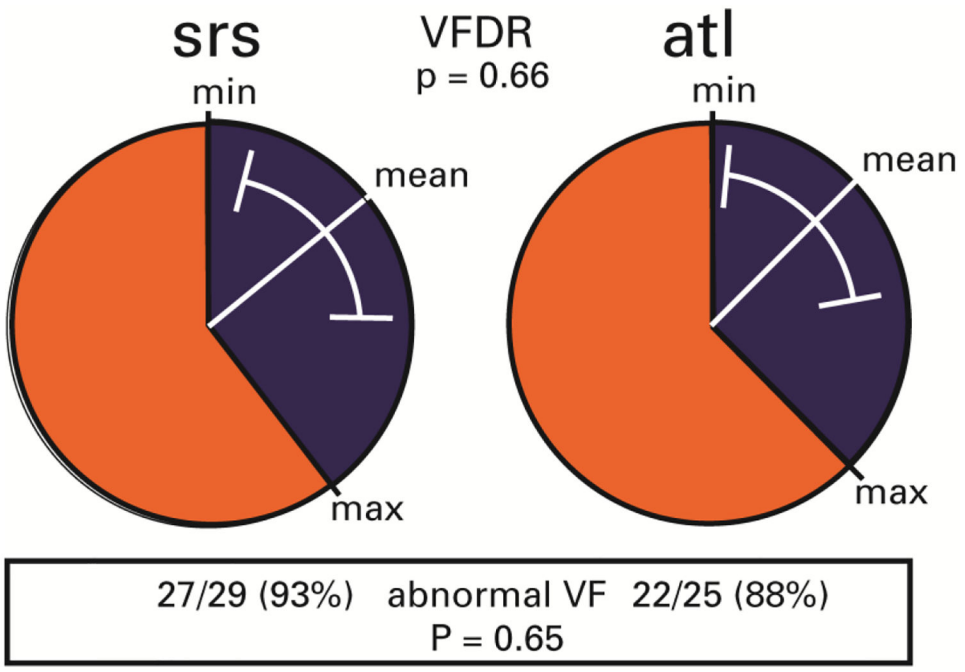

Figure 1.

Means, standard deviations, and minima/maxima of visual field defect ratios (VFDR) by treatment arm. VFDR did not differ significantly by treatment arm (P value =0.66 via Mann-Whitney U test). The incidence of abnormal visual fields determined by blinded interpretation of perimetry also did not vary significantly by arm (P value=0.65 via Fisher's Exact Test).

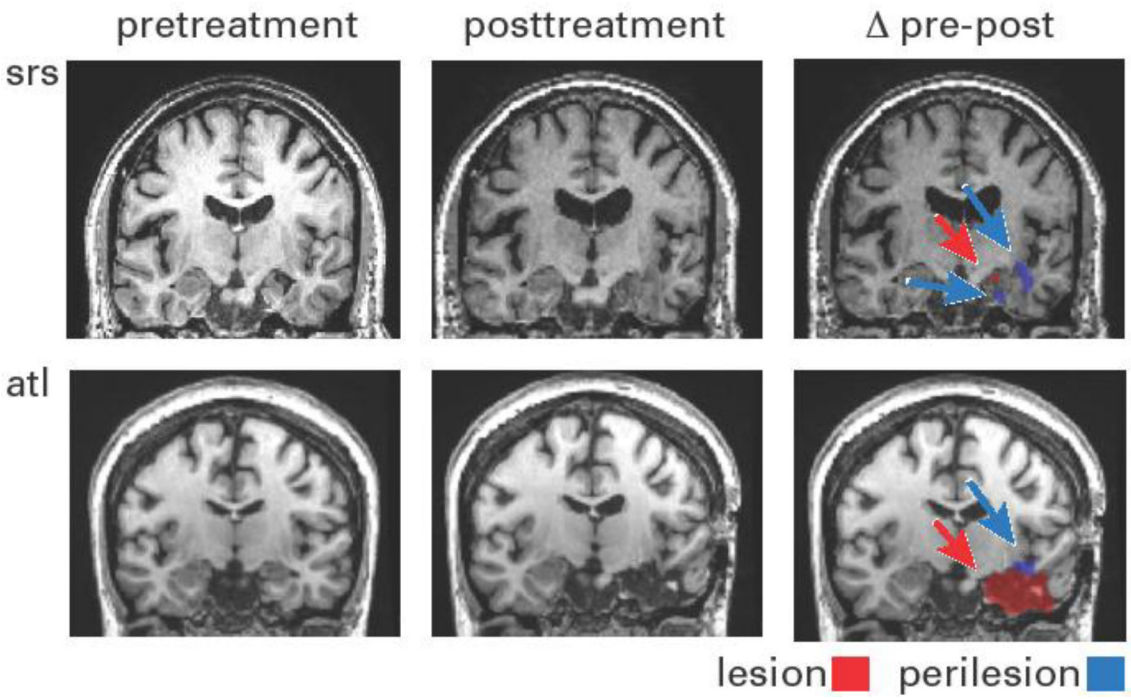

Figure 2.

Representative examples of the post-treatment defect volumetry following stereotactic radiosurgery (SRS) or anterior temporal lobectomy (ATL). Arrows identify areas of post-treatment volume loss. Lesion (red) corresponds to grey or white matter tissue replaced with CSF in the post-treatment MRI. Peri-lesion (blue) corresponds to necrotic tissue, i.e., white matter with hypointense appearance on a T1 weighted image, that often surrounds the CSF defect. Please see methods section for details on how these two volumes were calculated.

Table 1.

Blinded, expert interpretations of visual field defects (VFD) obtained from formal perimetry did not differ significantly by treatment arm. SRS = stereotactic radiosurgery; ATL = anterior temporal lobectomy. Sup HH = superior homonymous hemianopsia. P value from Fisher's exact test.

Interpretation	Total		SRS		ATL		P Value
No VFD	5 (9%)		2 (7%)		3 (12%)		0.65
VFD	49 (91%)		27 (93%)		22 (88%)		
VFD:Sup HH macular sparing	39	(80%)	22	(81%)	17	(77%)	
VFD:Sup HH macular involvement	10	(20%)	5	(19%)	5	(23%)	
Total	54		29		25		

Table 2.

Univariate analyses of visual field defect ratio (VFDR) with baseline covariates. VFDR did not differ significantly by treatment arm; of potential covariates, only age of diagnosis significantly negatively correlated with VFDR. SRS = stereotactic radiosurgery; ATL = anterior temporal lobectomy; Ip:Con = surgery ipsilateral or contralateral to language dominance. a P value from Mann-Whitney U test; b Spearman correlation coefficient (Corr Coeff) with P value.

Variable	Category	Mean ± SD	Corr Coeff.	P
Arm	SRS:ATL	0.28±0.21: 0.25±0.20		0.66a
Sex	M:F	0.28±0.23: 0.28±0.23		0.66a
Language Dominant Surgery	Ip: Con	0.27±0.23 0.27±0.16		0.42a
Age Diagnosis (years)		(13±13)	−0.395	0.003b
Age Surgery (years)		(40±14)	−0.115	0.414b
Duration Epilepsy (years)		(26±14)	0.199	0.153b

Table 3.

Regression analyses of VFDR against significant variables from univariate analyses. Model 1 contains the treatment arm indicator variable alone. Model 2 contains the treatment arm indicator variable and age of diagnosis. a The estimated mean difference in VFDR for ATL vs. SRS. b The estimated mean difference in VFDR corresponding to 1 year increase of age diagnosis.

Model		Regression coefficient	95% confidence limits	P
1. Arm (ATL vs. SRS)		−0.033a	−0.146 – 0.79	0.079
2. Arm (ATL vs. SRS)		−0.061a	−0.171 – 0.049	0.269
Age diagnosis (years)		−0.005b	−0.009 - −0.001	0.016

Table 4

Associations of brain region volumes obtained from quantitative MRI volumetry with visual field defects in dichotomous and continuous scales. HV = presurgical hippocampal volume; GMV,WMV,PLV, TV = postsurgical 36 month grey, white matter, perilesional, and total volume losses at the surgical target; T2V = postsurgical T2weighted edema at 12 months after stereotactic radiosurgery. VFD = blinded interpretation of visual field perimetry. Volumes = mm3. a P value from Mann-Whitney U test for the difference in brain region volume between VFD and No-VFD. b Spearman correlation coefficient (VFDR CC) between VFDR and brain region volume with pvalue.

	SRS					**ATL**				
Region	**VFD**	**No VFD**	**P valuea**	**VFDRCCb**	**VFDR P value b**	**VFD**	**No VFD**	**P valuea**	**VFDR CCb**	**VFDR P value b**
HV	2381±283	1961±561	0.14	−.433*	0.024	2180±1100	1971±422	1	0.11	0.634
GMV	1192	1636±2560	0.6	−0.036	0.881	5387	10581±3750	0.27	.601*	0.018
WMV	159	1636±2560	0.94	0.335	0.188	1184	3109±1158	0.13	0.382	0.16
PLV	1330±325	1491±959	0.89	0.263	0.195	103	794±556	0.13	−0.146	
TV	2911	3875±2817	1	0.154	0.555	6673	14362±4559	0.27	.556*	0.031
T2V	57±80	24±34	0.76	−0.104	0.597					