


Radiosurgery versus open surgery for mesial temporal lobe epilepsy: The randomized, controlled ROSE trial

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Summary

Objective: To compare stereotactic radiosurgery (SRS) versus anterior temporal lobectomy (ATL) for patients with pharmacoresistant unilateral mesial temporal lobe epilepsy (MTLE).

Methods: This randomized, single-blinded, controlled trial recruited adults eligible for open surgery among 14 centers in the USA, UK, and India. Treatment was either SRS at 24 Gy to the 50% isodose targeting mesial structures, or standardized ATL. Outcomes were seizure remission (absence of disabling seizures between 25 and 36 months), verbal memory (VM), and quality of life (QOL) at 36-month follow-up.

Results: A total of 58 patients (31 in SRS, 27 in ATL) were treated. Sixteen (52%) SRS and 21 (78%) ATL patients achieved seizure remission (difference between ATL and SRS = 26%, upper 1-sided 95% confidence interval = 46%, *P* value at the 15% noninferiority margin = .82). Mean VM changes from baseline for 21 English-speaking, dominant-hemisphere patients did not differ between groups; consistent worsening occurred in 36% of SRS and 57% of ATL patients. QOL improved with seizure remission. Adverse events were anticipated cerebral edema and related symptoms for some SRS patients, and cerebritis, subdural hematoma, and others for ATL patients.

Significance: These data suggest that ATL has an advantage over SRS in terms of proportion of seizure remission, and both SRS and ATL appear to have effectiveness and reasonable safety as treatments for MTLE. SRS is an alternative to ATL for patients with contraindications for or with reluctance to undergo open surgery.

KEYWORDS

clinical trial, epilepsy surgery, focal epilepsy, quality of life, radiosurgery

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1 | INTRODUCTION

Seizure-free rates after open surgery for intractable mesial temporal lobe epilepsy (MTLE) vary from 60% to 90%.^{1–5} Based on these outcomes, the American Academy of Neurology recommends open surgery as the treatment of choice,⁶ but it remains underutilized for many eligible patients.⁷

Concerns over risks including stroke, postsurgical bleeding, blood loss, and infection may limit wider use of open surgery.^{5,8,9} Other limitations include neurocognitive impairment (especially of the language-dominant side), acute adjustment reactions, and mood disorders.^{10–13} Furthermore, open surgery is costly. Thus, efforts to reduce the overall morbidity and cost of epilepsy surgery are important.

Key Points

- This randomized, controlled trial evaluated SRS versus standard open surgery for patients with mesial temporal lobe epilepsy
- Thirty-one patients underwent SRS and 27 underwent ATL; they were monitored for 3 years with outcomes evaluated between months 25 and 36
- Sixteen (52%) SRS and 21 (78%) ATL patients achieved seizure remission
- VM changes of language-dominant patients were not significantly different between arms, and QOL tracked seizure remission in both arms
- SRS is a minimally invasive surgery technique that offers another pathway to epilepsy surgery

Stereotactic radiosurgery (SRS) with the use of the Gamma Knife (Elekta, Stockholm, Sweden) or other systems has been studied since 1995 in the treatment of MTLE.^{14–21} Although results have varied—possibly due to patient selection or dose/target protocols—larger prospective, multicenter studies showed that SRS offered seizure remission rates similar to those of anterior temporal lobectomy (ATL).^{22,23} In addition, the multicenter U.S. pilot study of SRS showed that neurocognition—specifically verbal memory (VM)—was spared relative to that reported for open surgery.²⁴ In 13 trials of SRS for MTLE included in a recent meta-analysis of SRS, 51% of patients achieved seizure remission as defined by varying criteria.²⁵ However, randomized controlled studies that compare outcomes of SRS and ATL are lacking.

We initiated a randomized trial in 2009, with 3 years planned for recruitment and an additional 3 years of follow-up for evaluating outcomes for patients randomized to receive SRS or ATL. In this paper, we describe the findings from this 6-year study, including seizure-free outcome, cognitive and VM outcomes for those treated for language-dominant temporal lobe seizures, and quality of life (QOL) improvement for SRS compared to ATL. We also provide more detailed information about adverse events associated with SRS or ATL.

2 | MATERIALS AND METHODS

2.1 | Patients

Institutional review boards of the 14 treatment centers based in the USA, UK, and India approved the study (<https://clinicaltrials.gov/ct2/show/NCT00860145>).

Candidates were eligible for ATL to treat pharmacoresistant unilateral MTLE. Patients had sufficient continuous video-electroencephalography to determine a unilateral medial temporal seizure focus, had magnetic resonance imaging (MRI) evidence of concordant unilateral hippocampal sclerosis without significant secondary cortical lesions, a Wada test or functional MRI to lateralize language, and a standard battery of neuropsychological testing (Table S1). In addition, patients were ≥ 18 years old, documented 3 months during which at least 3 focal-onset seizures with impairment of consciousness occurred during stable anticonvulsant administration, and lacked neurological or visual deficits that would confound follow-up. Exclusions were pregnancy, supratentorial MRI abnormalities, diabetes mellitus, use of vigabatrin, psychiatric diagnoses that would make it difficult to accurately assess seizures, significant comorbidities, poor compliance, or current drug abuse. Patients provided written consent, or, if a candidate had an intelligence quotient < 70 , centers could offer the option to conduct a formal evaluation of capacity to provide assent and consent. Centers undertook initial

screening, and the central study center provided final screening approval before randomization.

2.2 | Treatment protocols

Randomization occurred at enrollment with stratification by treatment center and language lateralization (for number recruited by center, see Table S2, ROSE Trial Recruitment by Trial Center.).

2.2.1 | SRS

The SRS protocol²³ consisted of a single outpatient session of a 24-Gy dose delivered to a 50% isodose volume between 5.5 and 7.5 cm² comprising the amygdala, anterior 2 cm of hippocampus, and parahippocampal gyrus. No limit was specified for the number of isocenters. Safety factors limited the dose to a maximum of 10 Gy to the brainstem and 8 Gy to the optic nerves and chiasm. The central study center reviewed each plan to insure protocol compliance.

2.2.2 | ATL

ATL is an inpatient procedure, and consisted of a standard protocol²⁶ of resection of 1–2 cm of the anterior superior temporal gyrus and 3 cm 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. Participating neurosurgeons were documented to have performed at least 25 ATLs.

2.3 | Postoperative follow-up, masking, and outcome measures

Patients were evaluated in person every 3 months for the first 18 months and then at 24, 30, and 36 months supplemented with telephone interviews every 3 months for the last 18 months. Blinded reviewers provided outcomes. Possible adverse events identified by blinded reviewers were evaluated by nonblinded neurologists and nurse coordinators. Blinding was maintained by having patients wear large hats during reviews to obscure SRS pin marks or ATL craniotomies and providing strict instructions to patients not to reveal treatment arm.

2.3.1 | Seizure remission and adverse events

Seizure diaries, reviewed by blinded neurologists at each treatment center, were reviewed by a blinded, central adjudicator when seizure types changed or were edited. We defined seizure remission as the absence of seizures that caused impairment of consciousness between months 25 and 36, analogous to at least Engel class IB.

Safety monitoring included: (1) clinic visits; (2) postoperative MRI obtained at 3 months following ATL, and 12, 24, and 36 months following SRS; (3) cognitive screening with the use of the Hopkins Verbal Learning Test-Revised; and (4) visual field testing with Humphrey 120 perimetry at baseline and 24 months. If SRS-related edema merited, treatment with a standardized protocol of oral steroid administration was initiated. Adverse events were adjudicated by an independent medical monitor. A National Institute of Neurological Disorders and Stroke sponsored Data Safety Monitoring Board monitored the study.

2.3.2 | VM

VM was evaluated at baseline and 12, 24, and 36 months following treatment measured by the long delay free recall score of the California Verbal Learning Test (CVLT) and the delayed recall score of the Logical Memory subtest from the Wechsler Memory Scale-Third Edition (WMS) for English speakers. Based on reliable change indices (RCI) to account for test-retest and measurement error,¹² we designated patients as having “significant improvement,” “no change,” and “significant impairment.” RCI values for post-pre changes were as follows: CVLT = (≤ -3 , $\geq +7$) and WMS = (≤ -4 , $\geq +4$).

2.3.3 | QOL

QOL was assessed with the Quality of Life in Epilepsy (QOLIE-89) for English and Spanish speakers measured at baseline and 12, 24, and 36 months.

2.4 | Statistical analysis

The ROSE trial was planned to have >85% power to test the hypothesis that SRS would be noninferior to ATL with respect to the seizure-free rate between 25 and 36 months with a noninferiority margin of 15%. Because accrual lagged, the sponsor stopped recruitment at 58 patients, resulting in a power of 41% for the primary hypothesis. Therefore, we revised our analysis plan. In addition to performing originally proposed hypothesis testing, we recognized a limitation of lower statistical power and also performed more descriptive analyses, including confidence intervals (CIs; whenever helpful) and details on adverse events.

2.4.1 | Seizure remission

Seizure remission outcome is defined by the seizure-free rate between 25 and 36 months. SRS was considered noninferior to ATL if the upper bound of the 1-sided 95% CI for the difference in seizure-free rates between ATL and

SRS was <15%, chosen given the 30% spread in seizure-free rates.^{1–5} A range for the possible true difference between ATL and SRS was estimated by the 2-sided 90% CI, the lower and upper limits of which are consistent with the lower and upper 1-sided 95% confidence limits. To track the longitudinal development of seizure remission and relapse, we also calculated seizure-free rates for each 3-month follow-up interval.

2.4.2 | VM

CVLT and WMS were examined in English-speaking patients who underwent language-dominant surgery. We used a linear mixed-effects model with repeated measures to estimate the mean change from baseline to postoperative 12, 24, and 36 months. We also compared descriptively the proportions of those who experienced significant reductions as measured by RCI thresholds.

2.4.3 | QOL

A linear mixed-effects model was also used to estimate the mean changes in the QOLIE-89 in the 2 groups for English and Spanish speakers. SRS was considered noninferior to ATL if the upper bound of the 1-sided 95% CI for the difference in mean changes of the QOLIE-89 score between ATL and SRS was below a noninferiority margin of 5.2 points.

3 | RESULTS

3.1 | Study population

Of the 453 patients screened, 138 met entry criteria (Figure S1). Of the 63 who passed initial screening and were offered participation, 32 (39%) did not want to be randomized, 19 (23%) did not want to wait for SRS effects, 12 (14%) cited other concerns, 11 (13%) were afraid of clinical research in general, 6 (7%) would refuse ATL, and 3 (4%) were afraid of radiation (patients could select >1 reason). Consenting patients who passed subsequent central screening were randomized ($n = 63$); failures consisted of MRI with insufficient evidence of hippocampal sclerosis, and possible secondary lesions.

Five dropped out after randomization but before surgery. A local institutional review board withdrew 1 when the trial ceased recruitment. Four others (2 in each arm) chose to withdraw before surgery. Two patients who underwent surgery withdrew before reaching the 36-month evaluation. One withdrew 14 months following SRS for early ATL because of poorly tolerated, simple partial seizures. Another withdrew 10 months following ATL and was lost to follow-up. These 2 patients were designated as “not

seizure-free." Untreated patients were excluded from analysis, as treatment-based outcomes could not be evaluated.

The final sample consisted of 31 SRS and 27 ATL patients (Table 1). VM was tested in those with English as their primary language or who learned English at <5 years of age and for whom their education was provided in English, leaving 21 dominant-hemisphere surgery patients (14 in SRS, 7 in ATL) for VM analysis. QOLIE-89 data were assessed in 43 English- or Spanish-speaking patients (23 in SRS, 20 in ATL).

All SRS and ATL procedures conformed to protocol. Histopathology in U.S. ATL patients (sending tissue samples across borders was not permitted) confirmed hippocampal sclerosis in all 20 available cases.

3.2 | Clinical outcomes

A total of 37 (64%) patients achieved seizure remission, with 16 (52%) in SRS and 21 (78%) in ATL. The difference between ATL and SRS was 26%, with the upper bound of the 1-sided 95% CI at 46%. Because the upper

TABLE 1 Baseline demographic and clinical characteristics by treatment group

| Variable | SRS, n = 31 | ATL, n = 27 |
|---|---------------------------|--------------------------|
| Age at surgery, y | 39.16 ± 13.81 | 41.33 ± 12.90 |
| Male, n (%) | 14 (45.2) | 14 (51.9) |
| English primary language, n (%) | 23 (74.2) | 19 (70.4) |
| Age at diagnosis, y | 16.31 ± 14.92 | 9.96 ± 10.94 |
| Duration of epilepsy, y | 22.85 ± 14.54 | 31.37 ± 14.43 |
| Number of AEDs | 2.35 ± 1.08 | 2.52 ± 1.09 |
| Baseline monthly seizure frequency ^a | 3.67 (6.67) | 3.33 (4.33) |
| QOLIE-89 total score ^b | 60.06 ± 14.03 | 60.10 ± 20.74 |
| Surgery on language-dominant side, n (%) | 21 (67.7) | 12 (44.4) |
| Dominant hemisphere CVLT ^c | 8.21 ± 2.29 | 9.50 ± 2.17 ^d |
| Dominant hemisphere WMS-3 ^c | 17.31 ± 8.26 ^e | 13.71 ± 7.30 |

Continuous data are presented as mean ± standard deviation unless otherwise noted.

AED, antiepileptic drug; ATL, anterior temporal lobectomy; CVLT, California Verbal Learning Test; QOLIE, Quality of Life in Epilepsy; SRS, stereotactic radiosurgery; WMS, Wechsler Memory Scale.

^aMedian and interquartile range.

^bAssessed for 43 English and Spanish speakers (SRS = 23, ATL = 20).

^cAssessed for 21 English speakers (SRS = 14, ATL = 7) treated for dominant-side surgery.

^dMissing in 1 ATL patient.

^eMissing in 1 SRS patient.

bound exceeded the noninferiority margin of 15% (P value was .82), noninferiority of SRS compared to ATL was not demonstrated. The corresponding 2-sided 90% CI for the difference in seizure-free rates between ATL and SRS ranged from 6% to 46%.

The course of seizure remission varied by treatment arm (Figure 1). Patients treated with SRS demonstrated a gradual increase in the proportion of seizure remission; after SRS only 2 (6%) patients had no seizures within the first 3 months, whereas 22 (81%) ATL patients experienced remission in the same period. By the final 3-month follow-up period (months 34-36), 23 (74%) of SRS patients and 23 (85%) of ATL patients experienced short-term seizure remission.

Among 21 English-speaking, language-dominant surgery patients (14 in SRS, 7 in ATL), mean CVLT changes from baseline were significantly better in SRS patients for the first 24 months after treatment ($P = .033$ at 12 months and $P = .044$ at 24 months), but change scores converged between treatment groups at final follow-up ($P = .491$; Figure 2). Mean WMS changes from baseline were also better for SRS patients compared to ATL patients, but the differences between the two groups were not statistically significant. Using RCI thresholds, VM worsened consistently (no mixed results/improvements) in 5 (36%) SRS patients and in 4 (57%) ATL patients (Table 2). Therefore, among English-speaking patients who underwent surgery in the language-dominant hemisphere, 9 (64%) SRS patients and 3 (43%) ATL patients were spared from consistent deficits in postsurgical VM.

Both groups showed improvement in mean QOLIE-89 scores (Figure 2C). Noninferiority of SRS compared to ATL in QOL improvement at year 3 was not indicated ($P > .05$). We note that mean changes over time differed by group (Figure 2C). In the SRS group, QOL scores improved significantly at 24 months and remained steady

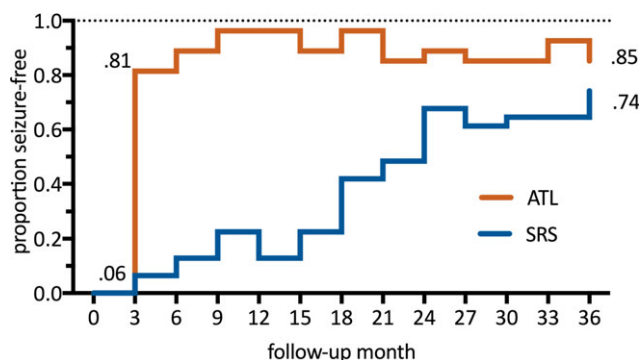


FIGURE 1 Proportion of seizure-free patients within 3-month blocks over the course of the study. ATL, anterior temporal lobectomy; SRS, stereotactic radiosurgery

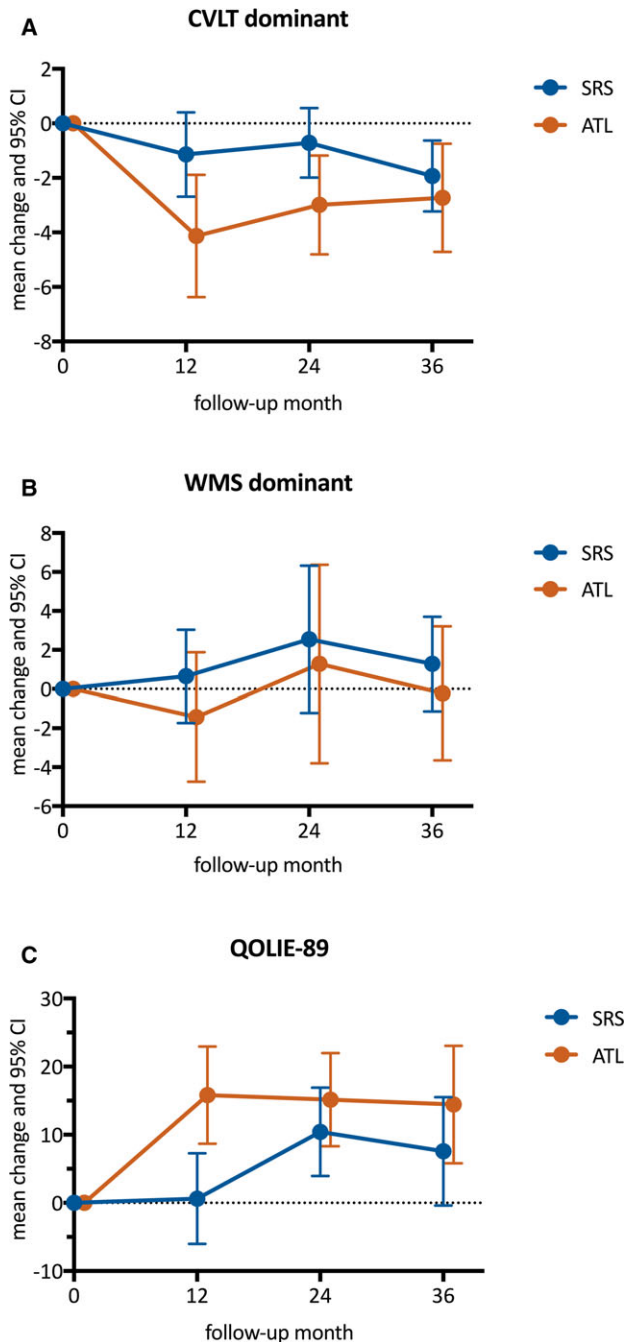


FIGURE 2 Estimated mean changes at postoperative annual visits from baseline for verbal memory measures among English-speaking, language-dominant surgery patients (n = 14 in stereotactic radiosurgery [SRS], n = 7 in anterior temporal lobectomy [ATL]). A, California Verbal Learning Test–Long-Term Delayed Recall (CVLT). B, Delayed recall score of the Logical Memory subtest from the Wechsler Memory Scale-Revised (WMS). The difference between the 2 groups at 12 months was P = .033 and at 24 months was P = .044 for CVLT; it was nonsignificant at P < .05 at 36 months and all WMS time points. C, Estimated mean changes at postoperative annual visits from baseline for the Quality of Life in Epilepsy (QOLIE-89; n = 23 in SRS, n = 20 in ATL, excluding 15 Hindi-speaking patients. Noninferiority of SRS compared with ATL in QOLIE-89 by year 3 was nonsignificant at P < .05. CI, confidence interval

TABLE 2 Relative change indices determined clinically relevant changes in verbal memory at 36 months as “significantly improved,” “no change,” or “significantly worsened” among English-speaking, dominant-hemisphere patients

| | WMS | | |
|-----------------------|----------|----------------|----------------|
| | Improved | No change | Worse |
| SRS | | | |
| CVLT | | | |
| Improved | 0 | 0 | 0 |
| No change | 1 | 6 | 1 ^a |
| Worse | 2 | 2 ^a | 2 ^a |
| Worse in 1 or 2 | | 5 | 36% |
| Improve/no change/mix | | 9 | 64% |
| ATL | | | |
| CVLT | | | |
| Improved | 0 | 0 | 0 |
| No change | 0 | 2 | 1 ^a |
| Worse | 1 | 3 ^a | 0 ^a |
| Worse in 1 or 2 | | 4 | 57% |
| Improve/no change/mix | | 3 | 43% |

ATL, anterior temporal lobectomy; CVLT, long delay free recall score of the California Verbal Learning Test; SRS, stereotactic radiosurgery; WMS: delayed recall score of the Logical Memory subtest from the Wechsler Memory Scale-Third Edition.

^aThose with consistent worsening (no improvements or mixed changes).

at 36 months. In contrast, in the ATL group, QOL score improvement was immediately noticeable at 12 months.

When the 2 treatment groups were combined, the 24 patients who were seizure-free had significantly more improvement than the 19 patients who were not seizure-free (mean change ± standard error of QOLIE-89 at 36 months from baseline = 16.11 ± 3.94 vs 3.64 ± 3.94, P value = .033).

3.3 | Adverse events, steroids use, and visual assessment

Adverse events adjudicated as definitely related to treatment consisted of 14 events (5 serious and 9 nonserious) in 12 (39%) SRS patients and 5 events (2 serious and 3 nonserious) in 3 (11%) ATL patients (Table 3). Adverse events did not overlap between the treatment groups.

One SRS patient experienced an early nonserious frame pin-site infection. Other adverse events in the SRS group centered on expected transient cerebral edema that occurred between 11 and 27 months. Examples were new onset headaches, new but transient neurological deficits, and transient exacerbations of seizures. Edema was not recorded uniformly; for example, 1 patient had 2 simultaneous serious adverse events of headache and a new neurological

TABLE 3 Serious and nonserious AEs adjudicated as definitely related to treatment

| Patient | A | B | C | D | E | F | G | H | I | Serious AEs | Total AEs |
|-------------|-----------------|-----------------|-----------------|-----------------|---|---|---|----------------|---|-------------|-----------|
| SRS 1 | 0 | | | | | | | | | 0 | 1 |
| SRS 2 | 11 | | | | | | | | | 0 | 1 |
| SRS 3 | | 15 | | | | | | | | 0 | 1 |
| SRS 4 | 11 | | | | | | | | | 0 | 1 |
| SRS 5 | | | 9 | | | | | | | 0 | 1 |
| SRS 6 | | 14 | | | | | | | | 0 | 1 |
| SRS 7 | | | | 28 | | | | | | 0 | 1 |
| SRS 8 | | | | 11 ^a | | | | | | 1 | 1 |
| SRS 9 | | | | | 0 | | | | | 0 | 1 |
| SRS 10 | | | | 13 ^a | | | | | | 1 | 1 |
| SRS 11 | 16 ^a | | 16 ^a | | | | | | | 2 | 2 |
| SRS 12 | 11 | 11 ^a | | | | | | | | 1 | 2 |
| Serious AEs | 1 | 1 | 1 | 2 | 0 | | | | | | 5 |
| Total AEs | 5 | 3 | 2 | 3 | 1 | | | | | | 14 |
| ATL 1 | | | | | | | 1 | 1 ^a | 1 | 1 | 3 |
| ATL 2 | | | | | | | | 1 ^a | | 1 | 1 |
| ATL 3 | | | | | | 3 | | | | 0 | 1 |
| Serious AEs | | | | | | 0 | 0 | 2 | 0 | | 2 |
| Total AEs | | | | | | 1 | 1 | 2 | 1 | | 5 |

Numbers in columns indicate the postoperative month in which AE occurred.

A, headache; AE, adverse event; ATL, anterior temporal lobectomy; B, cerebral edema; C, new neurological deficit; D, seizure exacerbation; E, pin-site infection; F, subdural hematoma; G, deep venous thrombosis; H, wound dehiscence and infection; I, psychiatric; SRS, stereotactic radiosurgery.

^aSerious AE.

deficit of transient word-finding difficulties (that resolved with steroid treatment) at post-SRS month 16; this was likely due to cerebral edema that was not listed. Another patient had 2 events of new onset headache and edema (the latter listed as serious) 11 months after surgery. All resolved by the trial's end.

In the ATL arm, adverse events were confined to the first postoperative 3 months. One patient developed 3 simultaneous adverse events: a serious wound scalp dehiscence, deep venous thrombosis, and depression. Depression continued after the trial's end. Another developed serious cerebritis requiring repeat craniotomy. Another patient developed a nonserious, incidental subdural hematoma that spontaneously remitted over the trial's course and did not require surgery.

Twenty SRS patients (65%) were treated with steroids, 2 starting at the first 3 months, 3 at 9 months, 5 at 12 months, 6 at 15 months, and 4 after 18 months. The trial provided a standardized, recommended dexamethasone protocol (Table S3) that recommended a treatment with taper lasting 6 weeks. Seven of 27 (26%) ATL patients received steroids within the first 3 postoperative months, which may be underreported because intravenous steroid

use while hospitalized is routine after craniotomy, but medications were mainly documented by research nurses at posttreatment visits. No complications related to steroids were reported in either group.

Visual field testing could not be obtained in 2 SRS cases and 1 ATL case. In those that were evaluated, 34% (10/29) of SRS patients and 42% (11/26) of ATL patients had expected superior quadrantanopsias.

4 | DISCUSSION

As originally designed, the ROSE trial did not demonstrate noninferiority of SRS compared to ATL with respect to seizure-free rates. This may mean that the seizure-free rate of SRS is truly >15% lower than that of ATL, but because of low recruitment, could also mean that the seizure-free rate of SRS is close to that of ATL. Although the current study was not powered to point to which one, the estimated CI for a plausible true difference suggests that ATL has a better seizure-free rate, and SRS has a lower, but acceptable rate within a 3-year window of follow-up. Our longitudinal data suggest that SRS "catches up" with ATL with

time, but more extended follow-up was not possible. In addition, we found that SRS and ATL are associated with comparable neurocognitive deficits. Improvements in overall QOL are associated with seizure remission. We conclude that open surgery should be the treatment choice for unilateral MTLE. SRS, as a method of minimally invasive epilepsy surgery, offers reasonable efficacy and safety and is an alternative to open surgery for patients who may not be suitable for open surgery or are reluctant to have open surgery.

Patients in the ATL treatment arm achieved seizure remission within the expected range of 60%-90%.¹⁻⁵ Previous studies of SRS feature a wide range of dose and outcomes.¹⁴⁻²¹ Only 2 studies used radiosurgical dose protocols similar to this study; a European multicenter study achieved a seizure remission rate of 62%,²² and the U.S. pilot study reported a 77% seizure-free rate.²³ We plan to explore the possible effects of variations within the standardized treatment protocols in both arms on seizure-free outcome.

The trial was designed for 3 years of follow-up given the known latency of therapeutic changes following SRS treatment.^{22,23,27} Within this time frame, SRS patients showed a gradual increase in seizure remission. Thus, longer follow-up may have demonstrated greater seizure remission, resulting in less difference between treatment groups. However, we acknowledge that continuing seizures and delayed improvements in self-assessed QOL are disadvantages of gradual SRS effects.

We anticipated that SRS would spare VM, but mean change scores in either of the VM measures did not differ by treatment. The proportion of patients who experienced a consistent preservation of function (those without declines or mixed improvements/declines in either measure) was larger in the SRS arm, but precision was limited by the small sample size. We suspect that effective epilepsy treatment for MTLE requires a lesion large enough to interrupt the epileptic network; accordingly, lesions large enough for seizure remission also likely affect nearby cognitive networks. Our findings imply that changes in VM are not caused by the surgical path taken to reach the medial temporal lobe, but rather by the effects of removal or damaging the medial structures. We await reports with more substantial numbers and longer follow-up of other "minimally invasive" or "superselective" treatments to determine whether early reports of cognitive sparing hold true.²⁸

The course of overall QOL is generally consistent with prior studies showing a strong association with seizure remission.^{3,29} Further analyses will determine whether there are treatment-specific effects on QOL subdomains.

Adverse events occurred as was predicted for each arm. The trial demonstrates conclusively that, as noted in the

National Institutes of Health multicenter pilot study,²³ the latency to development of seizure remission, transient edema, and transient exacerbation of auras is unique to the SRS arm, whereas acute complications of open craniotomy are confined to ATL. The latency of the development of the radiosurgical lesion affected the type and timing of adverse events. Patients in the SRS group experienced the bulk of adverse events corresponding to the expected evolution of cerebral edema within the middle portion of the 3-year trial. Most patients had easily tolerated, transient symptoms well within standard SRS practice. Conversely, adverse events of the ATL group occurred in the early postoperative period. Problems after ATL such as scalp wound dehiscence, infection, and subdural hematoma fell within complications reported in earlier trials of open surgery.^{5,8,9}

The ROSE trial is the only randomized trial comparing SRS to open epilepsy surgery. It joins the short list of randomized controlled trials in epilepsy surgery in which patients are randomized to technique rather than surgical targets or volumes, testifying to the difficulty of undertaking such designs in nonmedication trials.^{3,5,30} Although the low recruitment hampered statistical power, loss to follow-up was low in our trial. Additionally, all VM testing data were obtained by blinded experts, which also eliminates potential bias, which is often inevitable without blinding. In addition, classification of seizure types and classification of adverse events are highly accurate in our study, because all of these data went through an independent adjudicating process. We conclude that despite low recruitment, our observations in the light of randomization are valuable for determining unbiased outcomes following either modality of epilepsy surgery. For example, the effect sizes of various outcomes provide important data for designing future studies of epilepsy surgery that may not have randomized designs.

Nonetheless, the main limitation of this study was the number of patients recruited. This study was designed when MTLE patients were plentiful, but conducted when fewer patients were available. We speculate that recruitment was difficult because of the overall underutilization of epilepsy surgery,⁷ the dispersal of specialized care beyond core academic centers,⁷ patient satisfaction with continuing seizures treated with easily tolerated anticonvulsants, and the presumptively rare incidence of new cases of straightforward MTLE.³¹ The perception of lack of equipoise from referring physicians or potential patients was also a factor. For example, about 50% of patients who refused participation did so because of their discomfort with randomization or fear of one or the other treatment modalities. Finally, because expertise was required in epilepsy surgery evaluation, open surgery, and radiosurgery, the number of eligible treatment centers was restricted.

The present study followed patients for 3 years. Based on the progressive attainment of short-term seizure remission following SRS, some subjects designated as “not seizure-free” may experience subsequent seizure remission. Studies of SRS with longer follow-up found that about 50% experience durable remission³²; those with relapse had epileptic zones that extended beyond mesial structures. Case reports cite longer-term development of delayed necrosis, angiopathy, or cyst formation in rare patients.²⁰ The incidence/prevalence of these complications is not available for MTL, but incidences for the common use of SRS for arteriovenous malformations range from 1.6% to 3.4% for follow-up periods exceeding 5 years.^{33,34} Thus, our follow-up of 3 years will limit observation of further remission, relapse, or complications of the radiosurgical lesion.

In summary, we present the results on various important aspects of the 6-year ROSE trial. The randomized controlled study suggests that ATL has an advantage over the minimally invasive alternative of SRS with respect to timing of effectiveness and of adverse events, and proportion of patients with seizure remission. Although SRS did not match ATL in these measures, it offers patients an alternative to open surgery. Considering the underutilization of epilepsy surgery, SRS—with adverse events and cognitive changes comparable to standard methods—offers a reasonable path to surgery for those opposed to or reluctant to undergo open surgery, or those for whom medical comorbidities present a barrier for open surgery.

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AUTHOR CONTRIBUTIONS

N.M.B. and M.Q. contributed to the conception and design of the study, acquisition and analysis of data, and drafting of the manuscript and figures. All authors contributed to the concept and design of the study and review of the final manuscript version.

DISCLOSURE

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCES

1. Wyler AR, Hermann BP, Somes G. Extent of medial temporal resection on outcome from anterior temporal lobectomy: a randomized prospective study. *Neurosurgery*. 1995;37:982–90.
2. Sperling MR, O’Connor MJ, Saykin AJ, et al. Temporal lobectomy for refractory epilepsy. *JAMA*. 1996;276:470–5.
3. Wiebe S, Blume WT, Girvin JP, et al. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med*. 2001;345:311–8.
4. Spencer SS, Berg AT, Vickrey BG, et al. Initial outcomes in the Multicenter Study of Epilepsy Surgery. *Neurology*. 2003; 61:1680–5.
5. Engel J Jr, McDermott MP, Wiebe S, et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. *JAMA*. 2012;307:922–30.
6. Engel J Jr, Wiebe S, French J, et al. Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in Association with the American Epilepsy Society and the American Association of Neurological Surgeons. *Neurology*. 2003;60:538–47.
7. Englot DJ, Ouyang D, Garcia PA, et al. Epilepsy surgery trends in the United States, 1990–2008. *Neurology*. 2012;78: 1200–6.
8. Behrens E, Schramm J, Zentner J, et al. Surgical and neurological complications in a series of 708 epilepsy surgery procedures. *Neurosurgery*. 1997;41:1–9.

9. Sperling MR, Feldman H, Kinman J, et al. Seizure control and mortality in epilepsy. *Ann Neurol*. 1999;46:45–50.
10. Hermann BP, Davies K, Foley K, et al. Visual confrontation naming outcome after standard left anterior temporal lobectomy with sparing versus resection of the superior temporal gyrus: a randomized prospective clinical trial. *Epilepsia*. 1999;40:1070–6.
11. Quigg M, Broshek DK, Heidal-Schiltz S, et al. Depression in intractable partial epilepsy varies by laterality of focus and surgery. *Epilepsia*. 2003;44:419–24.
12. Stroup E, Langfitt J, Berg M, et al. Predicting verbal memory decline following anterior temporal lobectomy (ATL). *Neurology*. 2003;60:1266–73.
13. Devinsky O, Barr WB, Vickrey BG, et al. Changes in depression and anxiety after resective surgery for epilepsy. *Neurology*. 2005;65:1744–9.
14. Kawai K, Suzuki I, Kurita H, et al. Failure of low-dose radiosurgery to control temporal lobe epilepsy. *J Neurosurg*. 2001;95:883–7.
15. Cmelak AJ, Abou-Khalil B, Konrad PE, et al. Low-dose stereotactic radiosurgery is inadequate for medically intractable mesial temporal lobe epilepsy: a case report. *Seizure*. 2001;10:442–6.
16. McDonald CR, Norman MA, Tecoma E, et al. Neuropsychological change following Gamma Knife surgery in patients with left temporal lobe epilepsy: a review of three cases. *Epilepsy Behav*. 2004;5:949–57.
17. Régis J, Peragui J, Rey M, et al. First selective amygdalohippocampal radiosurgery for ‘mesial temporal lobe epilepsy’. *Stereotact Funct Neurosurg*. 1995;64(suppl 1):193–201.
18. Srikijvilaikul T, Najm I, Foldvary-Schaefer N, et al. Failure of Gamma Knife radiosurgery for mesial temporal lobe epilepsy: report of five cases. *Neurosurgery*. 2004;54:1395–402.
19. Vojtěch Z, Vladyka V, Kalina M, et al. The use of radiosurgery for the treatment of mesial temporal lobe epilepsy and long-term results. *Epilepsia*. 2009;50:2061–71.
20. Usami K, Kawai K, Koga T, et al. Delayed complication after Gamma Knife surgery for mesial temporal lobe epilepsy. *J Neurosurg*. 2012;116:1221–5.
21. Liang S, Liu T, Li A, et al. Long-term follow up of very low-dose LINAC based stereotactic radiotherapy in temporal lobe epilepsy. *Epilepsy Res*. 2010;90:60–7.
22. Régis J, Rey M, Bartolomei F, et al. Gamma knife surgery in mesial temporal lobe epilepsy: a prospective multicenter study. *Epilepsia*. 2004;45:504–15.
23. Barbaro NM, Quigg M, Broshek DK, et al. A multicenter, prospective pilot study of Gamma Knife radiosurgery for mesial temporal lobe epilepsy: seizure response, adverse events, and verbal memory. *Ann Neurol*. 2009;65:167–75.
24. Quigg M, Broshek DK, Barbaro NM, et al. Neuropsychological outcomes after Gamma Knife radiosurgery for mesial temporal lobe epilepsy: a prospective multicenter study. *Epilepsia*. 2011;52:909–16.
25. Feng ES, Sui CB, Wang TX, et al. Stereotactic radiosurgery for the treatment of mesial temporal lobe epilepsy. *Acta Neurol Scand*. 2016;134:442–51.
26. Spencer DD, Spencer SS, Mattson RH, et al. Access to the posterior medial temporal lobe structures in the surgical treatment of temporal lobe epilepsy. *Neurosurgery*. 1984;15:667–71.
27. Chang EF, Quigg M, Oh MC, et al. Predictors of efficacy after stereotactic radiosurgery for medial temporal lobe epilepsy. *Neurology*. 2010;74:165–72.
28. Willie JT, Laxpati NG, Drane DL, et al. Real-time magnetic resonance-guided stereotactic laser amygdalohippocampotomy for mesial temporal lobe epilepsy. *Neurosurgery*. 2014;74:569–84.
29. Spencer SS, Berg AT, Vickrey BG, et al. Health-related quality of life over time since resective epilepsy surgery. *Ann Neurol*. 2007;62:307–8.
30. Dwivedi R, Ramanujam B, Chandra PS, et al. Surgery for drug-resistant epilepsy in children. *N Engl J Med*. 2017;377:1639–47.
31. Rossi MA. Where have all the temporal lobe epilepsy surgeries gone? *Epilepsy Curr*. 2015;15:126–8.
32. Rheims S, Fischer C, Ryvlin P, et al. Long-term outcome of Gamma-Knife surgery in temporal lobe epilepsy. *Epilepsy Res*. 2008;80:23–9.
33. Pan HC, Sheehan J, Stroila M, et al. Late cyst formation following Gamma Knife surgery of arteriovenous malformations. *J Neurosurg*. 2005;102(suppl):124–7.
34. Izawa M, Hayashi M, Chernov M, et al. Long-term complications after Gamma Knife surgery for arteriovenous malformations. *J Neurosurg*. 2005;102:34–7.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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