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LITERATURE REVIEW

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Lateral versus vertical hemispheric disconnection for epilepsy: a systematic review and meta-analysis

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OBJECTIVE Lateral periinsular hemispherotomy (LPH) and vertical parasagittal hemispherotomy (VPH) are the most popular disconnective techniques for intractable epilepsies associated with unilateral hemispheric pathologies. The authors aimed to investigate possible differences in seizure outcome and complication rates between patients who underwent LPH and VPH.

METHODS A comprehensive literature search of PubMed and Embase identified English-language articles published from database inception to December 2019 that reported series (minimum 12 patients with follow-up ≥ 12 months) on either LPH or VPH. Pooled rates of seizure freedom and complications (with a particular focus on hydrocephalus) were analyzed using meta-analysis to calculate both fixed and random effects. Heterogeneity (Cochran's Q test) and inconsistency (fraction of Q due to actual heterogeneity) were also calculated.

RESULTS Twenty-five studies were included. Data from 825 patients were available for seizure outcome analysis (583 underwent LPH and 242 underwent VPH), and data from 692 patients were available for complication analysis (453 underwent LPH and 239 underwent VPH). No differences were found in the pooled rates of Engel class I seizure outcome between patients who underwent LPH (80.02% and 79.44% with fixed and random effects, respectively) and VPH (79.89% and 80.69% with fixed and random effects, respectively) ($p = 0.953$). No differences were observed in the pooled rates of shunted hydrocephalus between patients who underwent LPH (11.34% and 10.63% with fixed and random effects, respectively) and VPH (11.07% and 9.98% with fixed and random effects, respectively) ($p = 0.898$). Significant heterogeneity and moderate inconsistency were determined for hydrocephalus occurrence in patients who underwent both LPH and VPH.

CONCLUSIONS LPH and VPH techniques present similar excellent seizure outcomes, with comparable and acceptable safety profiles.

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KEYWORDS hemispherotomy; meta-analysis; epilepsy surgery; seizure outcome; complications

Hemispheric surgery is recognized as an effective treatment option for patients, mostly children, with severe drug-resistant focal epilepsy associated with large monolateral hemispheric lesions.[1,2] Owing to the high rate of surgical complications, including hydrocephalus and superficial hemosiderosis, anatomical hemispherectomy was progressively replaced with alternative techniques in which a large amount of the hemisphere is disconnected and left in place with limited tissue resection. Since the report of Theodore Rasmussen in 1983, who described functional hemispherectomy (resection of the temporal lobe and suprasylvian parenchyma, with disconnection of the residual hemisphere),[3] several variations of hemispheric disconnection (hemispherotomy) have been described. With these techniques, tissue removal is minimized, and the rest of the hemisphere is isolated with sectioning of the projection, association, and commissural white matter fibers. Basically, two main approaches have been described: lateral periinsular hemispherotomy (LPH)[4,5] and vertical parasagittal hemispherotomy (VPH).[6]

Previous studies have provided a considerable body of evidence regarding the postoperative results obtained after the adoption of different types of hemispheric surgery, with lower rates of complications reported for discon-

ABBREVIATIONS LPH = lateral periinsular hemispherotomy; NOS = Newcastle-Ottawa Scale; VPH = vertical parasagittal hemispherotomy.

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nective techniques than anatomical hemispherectomy.[7,8] However, the impact of the technical approach on seizure outcome and morbidity is unclear. Available evidence suggests that although the underlying pathology plays a significant role in determining seizure outcome,[1,9] the technical approach has a greater impact on complication rates.[10] A meta-analysis highlighted that the employment of disconnective or resective techniques did not significantly affect the seizure outcomes of hemispheric surgery.[1] In particular, although LPH and VPH have progressively emerged as the most popular techniques employed for hemispheric surgery, studies aimed at comparing the surgical results and morbidity rates of these two procedures are scarce. The only available data were provided by a recent analysis of a multicentric cohort of 92 patients, which showed no significant differences in seizure outcome and complication rates between patients who underwent VPH or LPH.[11] Therefore, the choice between these two techniques seems to depend on the surgeon's preference and experience rather than sound evidence for the superiority of one technique over the other in terms of efficacy and safety.

In the present study, using the population, intervention, comparison, and outcome (PICO) model,[12] we performed a systematic review and meta-analysis of published studies focused on patients with refractory epilepsy (population) who underwent either LPH or VPH (intervention and comparison), with the aim of investigating whether the two techniques differ in terms of seizure outcome and complication rates (outcome).

Methods

This study was discussed with and planned by members of the Commission for Epilepsy Surgery of the Italian League Against Epilepsy (LICE) (*Appendix*). The PRISMA guidelines and recommendations[13] were implemented to carry out the present retrospective review.

Data Sources and Search Strategy

A comprehensive literature review was performed by querying PubMed and Embase on January 9, 2020, using the following search criteria, which were limited to human studies published in English: ((hemispherectomy OR (hemispheric AND surgery) OR hemispherotomy OR (hemispheric AND disconnect*)) AND (seizure* OR epilep*). Other sources, such as the Cochrane Library, DynaMed, and ClinicalTrials.gov, were consulted using the keywords "hemispherotomy" and "hemispherectomy." Articles published from database inception to December 2019 were included.

The reference lists of the original articles, as well as those of the reviews and book chapters, were manually reviewed to look for additional pertinent studies that were not retrieved with the electronic search.

Study Selection

Three authors (M.C., A.D.B., and M.R.) independently reviewed the title, abstract, or full-text of each retrieved article. Studies were selected according to the following inclusion criteria: full text available; inclusion of at least 12 patients who underwent LPH or VPH (to limit changes in heterogeneity);[14] postoperative follow-up duration of at least 12 months; and seizure outcome measured with the Engel seizure outcome classification scale[15] or other comparable scales. The included variations of LPH were described by Villemure and Mascott,[4] Schramm et al.,[5,16] Shimizu and Maehara,[17] and Cook et al.[8] Classic functional hemispherectomy[3] was excluded because the amount of resected tissue predominates over that of the disconnected areas. For VPH, we included studies that reported use of the traditional Delalande technique[6] and its variations.[18–20]

Data Extraction

All data concerning clinical outcomes were extracted independently from the study texts, tables, and figures by two authors (M.C. and M.R.). Possible discrepancies were discussed and resolved by consensus. The primary outcome of interest was the rate of Engel class I outcome after surgery. The secondary outcome of interest was the rate of postoperative major surgical complications, defined as the occurrence of one or more of any of the following: unexpected and permanent new neurological deficit, surgical complication requiring return to the operating room, and death.[21] Because hydrocephalus is recognized as the most frequent postoperative complication of hemispheric surgery,[22] we separately extracted the rate of postoperative hydrocephalus requiring external or internal cerebrospinal fluid shunting.

Meta-Analysis

The unit of the analysis was each selected study. Meta-analyses were conducted with respect to the proportions of patients with Engel class seizure outcomes (Engel class I vs classes II–IV), major complications (present vs absent), and shunted hydrocephalus (present vs absent) that were reported as results in the included studies, and both fixed and random effects were calculated. Heterogeneity was measured using Cochran's Q test, and inconsistency was measured as the fraction of Q due to actual heterogeneity (I^2, i.e., heterogeneity not attributable to chance). Possible publication bias was evaluated using both Egger's and Begg's tests. Comparison of the meta-analyses of LPH and VPH was carried out with Cochran's Q test, as previously reported.[23]

Statistical significance was set at $p < 0.05$. Statistical analysis was performed with Stata/SE version 16.1 (StataCorp).

Quality Assessment

The quality of evidence of each study was evaluated using a modified version of the Newcastle-Ottawa Scale (NOS) for the assessment of noncomparative studies.[24,25] The modified NOS was employed to assess the quality of each paper using a predefined set of 5 criteria that were tailored to the purposes of our study. Items were scored in response to each question as negative (score 0) or positive (1), as follows: 1) Did the patients represent all patients treated at the medical center (i.e., were all patients managed in the study period included in the study)? 2) Was the diagnosis correct? 3) Was the follow-up period long enough for outcomes to occur (i.e., did study have the

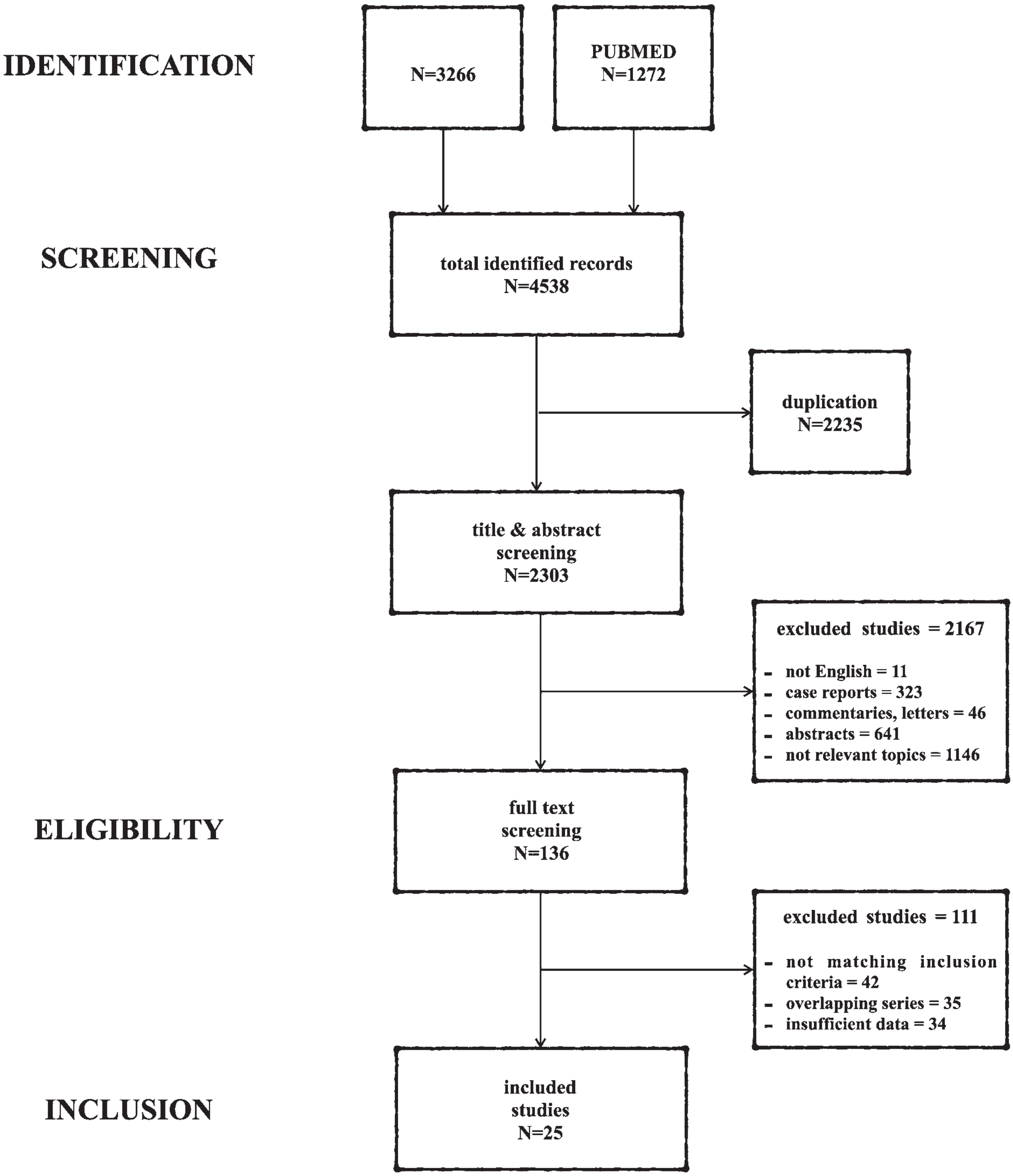


FIG. 1. Results of the PRISMA search strategy.

minimum postoperative follow-up period of 12 months)? 4) Were all important data cited in the report? 5) Was the outcome correctly ascertained (i.e., was seizure outcome defined on the basis of dedicated scales)?

Results

Literature Search Results

Study selection is summarized in Fig. 1. The initial search identified 4538 records (1272 from PubMed and 3266 from Embase). No relevant records were obtained from the other sources. After exclusion of duplicates, 2303 records were available for screening. After title and abstract review, 2167 studies were excluded for the following reasons: reports on nondisconnective surgery or irrelevant topics (1146 records); case reports (323 records); conference abstracts (641 records); letters, reviews, and commentaries (46 records); and non–English-language studies (11

TABLE 1. Study characteristics and demographic data

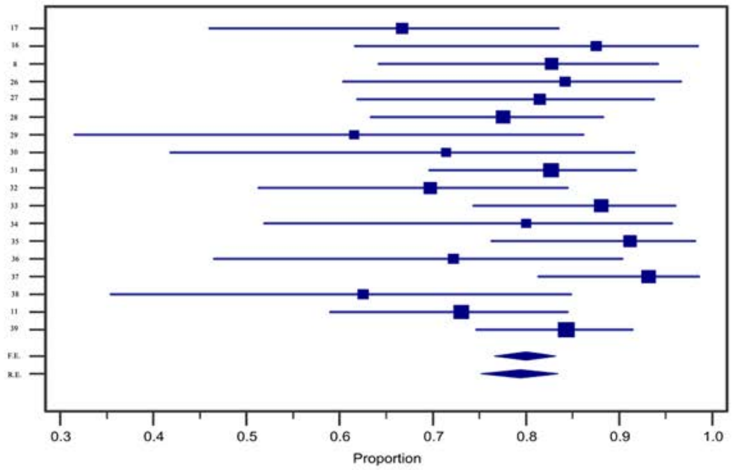
Authors & Year	Design	Total NOS Score	Overall Study Quality	Period	No. of Patients: Total	Available SO Data	Available Complications Data	Mean Age (range)	Etiology	Mean Follow-Up (mos)
LPH										
Shimizu & Maehara, 2000[17]	RCS	5	High	1993–1999	27	27	27	6.9 yrs (3 mos to 30 yrs)	FCD	NA
Schramm et al., 2001[16]	RCS	4	High	NA	20	16	20	14.3 (0.75–38) yrs	Mixed	46
Cook et al., 2004[8]	RCS	5	High	1997–2002	29	29	NA	NA*	Mixed	SO at 24 mos
Basheer et al., 2007[26]	RCS	5	High	1993–2004	19	19	19	NA†	Mixed	NA†
Cats et al., 2007[27]	RCS	5	High	1992–2004	28	27	28	5.8 yrs (3 mos to 24.5 yrs)	Mixed	NA
Limbrick et al., 2009[28]	RCS	5	High	1995–2008	49	49	49	NA (0.2–20.5 yrs)	Mixed	28.6
Marras et al., 2010[29]	RCS	5	High	2000–2007	13	13	13	7.3 yrs (9 mos to 16 yrs)	Mixed	54
Scavarda et al., 2010[30]	RCS	5	High	1993–2007	14	14	14	8 yrs (21 mos to 18 yrs)	Mixed	84‡
Ramantani et al., 2013[31]	RCS	5	High	2002–2011	52	52	52	6.7 (0.6–18) yrs	Mixed	39.6
Buckley et al., 2014[32]	RCS	4	High	1997–2012	39	33	39	6.7 yrs (1 mos to 18.9 yrs)	Mixed	56.4
Lew et al., 2014[33]	RCS	5	High	2004–2012	42	42	38	NA†	Mixed	NA†
Kumar et al., 2015[34]	RCS	5	High	2002–2013	15	15	15	3.9 (0.25–11.5) mos§	Mixed	64.7
Nelles et al., 2015[35]	RCS	5	High	2005–2013	34	34	NA	12 (0–55) yrs	Mixed	NA
Guan et al., 2017[36]	RCS	5	High	2004–2015	18	18	18	NA†	RE	NA†
Abraham et al., 2019[37]	RCS	5	High	2005–2016	45	44	44	8 yrs (10 mos to 17 yrs)	Mixed	48
Arifin et al., 2019[38]	RCS	5	High	1999–2019	23	16	23	12.8 (2–28) yrs	Mixed	24–160¶
de Palma et al., 2019[11]	RCS	5	High	2006–2016	54	52	54	NA†	Mixed	NA†
Ji et al., 2019[39]	RCS	5	High	2014–2017	83	83	NA	5 (0.8–14) yrs	Mixed	36
Overall sum					604	583	453			
VPH										
Delalande et al., 2007[6]	RCS	5	High	1990–2000	83	81	83	8 (0.2–36) yrs	Mixed	NA
Dorfer et al., 2013[40]	RCS	5	High	1998–2013	40	37	40	5.5 yrs‡	Mixed	44.4‡
Honda et al., 2013[41]	RCS	5	High	2000–2009	12	12	12	4.3 (2–9) mos§	HME	74.8
Panigrahi et al., 2016[42]	RCS	5	High	NA	16	16	16	6.5 yrs	Mixed	NA†
Chipaux et al., 2017[43]	RCS	5	High	2002–2014	19	18	NA	2.6 yrs (3 mos to 7.7 yrs)	Mixed	NA†
Chandra et al., 2018[44]	RCS**	5	High	2013–2017	32	23	32	8.6 yrs	Mixed	23.6
Fohlen et al., 2019[45]	RCS	5	High	2000–2017	18	17	18	7.2 (4.9–11.1) yrs	PMG	153.6
de Palma et al., 2019[11]	RCS	5	High	2006–2016	38	38	38	NA†	Mixed	NA†
Overall sum					258	242	239			

FCD = focal cortical dysplasia; HME = hemimegalencephaly; NA = not available; PMG = polymicrogyria; RCS = retrospective case series; RE = Rasmussen's encephalitis; SO = seizure outcome.
* This study included only children.
† Value could not be extracted from aggregate data.
‡ The median is shown.
§ Study included only infants younger than 1 year.
¶ The range is shown.
** Despite the authors' statement, this study was classified as a retrospective case series.

records). Therefore, 136 studies were eligible for full-text screening. After exclusion of 111 studies (42 did not meet the inclusion criteria, 35 included overlapping populations, and 34 had insufficient data), a total of 25 studies met the inclusion criteria and were included in our study.[6,8,11,16,17,26–45] All 25 studies were retrospective consecutive case series and published between 2000 and 2019, with the cumulative studied period ranging from 1990 to 2017. Seventeen studies reported on LPH, 7 reported on VPH, and 1 included both techniques (Table 1). Data on surgical complications were available from 21 studies. Data on a total of 825 patients (583 underwent LPH and 242 underwent VPH) were available for analysis of seizure outcome, and data on 692 patients (453 underwent LPH and 239 underwent VPH) were available for the analyses of major complications and shunted hydrocephalus.

Variable for studies: Authors
Variable for total number of cases: N. of patients selected for outcome
Variable for number of positive cases: N. of patients in Engel Class I

Study	Sample size	Proportion (%)	95% CI	Weight (%) Fixed	Weight (%) Random
Shimizu & Maehara, 2000[17]	27	66.667	46.039 to 83.481	4.66	5.24
Schramm et al., 2001[16]	16	87.500	61.652 to 98.449	2.83	3.62
Cook et al., 2004[8]	29	82.759	64.225 to 94.154	4.99	5.49
Basheer et al., 2007[26]	19	84.211	60.422 to 96.617	3.33	4.10
Cats et al., 2007[27]	27	81.481	61.917 to 93.700	4.66	5.24
Limbrick et al., 2009[28]	49	77.551	63.376 to 88.226	8.32	7.54
Marras et al., 2010[29]	13	61.538	31.578 to 86.142	2.33	3.09
Scavarda et al., 2010[30]	14	71.429	41.896 to 91.611	2.50	3.27
Ramantani et al., 2013[31]	52	82.692	69.672 to 91.767	8.82	7.79
Buckley et al., 2014[32]	33	69.697	51.289 to 84.408	5.66	5.97
Lew et al., 2014[33]	42	88.095	74.368 to 96.019	7.15	6.91
Kumar et al.[5], 2015[34]	15	80.000	51.911 to 95.669	2.66	3.45
Nelles et al., 2015[35]	34	91.176	76.322 to 98.142	5.82	6.08
Guan et al., 2017[36]	18	72.222	46.520 to 90.305	3.16	3.94
Abraham et al., 2019[37]	44	93.182	81.344 to 98.571	7.49	7.10
Arifin et al., 2019[38]	16	62.500	35.435 to 84.802	2.83	3.62
De Palma et al., 2019[11]	52	73.077	58.976 to 84.432	8.82	7.79
Ji et al., 2019[39]	83	84.337	74.707 to 91.388	13.98	9.75
	583	80.022	76.598 to 83.148	100.00	100.00
	583	79.436	75.178 to 83.389	100.00	100.00



Test for heterogeneity

Q	25.7780
DF	17
Significance level	P = 0.0786
I^2 (inconsistency)	34.05%
95% CI for I^2	0.00 to 62.64

Publication bias

Egger's test

Intercept	-1.9599
95% CI	-4.2159 to 0.2962
Significance level	P = 0.0841

Begg's test

Kendall's Tau	-0.3036
Significance level	P = 0.0785

FIG. 2. Forest plots of the relative incidence rates of Engel class I seizure outcome in patients who underwent LPH, together with the results of the tests for heterogeneity and publication bias, as determined with meta-analysis. DF = degrees of freedom; FE = fixed effects; RE = random effects. Figure is available in color online only.

Quality Assessment of the Included Studies

The modified NOS provided a median (range) score of 5 (4–5); 23 studies had a score of 5, and 2 had a score of 4 of 5. The quality of all selected studies was therefore classified as high (Table 1).

Clinical Features

Six studies (5 in the LPH group and 1 that reported both LPH and VPH cases) did not report mean age at surgery, and 1 study included in the VPH group provided median age at surgery (Table 1). Mean age at surgery was therefore available from 18 studies, and the pooled mean ages at surgery were 7.5 years for the LPH group (12 studies) and 6.8 years for the VPH group (6 studies).

On the whole, pediatric cases largely prevailed across studies, with 2 studies including only infants younger than 12 months of age.[34,41] Most studies included unselected (or mixed) etiologies. Patients were selected for etiology in 4 studies (2 in the LPH group and 2 in the VPH group), as detailed in Table 1.

There was high inhomogeneity in follow-up duration after surgery (Table 1). Nevertheless, 10 studies[6,16,27,32,37,38,40,43,44,45] included patients with follow-up < 12 months who could be identified and were excluded from the analysis of seizure outcome. The other 15 studies maintained a minimum follow-up of 12 months for all participants.

The proportions of patients with Engel class I seizure outcome, major complications, and shunted hydrocephalus are reported in Figs. 2–7. The proportions of patients with Engel class I seizure outcome ranged from 61.5% to 93.2% for the LPH group and from 66.7% to 93.8% for the VPH group. Major complications occurred in 0% to 33.3% of patients in the LPH group and 6.3% to 21.1% of patients in the VPH group. The rates of hydrocephalus requiring shunting—which represented by far the most frequently reported major complication—ranged from 0% to 26.7% for LPH and from 0% to 21.1% for VPH.

Pooled Seizure Outcomes

The numbers of patients with evaluable data for seizure outcome were 583 for LPH and 242 for VPH.

For LPH, 468/583 patients had class I seizure outcome, resulting in a proportion of 80.02% (95% CI 76.60%–83.15%) for computing fixed effects and a proportion of 79.44% (95% CI 75.18%–83.39%) for computing random effects. The Q test calculated p = 0.079, and inconsistency was 34.05% (95% CI 0.00%–62.64%). Neither Egger's test (p = 0.084) nor Begg's test (p = 0.079) showed significant publication bias (Fig. 2).

For VPH, 194/242 patients had class I seizure outcome, resulting in a proportion of 79.89% (95% CI 74.38%–84.68%) for computing fixed effects and a proportion of 80.69% (95% CI 74.04%–86.57%) for computing random effects. The Q test calculated p = 0.168, and inconsistency was 32.58% (95% CI 0.00%–70.07%). Neither Egger's test (p = 0.414) nor Begg's test (p = 0.322) showed significant publication bias (Fig. 3).

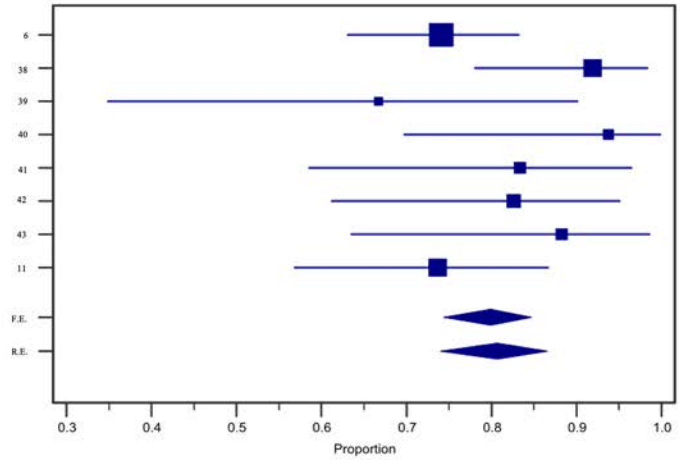
Comparing these meta-analyses, we saw that the 95% CIs for the outcome proportions for LPH and VPH largely overlapped for both fixed and random effects, and the result of the Q test (p = 0.953) was far from statistical significance.

Pooled Major Complications

The numbers of patients with evaluable data for major complications were 453 for LPH and 239 for VPH.

Variable for studies	Authors
Variable for total number of cases	N. of patients selected for outcome
Variable for number of positive cases	N. of patients in Engel Class I

Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Delalande et al., 2007[6]	81	74.074	63.140 to 83.180	32.80	22.99
Dorfer et al., 2013[40]	37	91.892	78.090 to 98.296	15.20	15.42
Honda et al., 2013[41]	12	66.667	34.888 to 90.075	5.20	7.07
Panigrahi et al., 2016[42]	16	93.750	69.768 to 99.842	6.80	8.77
Chiapaux et al., 2017[43]	18	83.333	58.582 to 96.421	7.60	9.55
Chandra et al., 2018[44]	23	82.609	61.219 to 95.049	9.60	11.35
Fohlen et al., 2019[45]	17	88.235	63.559 to 98.542	7.20	9.17
De Palma et al., 2019[11]	38	73.684	56.899 to 86.597	15.60	15.67
	242	79.890	74.378 to 84.677	100.00	100.00
	242	80.690	74.038 to 86.565	100.00	100.00



Test for heterogeneity

Q	10.3829
DF	7
Significance level	P = 0.1679
I^2 (inconsistency)	32.58%
95% CI for I^2	0.00 to 70.07

Publication bias

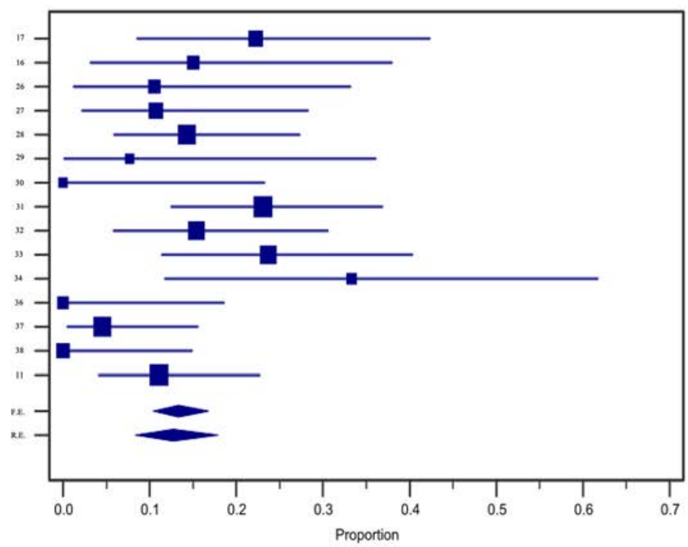
Egger's test	
Intercept	1.2899
95% CI	-2.3095 to 4.8892
Significance level	P = 0.4143

Begg's test	
Kendall's Tau	0.2857
Significance level	P = 0.3223

FIG. 3. Forest plots of the relative incidence rates of Engel class I seizure outcome in patients who underwent VPH, together with the results of the tests for heterogeneity and publication bias, as determined with meta-analysis. See Fig. 2 for definitions of abbreviations. Figure is available in color online only.

Variable for studies	Authors
Variable for total number of cases	N. of patients selected for outcome
Variable for number of positive cases	N. of patients with major complications

Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Shimizu & Maehara, 2000[17]	27	22.222	8.622 to 42.258	5.98	6.69
Schramm et al., 2001[16]	20	15.000	3.207 to 37.893	4.49	5.81
Basheer et al., 2007[26]	19	10.526	1.301 to 33.138	4.27	5.67
Cats et al., 2007[27]	28	10.714	2.267 to 28.226	6.20	6.79
Limbrick et al., 2009[28]	49	14.286	5.942 to 27.242	10.68	8.34
Marras et al., 2010[29]	13	7.692	0.195 to 36.030	2.99	4.61
Scavarda et al., 2010[30]	14	0.000	0.000 to 23.164	3.21	4.81
Ramantani et al., 2013[31]	52	23.077	12.532 to 36.840	11.32	8.49
Buckley et al., 2014[32]	39	15.385	5.862 to 30.528	8.55	7.73
Lew et al., 2014[33]	38	23.684	11.444 to 40.241	8.33	7.66
Kumar et al.§, 2015[34]	15	33.333	11.824 to 61.620	3.42	5.00
Guan et al., 2017[36]	18	0.000	0.000 to 18.530	4.06	5.51
Abraham et al., 2019[37]	44	4.545	0.555 to 15.473	9.62	8.06
Arifin et al., 2019[38]	23	0.000	0.000 to 14.819	5.13	6.22
De Palma et al., 2019[11]	54	11.111	4.188 to 22.631	11.75	8.59
	453	13.342	10.394 to 16.762	100.00	100.00
	453	12.742	8.379 to 17.863	100.00	100.00



Test for heterogeneity

Q	32.7342
DF	14
Significance level	P = 0.0031
I^2 (inconsistency)	57.23%
95% CI for I^2	23.99 to 75.23

Publication bias

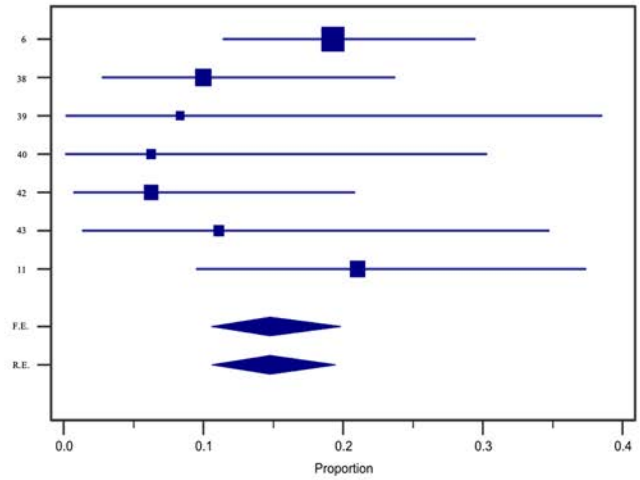
Egger's test	
Intercept	-1.7144
95% CI	-5.5231 to 2.0943
Significance level	P = 0.3486

Begg's test	
Kendall's Tau	-0.1429
Significance level	P = 0.4579

FIG. 4. Forest plots of the relative incidence rates of major complications in patients who underwent LPH, together with the results of the tests for heterogeneity and publication bias, as determined with meta-analysis. See Fig. 2 for definitions of abbreviations. Figure is available in color online only.

Variable for studies	Authors
Variable for total number of cases	N. of patients selected for outcome
Variable for number of positive cases	N. of patients with major complications

Study	Sample size	Proportion (%)	95% CI	Weight (%) Fixed	Weight (%) Random
Delalande et al., 2007[6]	83	19.277	11.439 to 29.409	34.15	34.15
Dorfer et al., 2013[40]	40	10.000	2.793 to 23.664	16.67	16.67
Honda et al., 2013[41]	12	8.333	0.211 to 38.480	5.28	5.28
Panigrahi et al., 2016[42]	16	6.250	0.158 to 30.232	6.91	6.91
Chandra et al., 2018[44]	32	6.250	0.766 to 20.807	13.41	13.41
Fohlen et al., 2019[45]	18	11.111	1.375 to 34.712	7.72	7.72
De Palma et al., 2019[11]	38	21.053	9.554 to 37.319	15.85	15.85
	239	14.762	10.575 to 19.822	100.00	100.00
	239	14.762	10.616 to 19.458	100.00	100.00



Test for heterogeneity

Q	5.8717
DF	6
Significance level	P = 0.4377
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 70.66

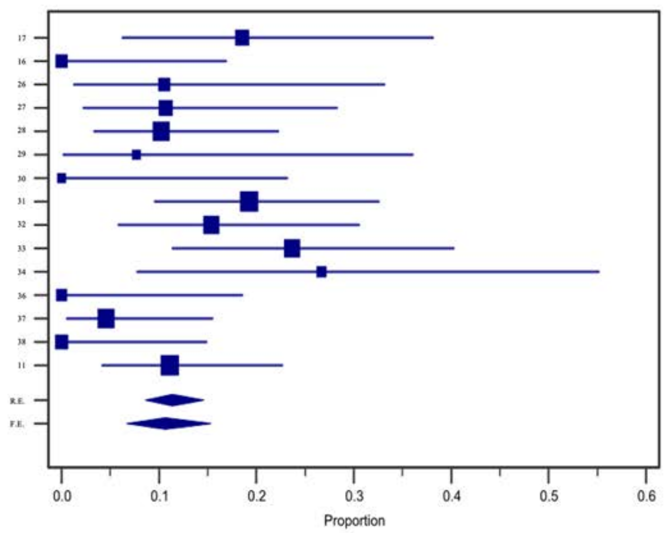
Publication bias

Egger's test		Begg's test	
Intercept	-1.8670		
95% CI	-4.7129 to 0.9789	Kendall's Tau	-0.3333
Significance level	P = 0.1525	Significance level	P = 0.2931

FIG. 5. Forest plots of the relative incidence rates of major complications in patients who underwent VPH, together with the results of the tests for heterogeneity and publication bias, as determined with meta-analysis. See Fig. 2 for definitions of abbreviations. Figure is available in color online only.

Variable for studies	Authors
Variable for total number of cases	N. of patients selected for outcome
Variable for number of positive cases	N. of patients with shunted hydrocephalus

Study	Sample size	Proportion (%)	95% CI	Weight (%) Fixed	Weight (%) Random
Shimizu & Maehara, 2000[17]	44	4.545	0.555 to 15.473	9.62	8.10
Schramm et al., 2001[16]	23	0.000	0.000 to 14.819	5.13	6.20
Basheer et al., 2007[26]	19	10.526	1.301 to 33.138	4.27	5.63
Cats et al., 2007[27]	39	15.385	5.862 to 30.528	8.55	7.76
Limbrick et al., 2009[28]	28	10.714	2.267 to 28.226	6.20	6.79
Marras et al., 2010[29]	49	10.204	3.397 to 22.228	10.68	8.39
Scavarda et al., 2010[30]	54	11.111	4.188 to 22.631	11.75	8.65
Ramantani et al., 2013[31]	18	0.000	0.000 to 18.530	4.06	5.48
Buckley et al., 2014[32]	15	26.667	7.787 to 55.100	3.42	4.96
Lew et al., 2014[33]	38	23.684	11.444 to 40.241	8.33	7.69
Kumar et al.[§], 2015[34]	13	7.692	0.195 to 36.030	2.99	4.56
Guan et al., 2017[36]	52	19.231	9.627 to 32.534	11.32	8.55
Abraham et al., 2019[37]	20	0.000	0.000 to 16.843	4.49	5.79
Arifin et al., 2019[38]	27	18.519	6.300 to 38.083	5.98	6.68
De Palma et al., 2019[11]	14	0.000	0.000 to 23.164	3.21	4.76
	453	11.344	8.616 to 14.571	100.00	100.00
	453	10.630	6.701 to 15.335	100.00	100.00



Test for heterogeneity

Q	31.7523
DF	14
Significance level	P = 0.0043
I^2 (inconsistency)	55.91%
95% CI for I^2	21.34 to 75.29

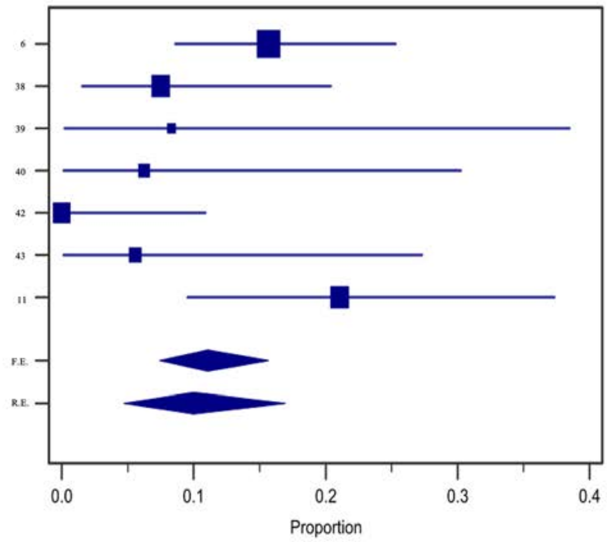
Publication bias

Egger's test		Begg's test	
Intercept	-2.2314		
95% CI	-5.8793 to 1.4165	Kendall's Tau	-0.1619
Significance level	P = 0.2091	Significance level	P = 0.4002

FIG. 6. Forest plots of the relative incidence rates of shunted hydrocephalus in patients who underwent LPH, together with the results of the tests for heterogeneity and publication bias, as determined with meta-analysis. See Fig. 2 for definitions of abbreviations. Figure is available in color online only.

Variable for studies	Authors
Variable for total number of cases	N. of patients selected for outcome
Variable for number of positive cases	N. of patients with shunted hydrocephalus

Study	Sample size	Proportion (%)	95% CI	Weight (%) Fixed	Weight (%) Random
Delalande et al., 2007[6]	83	15.663	8.612 to 25.293	34.15	20.39
Dorfer et al., 2013[40]	40	7.500	1.574 to 20.386	16.67	16.54
Honda et al., 2013[41]	12	8.333	0.211 to 38.480	5.28	9.21
Panigrahi et al., 2016[42]	16	6.250	0.158 to 30.232	6.91	10.87
Chandra et al., 2018[44]	32	0.000	0.000 to 10.888	13.41	15.18
Fohlen et al., 2019[45]	18	5.556	0.141 to 27.294	7.72	11.58
De Palma et al., 2019[11]	38	21.053	9.554 to 37.319	15.85	16.23
	239	11.070	7.437 to 15.674	100.00	100.00
	239	9.984	4.722 to 16.920	100.00	100.00



Test for heterogeneity

Q	14.1925
DF	6
Significance level	P = 0.0276
I^2 (inconsistency)	57.72%
95% CI for I^2	2.17 to 81.73

Publication bias

Egger's test	
Intercept	-1.8121
95% CI	-6.9474 to 3.3232
Significance level	P = 0.4059

Begg's test	
Kendall's Tau	0.04762
Significance level	P = 0.8806

FIG. 7. Forest plots of the relative incidence rates of shunted hydrocephalus in patients who underwent VPH, together with the results of the tests for heterogeneity and publication bias, as determined with meta-analysis. See Fig. 2 for definitions of abbreviations. Figure is available in color online only.

For LPH, 62/453 patients had major complications, resulting in a proportion of 13.34% (95% CI 10.39%–16.76%) for computing fixed effects and a proportion of 12.74% (95% CI 8.38%–17.86%) for computing random effects. The Q test calculated significant heterogeneity (p = 0.003), and inconsistency was 57.23% (95% CI 23.99%–75.93%). Neither Egger's test (p = 0.349) nor Begg's test (p = 0.458) showed significant publication bias (Fig. 4).

For VPH, 34/239 patients had major complications, resulting in a proportion of 14.76% for both fixed (95% CI 10.58%–19.82%) and random (95% CI 10.62%–19.46%) effects. The Q test was nonsignificant (p = 0.438), and inconsistency was 0.00% (95% CI 0.00%–70.66%). Neither Egger's test (p = 0.153) nor Begg's test (p = 0.293) indicated significant publication bias (Fig. 5).

Comparing these meta-analyses, we saw that the 95% CIs for the outcome proportions for LPH and VPH overlapped for both fixed and random effects, and the result of the Q test (p = 0.827) appeared to be far from statistical significance.

Pooled Analysis of Shunted Hydrocephalus

Hydrocephalus requiring shunting represented 85.5% of major complications in the LPH group and 79.5% in the VPH group.

For LPH, 53/453 patients had shunted hydrocephalus, resulting in a proportion of 11.34% (95% CI 8.62%–14.57%) for computing fixed effects and a proportion of 10.63% (95% CI 6.70%–15.34%) for computing random effects. The Q test calculated significant heterogeneity (p = 0.004), and inconsistency was 55.91% (95% CI 21.34%–75.29%). Neither Egger's test (p = 0.209) nor Begg's test (p = 0.400) indicated publication bias (Fig. 6).

For VPH, 27/239 patients had shunted hydrocephalus, resulting in a proportion of 11.07% for fixed effects (95% CI 7.44%–15.67%) and a proportion of 9.98% for random effects (95% CI 4.72%–16.92%). The Q test indicated significance (p = 0.0276), and inconsistency was 57.72% (95% CI 2.17%–81.73%). Neither Egger's test (p = 0.406) nor Begg's test (p = 0.881) indicated significant publication bias (Fig. 7).

Comparing these meta-analyses, we saw that the 95% CIs for the outcome proportions for LPH and VPH overlapped for both fixed and random effects, and the result of the Q test (p = 0.898) was far from statistical significance.

Other Major Complications

In the LPH group, 9 major complications other than hydrocephalus were reported: infection (2 patients [0.4%]), pericerebral fluid collection (3 [0.6%]), brain swelling (2 [0.4%]), intracerebral hematoma (1 [0.2%]), and status epilepticus (1 [0.2%]). Two (0.4%) of these patients died (1 of status epilepticus and 1 of brain swelling).

In the VPH group, 7 major complications other than hydrocephalus were reported: infection (1 patient [0.4%]), stroke (2 [0.8%]), hyponatremia (2 [0.8%]), pericerebral fluid collection (1 [0.4%]), and latex allergy (1 [0.4%]). Four (1.6%) of these patients died (2 of hyponatremia, 1 of stroke, and 1 of latex allergy). No deaths related to hydrocephalus were reported in either the LPH or VPH group.

Discussion

Summary of Evidence

In the present study, we conducted a systematic review and meta-analysis aimed at identifying and comparing the rates of seizure freedom and major complications (with a focus on hydrocephalus requiring shunting) associated with two techniques of hemispheric disconnection (LPH and VPH) in patients with drug-resistant epilepsy.

We found that the pooled rates of seizure freedom determined with analysis of LPH and VPH were very similar; these rates approached 80% of patients according to the analysis of the fixed- and random-effects models and were not significantly different ($p = 0.953$). Furthermore, our analysis also showed that the pooled rates of major surgical complications and postoperative shunted hydrocephalus were similar between patients who underwent LPH and VPH, with no statistically significant differences ($p = 0.827$ and $p = 0.898$, respectively)

LPH and VPH are the two most popular technical variations of hemispheric disconnection for patients with drug-resistant epilepsy who require hemispheric surgery. Although both were introduced several decades ago, comparative data regarding their respective merits and drawbacks in terms of efficacy and safety profiles are surprisingly poor. To the best of our knowledge, only a recent retrospective study conducted at three Italian centers specifically addressed this issue.[11] The authors found that use of lateral or vertical disconnective approaches did not significantly influence either seizure outcome or complication rates (including that of hydrocephalus). Another study included only the lateral and vertical disconnective variations, but the results were analyzed by comparing the vertical endoscope-assisted approach with open surgery techniques, in which both the lateral and vertical approaches were collapsed.[44] Other previous studies have focused on the impact of different hemispheric surgery techniques on seizure results and complications. Only the study by Holthausen et al. reported a relevant impact of surgical technique on effectiveness, with better seizure results observed in patients who underwent hemispheric disconnection than patients who underwent anatomical and functional hemispherectomy and hemidecortication.[46] A meta-analysis of hemispheric surgery highlighted a nonsignificant trend for better seizure outcomes provided by hemispheric disconnections compared with those of resective techniques.[1] Other studies found comparable efficacy profiles for different combinations of anatomical hemispherectomy, functional hemispherectomy, and hemidecortication and hemispheric disconnection.[7,8,22,47]

There is general consensus that the introduction of disconnective techniques has decreased the incidence of postoperative complications and particularly that of hydrocephalus, which is more frequently observed after resective hemispheric procedures.[48] Nevertheless, no definite data are available regarding the impacts of different variations of disconnections on the associated safety profiles. The only available data show a slightly higher, but not significant higher, rate of complications, including hydrocephalus, in patients who underwent vertical hemispherotomy.[11]

Study Limitations

Because our study included only retrospective case series, the levels of evidence of both the individual studies and the meta-analyses of their results may be low despite high quality as assessed with the modified NOS.

Another possible source of bias is the different numbers of patients who received each procedure. Nevertheless, we feel that the even distribution of patients among studies should have prevented or at least limited the impact of this issue on the final results.

Significant noncausal heterogeneities, with moderate inconsistency ($I^2 > 50\%$), were found in the analyses of major complications in patients who underwent LPH and of shunted hydrocephalus in patients who underwent both LPH and VPH. The unreliability of these meta-analyses could have been mitigated by computing random-effects models, but the findings concerning the safety profiles of the two techniques should be taken with great caution. We postulate that heterogeneity (the actual heterogeneity rather than heterogeneity due to chance) in this specific case may have been due to reporting bias for individual adverse events that were collapsed into the major complications variable, as well as due to the different thresholds and sensibilities used to indicate surgical treatment of postoperative hydrocephalus across studies.

No significant publication bias was detected. However, this finding must be interpreted with caution because both Egger's and Begg's tests have low power when the number of analyzed studies is small.[49,50]

Conclusions

The findings of this meta-analysis indicate that the lateral and vertical variations of hemispheric disconnection are similarly effective procedures for seizure control, with acceptable and comparable safety profiles. Therefore, because this study did not provide evidence useful for formulating recommendations in favor of one technique over the other, it is conceivable that each technical variation of hemispheric disconnection provides similar benefits with similar surgical risks in suitably skilled hands. In clinical practice, opting for one or the other technique should not significantly alter the perspective in terms of seizure outcome and the surgical safety profile of an individual patient requiring hemispheric disconnection, provided that the assigned neurosurgeon is appropriately trained in the selected procedure. Consequently, we believe that, at present, epilepsy neurosurgeons should acquire sufficient skills for mastering one of the two approaches. In addition, although hemispheric procedures represent 20%–30% of epilepsy surgical procedures performed on children,[49,50] the procedural volume is insufficient to allow for a successful learning curve for both techniques even at high-level centers.

Among the factors, other than type of surgery, that act as major determinants of seizure outcome in patients requiring hemispheric surgery, a relevant role has been evidenced for underlying pathological substrates. The best epileptological results have been reported for acquired and progressive etiologies, whereas congenital/developmental disorders are associated with less favorable outcomes.[1,7,9,10,22,29] At the same time, the incidence of postoperative hydrocephalus has been related to pathology.[10] Therefore, the contributions of different techniques to seizure outcome and morbidity should be ideally evaluated according to etiology. This may be a possible direction for future clinical research, with the aim of investigating if tailoring the disconnective technique to specific pathologies for further optimization of outcomes is a realistic target. A similar task should involve as many centers as possible in prospective data collection, because the number of patients managed by individual teams is insufficient to gather usable data, even if these patients are treated at experienced high-volume programs.

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Appendix

The members of the Commission for Epilepsy Surgery of the Italian League Against Epilepsy (LICE) include Carlo Efisio Marras, MD (coordinator),[1] Sofia Asioli, MD,[2] Carmen Barba, MD,[3] Massimo Caulo, MD,[4] Gabriella Colicchio, MD,[5] Alessandro Consales, MD,[6] Massimo Cossu, MD,[7] Luca De Palma, MD,[7] Giancarlo Di Gennaro, MD,[8] Giampaolo Vatti, MD,[9] Flavio Villani, MD,[10] and Nelia Zamponi, MD.[11]

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Disclosures

Dr. Rizzi served as a paid consultant for WISE S.r.l.

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Conception and design: Rizzi, Cossu. Acquisition of data: Rizzi, Cossu, De Benedictis. Analysis and interpretation of data: Rizzi, Cossu, De Benedictis. Drafting the article: Rizzi, Cossu, De Benedictis. Critically revising the article: Cossu, De Benedictis. Reviewed submitted version of manuscript: Cossu, De Benedictis. Statistical analysis: Nichelatti. Administrative/technical/material support: Rizzi. Study supervision: Cossu.

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