FULL-LENGTH ARTICLE NPub.org/igv3vh

Long-term follow-up, quality of life, and survival of patients with Lambert-Eaton myasthenic syndrome

Alexander F. Lipka, MD, Marion I. Boldingh, MD, PhD, Erik W. van Zwet, PhD, et al.

Cite as: *Neurology*® 2020;94:e511-e520. doi:10.1212/WNL.0000000000008747

Correspondence
Dr. Lipka
a.f.lipka@lumc.nl

Study objective and summary result

The present study examined survival outcomes, long-term functional impairment, and health-related quality of life (HRQoL) in patients with Lambert-Eaton myasthenic syndrome (LEMS). The results indicate that patients often have favorable outcomes in terms of survival and functional independence; and that patients have impaired physical HRQoL, but not impaired mental HRQoL.

What is known and what this paper adds

The medical literature provides incomplete information about survival outcomes, long-term functional impairment, and HRQoL in patients with LEMS. This investigation addresses that gap in the literature.

Participants and setting

The investigators reviewed data from 150 patients with LEMS who were treated at Dutch hospitals between July 1, 1998, and October 1, 2015.

Design, size, and duration

The investigators drew a distinction between patients with nontumor LEMS (NT-LEMS) and those with associated lung cancers, including patients with small cell lung cancer LEMS (SCLC-LEMS). The survival outcomes for the patients with LEMS were compared with survival data for the Dutch general population and patients with non-LEMS SCLC provided by Dutch statistical agencies. The modified Rankin Scale and the Karnofsky Performance Scale were used to assess functional impairment, and the Short Form–36 was used to assess HRQoL.

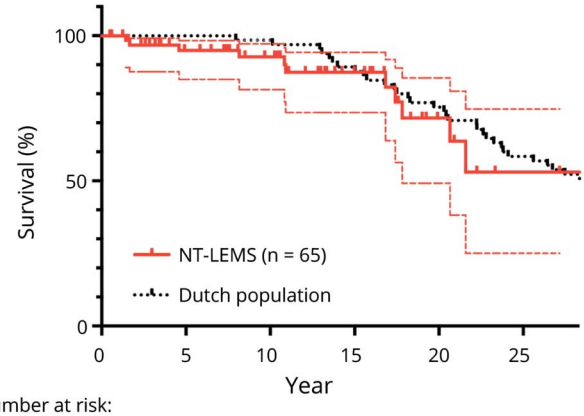
Primary outcome measures

The primary outcomes were comparisons of the patients' survival outcomes and the reference data for the general population and patients with non-LEMS SCLS.

Main results and the role of chance

The 65 patients with NT-LEMS had survival outcomes similar to those of the general population, and the 81 patients with SCLC-LEMS had better survival outcomes than patients with non-LEMS SCLC did ($p < 0.0001$). Of the 63 patients with complete follow-up data, 85% were functionally independent at a 1-year follow-up timepoint. Physical HRQoL was lower for the patients than for the general population ($p < 0.0001$), but this was not true for mental HRQoL.

Figure Survival outcomes for the general population (black) and patients with NT-LEMS (red, with 95% confidence intervals)



Bias, confounding, and other reasons for caution

The present study had a relatively small sample size.

Generalizability to other populations

The present study's reliance on data from the Netherlands may limit the generalizability of the results.

Study funding/potential competing interests

This study received no funding. Some authors report receiving committee appointments, consulting fees, travel expenses, and funding from healthcare companies and receiving funding from the NIH and the European Union. Go to Neurology.org/N for full disclosures.

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The corresponding author(s) of the full-length article and the journal editors edited and approved the final version.

 Copyright © 2020 American Academy of Neurology

Neurology®

Long–term follow–up, quality of life, and survival of patients with Lambert–Eaton myasthenic syndrome

Alexander F. Lipka, Marion I. Boldingh, Erik W. van Zwet, et al.

Neurology 2020;94;e511-e520 Published Online before print December 12, 2019

DOI 10.1212/WNL.0000000000008747

This information is current as of December 12, 2019

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/94/5/e511.full
References	This article cites 36 articles, 10 of which you can access for free at: http://n.neurology.org/content/94/5/e511.full#ref-list-1
Citations	This article has been cited by 1 HighWire-hosted articles: http://n.neurology.org/content/94/5/e511.full##otherarticles
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): **Cohort studies** http://n.neurology.org/cgi/collection/cohort_studies **Lambert-Eaton syndrome** http://n.neurology.org/cgi/collection/lamberteaton_syndrome **Quality of life** http://n.neurology.org/cgi/collection/quality_of_life
Errata	An erratum has been published regarding this article. Please see next page or: /content/97/22/1053.full.pdf
Permissions & Licensing	Information about reproducing this article in parts (figures,tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology ® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

AMERICAN ACADEMY OF NEUROLOGY®

Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Editor
Aravind Ganesh, MD, DPhil, FRCPC, Deputy Editor
Ariane Lewis, MD, Deputy Editor
James E. Siegler III, MD, Deputy Editor

Editors' Note: One-Stage, Limited-Resection Epilepsy Surgery for Bottom-of-Sulcus Dysplasia

In "One-Stage, Limited-Resection Epilepsy Surgery for Bottom-of-Sulcus Dysplasia," Macdonald-Laurs et al. described the performance of corticectomy guided by MRI and electrocorticography (ECoG) in 38 patients with bottom-of-sulcus dysplasia (BOSD). They found that at a median of 6 years postop, 87% of patients were seizure free and noted that their outcomes are similar to those reported in a small series of patients with BOSD who underwent stereotactic thermocoagulation (STC) and laser interstitial thermal therapy (LITT). Hu et al. reported that based on their recent LITT trial, in which they found that 6 of 7 (86%) patients with BOSD were seizure-free 6 months postop, they recommend minimally invasive procedures for BOSD. Harvey et al. agreed with the use of STC or LITT for BOSD in locations that are not easily accessible via a small craniotomy. However, these procedures preclude the use of ECoG to determine epileptogenicity, histopathologic confirmation, and genetic testing of the tissues. In addition, STC and LITT pose risk to surrounding normal cortex and are not widely available. The authors all agree that there is a need for additional long-term outcome data using different treatment strategies in larger cohorts of patients with BOSD.

Ariane Lewis, MD, and Steven Galetta, MD
Neurology® 2021;97:1051. doi:10.1212/WNL.0000000000012922

Reader Response: One-Stage, Limited-Resection Epilepsy Surgery for Bottom-of-Sulcus Dysplasia

Wenhan Hu (Beijing), Baotian Zhao (Beijing), Jianguo Zhang (Beijing), and Kai Zhang (Beijing)
Neurology® 2021;97:1051-1052. doi:10.1212/WNL.0000000000012924

Dr. Macdonald-Laurs et al. reported 38 patients with bottom-of-sulcus dysplasia (BOSD), who underwent a limited corticectomy and whose seizure outcomes indicated minor neurologic complications,[1] echoing previous literature.[2,3] Although subtle changes can be found from structural MRIs, combined fluorodeoxyglucose (FDG)-positron emission tomography (FDG-PET) and MRI imaging can produce high sensitivity in detecting these small lesions. Because these lesions are well confined, sulcus-centered resections could be considered for better function protection, while also guaranteeing the seizure outcome.[4]

The authors implied the outcome of conventional open surgery is similar to that of laser interstitial thermal therapy (LITT). In our recent LITT clinical trial, a subcohort of 7 patients with BOSD were included—6 achieved an Engel IA outcome and 1 an Engel IB outcome, postoperatively, with a mean follow-up of 6 months. In addition, patients were willing to consent to LITT, given its minimally invasive nature. Considering BOSD is mostly located outside the temporal lobe, the traditional viewpoint that extratemporal surgeries are less effective than temporal lobe ones may not apply to this condition.[5] The existing research stems from all

Author disclosures are available upon request (journal@neurology.org).

Copyright © 2021 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

retrospective studies—as such, multicenter collaborations could yield high class evidence that may profoundly change the treatment strategies for BOSDs.

1. Macdonald-Laurs E, Maixner WJ, Bailey CA, et al. One-stage, limited-resection epilepsy surgery for bottom-of-sulcus dysplasia. *Neurology*. 2021;97(2):e178-e190.
2. Harvey AS, Mandelstam SA, Maixner WJ, et al. The surgically remediable syndrome of epilepsy associated with bottom-of-sulcus dysplasia. *Neurology*. 2015;84(20):2021-2028.
3. Besson P, Andermann F, Dubeau F, Bernasconi A. Small focal cortical dysplasia lesions are located at the bottom of a deep sulcus. *Brain*. 2008;131(pt 12):3246-3255.
4. Zhao B, Zhang C, Wang X, et al. Sulcus-centered resection for focal cortical dysplasia type II: surgical techniques and outcomes. *J Neurosurg*. 2020;135(1):266-272.
5. Jobst BC, Cascino GD. Resective epilepsy surgery for drug-resistant focal epilepsy: a review. *JAMA*. 2015;313(3):285-293.

Copyright © 2021 American Academy of Neurology

Author Response: One-Stage, Limited-Resection Epilepsy Surgery for Bottom-of-Sulcus Dysplasia

A. Simon Harvey (Melbourne) and Emma Macdonald-Laurs (Melbourne)
Neurology® 2021;97:1052. doi:10.1212/WNL.0000000000012923

We thank Dr. Hu et al. for their encouraging comments on our article.[1] Both our groups advocate minimal, targeted resections of bottom-of-sulcus dysplasia (BOSD),[1,2] and we further promote omitting intracranial EEG monitoring in MRI-positive cases. As noted in references 41–45 in our article, laser interstitial thermal therapy (LITT) and stereotactic thermocoagulation (STC) are reported in BOSD, further minimize surgical intervention, and are appropriate for BOSD on the medial and basal cerebral surfaces—occurrences which are not as easily accessed with a small craniotomy as BOSD on the cerebral convexity. STC is typically undertaken in patients who undergo previous stereo-EEG with an electrode directly sited in an MRI-positive BOSD. The potential disadvantages of LITT and STC are the lack of confirmation of epileptogenicity with electrocorticography, a pathologic diagnosis from histopathology, and identification of genetic variants from deep sequencing of tissue.

It is important to consider that limiting thermal injury to the dysplastic cortex of the BOSD and avoiding injury to the surrounding normal cortex or white matter tracts is sometimes challenging with LITT and STC. In addition, many neurosurgical centers around the world, especially pediatric centers, do not have LITT or STC capabilities such that targeted small resections are their best option. We eagerly await publications from Dr Hu's group and others reporting large numbers of patients with BOSD undergoing LITT and STC with long follow-up periods, given the potential for temporary seizure remissions, and MRI figures highlighting the preoperative dysplastic and postoperative thermal lesions.

1. Macdonald-Laurs E, Maixner WJ, Bailey CA, et al. One-stage, limited-resection epilepsy surgery for bottom-of-sulcus dysplasia. *Neurology*. 2021;97(2):e178-e190.
2. Zhao B, Zhang C, Wang X, et al. Sulcus-centered resection for focal cortical dysplasia type II: surgical techniques and outcomes. *J Neurosurg*. 2020;135(1):266-272.

Copyright © 2021 American Academy of Neurology

Author disclosures are available upon request (journal@neurology.org).

Copyright © 2021 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

CORRECTION

Long-term Follow-up, Quality of Life, and Survival of Patients With Lambert-Eaton Myasthenic Syndrome

Neurology® 2021;97:1053-1054. doi:10.1212/WNL.0000000000011775

In the article "Long-term Follow-up, Quality of Life, and Survival of Patients With Lambert-Eaton Myasthenic Syndrome" by Lipka et al.,[1] table 2 was previously missing from the paper and is shown below. Further, the references to "table 1" in the last paragraph of the Results section, on page e516, should read "table 2." The authors regret the errors.

Reference

1. Lipka A, Boldingh M, van Zwet E, et al. Long-term follow-up, quality of life, and survival of patients with Lambert-Eaton myasthenic syndrome. *Neurology*. 2020;94(5):e511-e520.

Table 2 Predictors of Quality of Life in Patients With LEMS

Univariate analysis					
	No. of patients	**PCS (95% CI)**	***p***	**MCS**	***p***
Age			0.78		0.96
<50	19	57.1 (46–68)		72.0 (61–82)	
≥50	23	55.0 (45–64)		71.6 (63–81)	
Sex			0.22		0.18
Female	23	51.9 (42–62)		67.7 (58–78)	
Male	19	60.8 (50–72)		76.7 (68–86)	
Partner			0.079		0.018*
Yes	34	60.0 (51–67)		75.6 (69–82)	
No	8	43.0 (22–64)		55.8 (35–76)	
Employment			0.035*		0.042*
Employed	10	71.8 (56–88)		85.8 (81–91)	
Housekeeping	4	53.4 (22–85)		58.1 (28–115)	
Disability	9	41.6 (32–52)		71.0 (45–71)	
Retired	19	54.9 (43–67)		71.7 (59–83)	
Associated tumor			0.58		0.77
No tumor	36	56.8 (49–64)		71.4 (65–78)	
SCLC	6	51.0 (19–83)		74.3 (42–107)	
Other autoimmune disease			0.57		0.54
Yes	11	59.4 (44–75)		68.4 (52–85)	
No	31	54.7 (46–63)		73.0 (65–81)	
Muscle weakness			<0.0001*		0.14
No weakness	9	83.3 (71–95)		84.5 (69–100)	
Limited to legs only	6	57.2 (28–87)		69.1 (42–96)	
Generalised	27	46.6 (40–53)		68.2 (60–76)	

Continued

Copyright © 2021 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

Table 2 Predictors of Quality of Life in Patients With LEMS *(Continued)*

Univariate analysis					
	No. of patients	**PCS (95% CI)**	***p***	**MCS**	***p***
Medication			0.39		0.21
None	6	66.3 (35–98)		79.6 (52–107)	
Symptomatic	23	54.9 (47–63)		74.1 (67–81)	
Immunosuppression	10	51.0 (35–67)		63.0 (46–80)	
Modified Rankin Scale			0.008*		0.085
Correlation coefficient (r)			−0.44		−0.29
0	2	68.6 (−234 to 372)		62.9 (−306 to 432)	
1	2	77.8 (−30 to 185)		85.4 (17–153)	
2	25	52.2 (45–60)		72.3 (65–79)	
3	6	44.3 (18–71)		59.6 (30–89)	
4	1	8.8 (n/a)		18.3 (n/a)	
Multivariate analysis					
	No. of patients	**PCS**	***p***	**MCS**	***p***
Sex			n/a		0.031*
Female	23			67.7	
Male	19			76.7	
Partner			0.018*		0.015*
Yes	34	60.0		75.6	
No	8	43.0		55.8	
Employment			0.036*		0.012*
Employed	10	71.8		85.8	
Housekeeping	4	53.4		58.1	
Disability	9	41.6		71.0	
Retired	19	54.9		71.7	
Muscle weakness			<0.001*		n.s.[a]
No weakness	9	88.3		84.5	
Limited to legs only	6	57.2		69.1	
Generalised	27	46.6		68.2	
Modified Rankin Scale			0.25		0.31
0	2	68.6		62.9	
1	2	77.8		85.4	
2	25	52.2		72.4	
3	6	44.3		59.6	
4	1	8.8		18.3	

* Represents $p < 0.05$ for comparison.
[a] Bonferroni correction (of post-hoc pooled parameter estimates of the generalized linear model) results in a *p*-value > 1.
CI = confidence interval; MCS = mental composite score; PCS = physical composite score; SCLC = small cell lung cancer.

Copyright © 2021 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.