4-1-2020

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Robert C. Rennert
University of California - San Diego

Usman Khan
University of California - San Diego

Jiri Bartek
Karolinska Institutet

Stephen B. Tatter
Wake Forest University

Melvin Field
Orlando Neurosurgery

See next page for additional authors

Laser Ablation of Abnormal Neurological Tissue Using Robotic Neuroblate System (LAANTERN): Procedural Safety and Hospitalization

Robert C. Rennert, MD[*]
Usman Khan, MD, PhD[*]
Jiri Bartek, Jr, MD, PhD[‡§¶]
Stephen B. Tatter, MD, PhD[‖]
Melvin Field, MD[#]
Brian Toyota, MD[**]
Peter E. Fecci, MD[‡‡]
Kevin Judy, MD[§§]
Alireza M. Mohammadi, MD[¶¶]
Patrick Landazuri, MD[‖‖]
Andrew E. Sloan, MD[##]
Albert H. Kim, MD[***]
Eric C. Leuthardt, MD[***]
Clark C. Chen, MD, PhD[‡‡‡]

[*]Department of Neurosurgery, University of California San Diego, San Diego, California; [‡]Department of Neurosurgery, Karolinska University Hospital, Stockholm, Sweden;
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Correspondence:
Robert C. Rennert, MD,
University of California San Diego,
200 West Arbor Drive,
San Diego, CA 92103.
Email: rrennert@ucsd.edu

Received, August 14, 2018.
Accepted, December 25, 2018.
Published Online, May 11, 2019.

BACKGROUND: Stereotactic laser ablation (SLA) has demonstrated potential utility for a spectrum of difficult to treat neurosurgical pathologies in multiple small and/or retrospective single-institutional series. Here, we present the safety profile of SLA of intracranial lesions from the Laser Ablation of Abnormal Neurological Tissue using Robotic NeuroBlate System (LAANTERN; Monteris Medical) multi-institutional, international prospective observational registry.

OBJECTIVE: To determine the procedural safety of SLA for intracranial lesions.

METHODS: Prospective procedural safety and hospitalization data from the first 100 treated LAANTERN patients was collected and analyzed.

RESULTS: Mean age and baseline Karnofsky Performance Status (KPS) were 51(± 17) yr and 83(± 15), respectively. In total, 81.2% of patients had undergone prior surgical or radiation treatment. Most patients had a single lesion (79%) ablated through 1 burr hole (1.2 ± 0.7 per patient), immediately following a lesion biopsy. In total, >90% of the lesion was ablated in 72% of treated lesions. Average total procedural time was 188.2 ± 69.6 min, and average blood loss was 17.7 ± 55.6 ccs. The average length of intensive care unit (ICU) and hospital stays before discharge were 38.1 ± 62.7 h and 61.1 ± 87.2 h, respectively. There were 5 adverse events (AEs) attributable to SLA (5/100; 5%). After the procedure, 84.8% of patients were discharged home. There was 1 mortality within 30 d of the procedure (1/100; 1%), which was not attributable to SLA.

CONCLUSION: SLA is a safe, minimally invasive procedure with favorable postprocedural ICU and hospital utilization profiles.

KEY WORDS: Stereotactic laser ablation, Neuro-oncology, Safety

Neurosurgery 86:538–547, 2020 DOI:10.1093/neuros/nyz141 www.neurosurgery-online.com

Stereotactic laser ablation (SLA), also known as laser interstitial thermotherapy (LITT), is a minimally invasive procedure where a laser probe is stereotactically inserted into an abnormal target tissue. Laser activation triggers thermocoagulation and focused tissue destruction.[1] The extent of thermocoagulation is monitored under near real-time magnetic resonance thermometry to minimize the risk of injury to the surrounding cerebrum.[2-5] Emerging data support the safety and clinical efficacy of SLA as treatment for a spectrum of neurosurgical pathologies including low- and high-grade gliomas, brain metastases, radiation necrosis, and seizure foci (Table 1).[3-18] However, these datasets are mostly small (<50 patients) and/or retrospective reports of single-institutional series. Moreover, there is significant heterogeneity in these studies in terms of quality assurance, definition of complications, and data validation. These challenges limit the generalizability of the reported data. Additionally,

ABBREVIATIONS: AE, adverse event; **CSF,** Cerebrospinal fluid; **CT,** computed tomography; **IRB,** institutional review boards; **ICU,** intensive care unit; **LAANTERN,** Laser Ablation of Abnormal Neurological Tissue using Robotic NeuroBlate System; **LITT,** laser interstitial thermotherapy; **KPS,** Karnofsky performance status; **SLAS,** stereotactic laser ablation; **STROBE,** Strengthening the Reporting of Observational Studies in Epidemiology

interpretation of this data set is often confounded by various forms of biases inherent in retrospective, institutional studies.

To address these issues, we initiated a prospective, multi-institutional registry to track, analyze, and report unfiltered patterns of use and clinical outcomes for patients undergoing intracranial SLA, using a common set of definitions for complications and multi-step mechanisms for quality assurance and data validation. This ongoing study, termed Laser Ablation of Abnormal Neurological Tissue using Robotic NeuroBlate System (LAANTERN; Monteris Medical) is collecting indication, safety, efficacy, and quality of life data on a target population of 1000 total SLA patients. We have previously reported the clinical indications for the first 100 SLA-treated patients enrolled in LAANTERN.[19] Here, we present the procedural safety profile for this patient cohort.

METHODS

Study Design, Participants, and LAANTERN Registry

Details pertaining to the LAANTERN registry (ClinicalTrials.gov study ID # [NCT02392078 for review]) were previously described.[19] This registry includes consenting SLA patients (or those with a legally authorized proxy), who are expected to comply with clinical follow-up. More than 15 centers are actively participating in this study. The institutional review boards (IRB) of all participating centers reviewed and approved the study protocol. As previously described, pretreatment clinical parameters, postoperative neurologic condition, length of intensive care unit (ICU) stay, length of hospital stay, complications, discharge location, and other pertinent clinical parameters are collected by the site PI. At predefined follow-up intervals, the site PIs assess the patient and complete clinical outcome and quality of life surveys, as well as assess follow-up MRIs. Routine audits are performed to ensure compliance and data accuracy.[19] This manuscript was prepared in accordance with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

The LAANTERN study was designed to identify complications that occur at >0.1% frequency, with the target sample size of 1000 patients commonly used in observational studies aiming to characterize the safety of novel interventions.[20]

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[§]Department of Neurosurgery, Copenhagen University Hospital Rigshospitalet, Denmark; [¶]Department of Clinical Neuroscience and Department of Medicine, Karolinska Institutet, Stockholm, Sweden; [‖]Department of Neurosurgery, Wake Forest School of Medicine, Winston-Salem, North Carolina; [#]Orlando Neurosurgery, Orlando, Florida; [**]Division of Neurosurgery, University of British Columbia, Vancouver, Canada; [‡‡]Department of Neurosurgery, Duke University Medical Center, Durham, North Carolina; [§§]Department of Neurological Surgery, Thomas Jefferson University, Philadelphia, Pennsylvania; [¶¶]Department of Neurosurgery, Neurological Institute, Cleveland Clinic, Cleveland, Ohio; [‖‖]Department of Neurology, University of Kansas Medical Center, Kansas City, Kansas; [##]Department of Neurological Surgery, University Hospitals Cleveland Medical Center, Cleveland, Ohio; [***]Department of Neurosurgery, Washington University, St. Louis, Missouri; [‡‡‡]Department of Neurosurgery, University of Minnesota, Minneapolis, Minnesota

MRI-Guided Biopsy and SLA

The protocol for both MRI-guided biopsy and SLA using stereotaxis has been previously described,[4,5,19,21] and all procedures are performed based on institutional standards of care. Briefly, patients undergo general anesthesia, are pinned with an MRI-compatible head frame, positioned, cleaned, and prepared. An MRI visible grid is used to localize the entry site, and a frameless MRI-compatible stereotactic targeting cannula is aligned to the desired trajectory. A small burr hole and durotomy are created, and a ceramic stylet is moved to the target site. The stylet is removed after MRI confirmation, and replaced by a biopsy needle if biopsies are performed. The SLA probe is then inserted to the target site for thermal ablation under real-time MR thermometry as previously described.[3-5]

Clinical Variables Collected

The following parameters were extracted from the LAANTERN central data registry: age, baseline Karnofsky Performance Status (KPS), postprocedure KPS, prior surgical or radiation treatment, number of lesions treated, whether biopsies were performed prior to SLA, indication for surgery, percent of lesion ablated, total procedural time, total time spent in the ICU/hospital (immediate postoperative level of care was based on physician assessment), preprocedure medical conditions, and postprocedure morbidities.

Main Outcome: Adverse Events (AEs) and Complications

Study AEs (defined as any deviation from the normal or anticipated postoperative course) occurring within the initial 30-d postprocedure window were examined. Each AE could contain 1 or more complication(s). Subsequent to reporting, AEs were further broken down into specific complications based on the categorization schema for craniotomies introduced by Sawaya et al,[22] with all potential contributing factors also listed. This modified complication classification scheme was chosen for our initial AE data analysis and presentation to ensure capture of all potential complications related to each aspect of the procedure, and is summarized in Tables 2 and 3. While SLA is performed through a Burr hole, many of the lesion treated would have been approached through an open craniotomy if SLA were not available. In this context, we were interested in comparing the safety profile of SLA vs an open craniotomy approach. We adopted the AE schema developed for craniotomies in this context. For cases where the relative contribution of the biopsy and thermocoagulation (SLA) could not be easily determined (Table 3), both were listed as contributing factors.

To further assess the safety of SLA, AEs were classified by all participating authors of this manuscript based on their most likely etiology into the following: (1) medical AEs, (2) AEs related to surgical manipulation and the known risks of biopsy,[22,23] and (3) AEs likely related to thermo-coagulation injury by laser ablation.

Statistical Analysis

Continuous variables are reported as mean ± standard deviation (SD) or standard error of the mean (SEM) (median and ranges reported for selected parameters). Patients with incomplete data were excluded from pertinent categorical analyses.

TABLE 1. Summary of Previously Published Data on Intracranial SLA/LITT

Authors	Year	Total patients	Total targets	Study design	Institution	Clinical indication	Intracranial location	Lesion volume (cm^3) (median [range] or mean ± SD)	Pre-operative KPS (median [range] or mean ± SD)	Procedural time (minutes) (mean ± SD)	ICU stay (days) (median [range] or mean ± SD)	Hospital stay (days) (median [range] or mean ± SD)	Overall compli-cation rate	Neurologic compli-cation rate
Carpentier et al[10]	2008	6	6	Prospective case series	Single-institution	BMs	Frontal, temporal, parietal, occipital lobes	N/a	68.3 ± 23.1	N/a	N/a	N/a	0%	0%
Carpentier et al[9]	2011	7	15	Prospective case series	Single-institution	BMs	N/a	N/a	62 mean	135 mean	N/a	1.1 (mean)	26*%	13*%
Carpentier et al[7]	2012	4	4	Prospective case series	Single-institution	HGGs	Frontal, temporal lobes, CC	2.0 ± 2.0	N/a	N/a	N/a	N/a	50%	50%
Hawasli et al[6]	2013	17	17	Prospective case series	Single-institution	HGGs, BMs, Epilepsy	Frontal, parietal lobes, insula, thalamus, BG, CC	11.6 ± 9.6	74.1 ± 9.4	301 ± 88 for single trajectory; 480 ± 77 for multi-trajectory	1.8 ± 1.7	5.0 ± 6.4	41%	35%
Sloan et al[14]	2013	10	10	Prospective phase I trial	Multiinstitution	HGGs	Frontal, temporal, parietal lobes	6.8 ± 5.0	80 (70-90)	N/a	N/a	3 (median)	N/a	30%
Mohammadi et al[3]	2014	34	34	Retrospective case series	Multiinstitution	HGGs	Frontal, parietal, temporal lobes, insula, thalamus	10.1 (0.7-49.9)	80 (50-90)	N/a	N/a	3 (1-29)	37%	20%
Rao et al[8]	2014	14	15	Retrospective case series	Single-institution	BMs	Frontal, parietal, temporal lobes, cerebellum	3.6 ± 6.1	N/a	136 ± 27	N/a	1.2 (1-5)	13*%	6*%
Ali et al[4]	2016	23	26	Retrospective case series	Multiinstitution	BMs	Frontal, parietal, occipital lobes, insula, thalamus, BG, cerebellum	4.9 (0.4-28.9)	N/a	N/a	N/a	N/a	22ˆ%	13ˆ%
Rennert et al[5]	2016	10	10	Retrospective case series	Single-institution	HGGs	Frontal, temporal, parietal lobes, CC	10.2 ± 8.8	N/a	254 ± 28 for single trajectory; 321 ± 85 for 2-trajectory; 436 ± 102 for 3-trajectory	N/a	N/a	0%	0%
Thomas et al[13]	2016	21	21	Retrospective case series	Single-institution	HGGs	Parietal, temporal lobes, insula, thalamus, CC	14.6 to 22.4 (mean by clinical grouping)	80 to 85 (mean by clinical grouping)	N/a	N/a	N/a	9%	9%

TABLE 1. ***Continued***

Authors	Year	Total patients	Total targets	Study design	Institution	Clinical indication	Intracranial location	Lesion volume (cm^3) (median [range] or mean ± SD)	Pre-operative KPS (median [range] or mean ± SD)	Procedural time (minutes) (mean ± SD)	ICU stay (days) (median [range] or mean ± SD)	Hospital stay (days) (median [range] or mean ± SD)	Overall compli-cation rate	Neurologic compli-cation rate
Kang et al[15]	2016	20	20	Prospective case series	Single-institution	Epilepsy	Mesial temporal lobe	3.2 to 5.4 (mean by clinical grouping)	N/a	N/a	N/a	N/a	50%	10%
Patel et al[18]	2016	102	102	Retrospective case series	Single-institution	HGGs, BMs, Epilepsy, Chronic pain	N/a	N/a	N/a	171 ± 34	1.8 ± 3.4	3.6 ± 5.4	26%	13%
Kamath et al[16]	2017	120	133	Prospective case series	Single-institution	LGGs, HGGs, BMs, Epilepsy, Radionecrosis	Frontal, temporal, parietal, occipital lobes, insula, thalamus, CC, intraventricular, pons, pineal region, cerebellum	10.2 (0.3-62.8)	N/a	225 ± 110	1.2 to 1.9 (mean by clinical grouping)	2.2 to 4.0 (mean by clinical grouping)	13^%	11%
Donos et al[11]	2018	43	43	Retrospective case series	Single-institution	Epilepsy	Mesial temporal lobe	N/a	N/a	N/a	N/a	<24 h for all pts	2%	2%
Grewal et al[12]	2018	25	25	Retrospective case series	Multiinstitution	Epilepsy	Mesial temporal lobe	6.8 (3.0-11.5)	N/a	N/a	N/a	N/a	N/a	N/a
Ahluwalia et al[17]	2018	42	45	Prospective case series	Multiinstitution	BMs, Radionecrosis	Frontal, temporal, parietal, occipital lobes, thalamus, BG, cerebellum	6.4 (0.4-38.6)	82.1 ± 13.0	180 (84-582)	N/a	1.7-2.3 (mean by clinical grouping)	83^%	28^%

^reported or calculated based on total patients treated
*reported or calculated based on target lesions treated
Abbreviations: BG: basal ganglia; BM: brain metastases; CC: corpus callosum; HGG; high grade glioma; KPS: Karnofsky Performance Status; LITT: laser interstitial thermotherapy; LGG: low grade glioma; N/a: not applicable; SD: standard deviation; SLA; stereotactic laser ablation.

TABLE 2. Categorization Utilized for Reporting Adverse Event (AE) Related Complications

Neurologic	Regional	Systemic
(a) Deficits: Motor deficit (includes weakness and paresis); sensory deficit (hearing, touch, smell); aphasia/dysphasia; visual field deficit; memory loss/confusion/altered state of consciousness; abnormal gate/ataxia; (b) Seizures	Hematoma; bleeding/hemorrhage; hydrocephalus; pneumocephalus; meningitis; CSF leak; wound dehiscence; wound infection	Pulmonary infection/pneumonia; deep vein thrombosis; pulmonary embolism; sepsis/general systemic infection; psychosis; urinary tract infection; hyponatremia; reaction to medicines/anesthesia; problems with respiration due to anesthesia or intubation; BP related (hypotension/hypertension); cardiac related; hypokalemia

TABLE 3. Descriptions of Possible Factors Contributing to Surgical Complications

Contributing factor	Definition
Pre-existing condition	A patient condition, ailment, disease, previous injury, or other relevant information that was known to be present prior to the surgical procedure or SLA procedure.
Biopsy	A stereotactic needle biopsy performed immediately prior to the placement of the NeuroBlate Probe (Monteris).
Sedation	Anesthesia related to the surgical procedure
Surgical procedure	The surgical procedure regardless of the modality used to resect the intended cranial target, including anesthesia; placement of the stereotactic frame; drilling of the burr hole; placement of the mini-bolt/skull access; insertion and extraction of the laser probe; patient transport, etc.
SLA/LITT	Stereotactic laser ablation/laser interstitial thermal therapy: the part of the procedure in which the laser is activated to ablate tissue.
Disease progression	An expected event for this patient population due to progression of the disease process, ie, tumor recurrence, surgery failure

RESULTS

Participants and Demographic Data

The demographics of the first 100 LAANTERN patients was previously reported.[19] For ease of readership, this previously published data is included in Table 4. In brief, there were 58 male and 42 female patients, with a mean age of 51 yr (± 17). Average body mass index (BMI) was 28.0 ± 6.9. Regarding co-morbidities, 36.9% were current or former smokers, 13.6% had a history of cardiovascular disease, 7.6% had a history of coagulopathy, 28.8% had a history of hypertension, and 12.1% had a history of diabetes. In total, 49.2% of patients had a significant co-morbidity. Baseline KPS was 83.1 ± 14.7. In total, 87.8% of patients had neurological symptoms pre-operatively, ranging from subjective (24.4%), to mild objective (48.8%), to objective limiting independence/function (8.5%). A total of 81.2% of the patients had undergone prior treatments for the target lesion, including surgery, radiation, and chemotherapy in the 2 yr prior to SLA, with nearly 45% of these treated lesions considered difficult to access through open surgery.[19] As

TABLE 4. Summary of Patient Characteristics

	Measure	All patients (n = 100)*
Gender	Female	58.0%
	Male	42.0%
	Age (years)	Mean: 50.7 ± 17.3 (97) Median (range): 52.0 (10.0, 80.0)
Race (N = 98)	White	85.7%
	African American	7.1%
	Asian	2.0%
	Native American	1.0%
	Unknown	4.1%
	Body mass index (kg/m^2)	Mean: 28.0 ± 6.2 (48) Median (range): 27.1 (14.3, 41.1)
Medical history	Current/former smoker	36.9% (24/65)

*Data rows with N other than 100 as indicated.

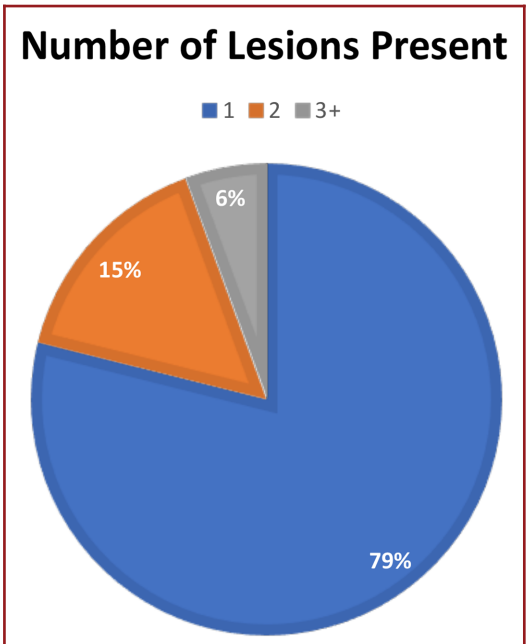

FIGURE 1. *Number of lesions present per patient. Most patients had a single lesion (79%) ablated through 1 burr hole (1.2 ± 0.7 per patient). The maximum number of lesions treated in a single procedure was 2, even in patients with 3+ lesions.*

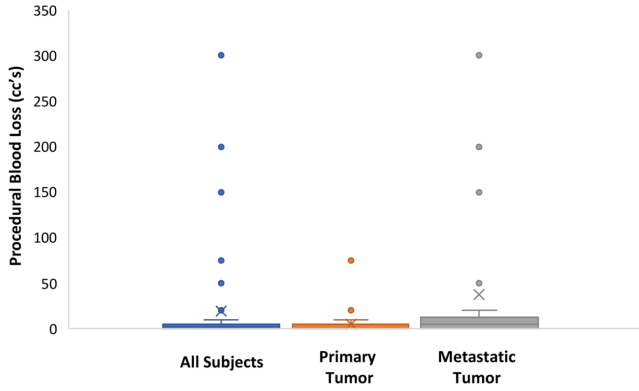

FIGURE 2. *Box and whisker plot of blood loss associated with SLA. Mean blood loss for SLA and lesional biopsy for all subjects (when performed) was 17.7 ± 55.6 ccs (median 0 [0.0, 300]) (n = 76). Data for primary vs metastatic tumors further displayed in plot.*

TABLE 5. Postoperative ICU Length of Stay

Length of ICU stay distribution	All subjects*	Primary tumor (n = 47)	Metastatic tumor (n = 33)
0 h	21 (25.0%)	6 (12.8%)	15 (45.5%)
>0 to 12 h	3 (3.5%)	2 (4.3%)	0 (0.0%)
>12 to 24 h	32 (38.0%)	15 (31.9%)	8 (24.2%)
>24 h	28 (33.3%)	16 (34.0%)	8 (24.2%)

*Sixteen total subjects with missing/unknown data regarding postoperative ICU length of stay, including 8 with primary tumors and 2 with metastatic tumors.

previously published, 48% of the treated patients had primary intracranial tumors, 34% suffered from brain metastases, 16% received SLA for epilepsy, and 2% of the patients were treated for other indications.[19] SLA target location for this study cohort has also already been reported, with 46% of treated lesions classified as deep.[19]

Procedural Outcomes and Hospitalization Data

Most patients underwent SLA for a single lesion (79%) through a single burr hole (1.2 ± 0.7 per patient; Figure 1). Sixty-six (66%) percent of patients underwent a lesional biopsy immediately preceding the SLA. The "blue" thermal damage lines on the M*Vision Pro™ Software (Monteris Medical) indicate regions of irreversible thermal damage.[14] Average target lesion volume was 9.8 ± 23.5 cm^3, and greater than 90% of the lesion was ablated to the "blue" thermal line in 72% of treated lesions. The average total procedural time was 188.2 ± 69.6 min, and average blood loss was 17.7 ± 55.6 ccs (Figure 2).

Twenty-one patients (25%) spent no postoperative time in the ICU (Table 5). The LAANTERN registry did not collect information on the specifics of the level of care that these patients required. The average length of ICU and hospital stays before discharge were 38.1 ± 62.7 h (median 21.5 [0.0, 335.6]; Figure 3) and 61.1 ± 87.2 h (median 27.0 [6.0, 612.0]), respectively. Upon discharge, 84.8% of patients went home, 7.6% to a rehabilitation facility, 4.3% to a skilled nursing facility, 1.1% to another acute care hospital, 2.2% to other locations, and 0% to hospice.

Main Results: SLA and Safety

At 1 mo of follow-up, there were 11 study AEs that occurred in 9 patients. To better understand the nature of these AEs, they were first categorized based on the schema published by Sawaya et al,[22] with an additional listing of all potential contributing factors (Table 6).

AEs were also classified based on their most likely etiology into medical, surgical, or SLA-related. Based on this final classification, 2 of the 11 AEs (2/100 or 2%) were medical conditions (AE2 [hypoxia] and AE8 [wide-complex tachycardia], with AE2 related to sedation and AE8 occurring in a patient with a prior history of cardiac arrhythmias).

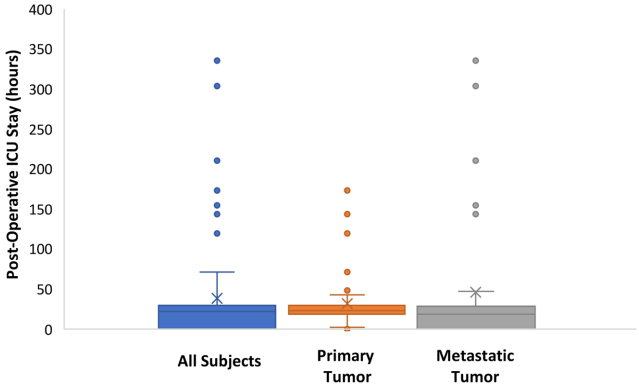

FIGURE 3. *Box and whisker plot of postprocedural ICU stays. Mean ICU stay after SLA was 38.1 ± 62.7 h (median 21.5 [0.0, 335.6]) (n = 84). Data for primary vs metastatic tumors further displayed in plot.*

Four of the 11 AEs (4/100 or 4%) were likely related to surgical manipulation (AE4 [wound dehiscence], AE 6 [subdural hematoma], AE 9 [bacteremia], and AE 11 [intraventricular hemorrhage]), with AEs 4 and 6 attributed to the surgery rather than the SLA since the target site for the SLA was located >2 cm away from the site of the dehiscence and the subdural hematoma, respectively. AE 9 was attributed to surgical manipulation as the infectious risk for these procedures is largely derived from skin entry. AE 11 is discussed in detail below.

Energy deposition from laser ablation likely contributed to 5 of the AEs (AEs 1, 3, 5, 7, and 10). Of these, there were 2 new neurologic deficits (1 patient with abnormal gait [AE 3] and 1 patient with hemibody weakness and sensory changes [AE 5]). There were 2 patients with postoperative seizures [AE 1 and AE 7] referable to increased peri-SLA edema or intraparenchymal hemorrhage after the procedure. AE 10 was a delayed intraparenchymal hemorrhage. While this AE may be the result of disease progression or SLA, we cannot exclude contribution from laser ablation. Since all of these patients underwent stereotactic biopsy as well as laser ablation, it was also not possible to determine the relative contributions of these procedures.

There was 1 death within the 30-d postoperative period (Patient I). In this patient, intraventricular hemorrhage [AE 11] involving the lateral, third, and fourth ventricles with associated hydrocephalus was noted on MRI immediately after biopsy, but before SLA. The surgeon opted to proceed with the SLA with a total lasing time of 1 min. The bleeding arrested after SLA and an external ventricular drain was placed. Subsequent head computed tomography (CT) showed no evidence of hemorrhagic progression, however, despite adequate cerebrospinal fluid (CSF) drainage the patient was made comfort measures only and expired on postoperative day 9.

DISCUSSION

Key Results

Here, we report the procedural safety and hospitalization data for SLA for intracranial pathologies from the first 100 patients enrolled and treated in the LAANTERN study. Overall, the safety profile in this registry appears favorable, with 4 AEs (4%) related to surgical manipulation and 5 AEs (5%) potentially attributable to laser ablation. The average hospital stay before discharge was 61.1 ± 87.2 h, with the majority of patients discharged home within 2 d of the procedure. Compared to previously published SLA studies,[3-7,13,15,24,25] the majority of LAANTERN patients harbor more severe baseline comorbidities and neurologic complaints. Moreover, nearly half of the lesions treated were considered difficult to access through conventional surgical approaches.[19] These results highlight the utility of a prospective registry for assessing the real-world uses and outcomes of an emerging technology like SLA compared to the more restricted and often less generalizable data associated with randomized clinical trials (or for patient populations not amenable to randomization), as well as the clinical potential of this technique.

Interpretation

The 9% rate of potentially referable AEs to the combination of surgical manipulation/stereotactic biopsy and laser ablation represents an estimate of the complication rate directly associated with SLA as performed in the LAANTERN patient cohort. Including all recorded AEs, the per patient overall complication rate in this cohort was also 9%. These findings are within the wide range of previously reported 0% to 83% overall, and 0% to 50% neurologic complication rates with SLA (Table 1),[3-11,13-18] and slightly lower than the 13% to 26% overall and 11% to 13% neurologic complication rates of recent larger cohort studies (n > 100 patients).[16,18] In fact, our findings are comparable to the published complication rates of up to 7% for stereotactic biopsy alone,[23,26-28] suggesting that the addition of laser ablation to stereotactic biopsy may not significantly elevate the risk of postoperative morbidity relative to patients treated with biopsy only. Notably, our complication rate is lower than that reported for open craniotomies as treatment for difficult to access tumors.[22,23] Average blood loss was also trivial with SLA (mean of 17.7 ± 55.6 cc's), consistent with the minimally invasive nature of this technique.

Regarding the overall complication rate for this cohort, we believe a per-patient calculation (9 patients with 11 total AEs, or a 9% overall complication rate [Table 6]) is reasonable. As an example of the potential pitfalls of including multiple complications per patient in this calculation, if half of a theoretical patient cohort suffered 2 complications, summing the total number of complications and dividing by the total number of patients would yield a 100% complication rate. However, this number is misleading, as a 100% complication rate is likely to be interpreted that all patients (rather than half) in the theoretical cohort

TABLE 6. Description of Adverse Event (AEs) Occurring Within 30 d With Assigned Complication Categorizations and Contributing Factors

Adverse event#	Patient ID	Adverse event description	Days to event	Complications	Contributing factor(s)	Resolution (days to resolution)
1	A	Intraparenchymal hemorrhage and increased seizure activity	0	Neurologic: Seizure Regional: Bleeding/Hemorrhage	-Pre-existing condition (seizure) -SLA	Resolved (7)
2	A	Hypoxia	0	Systemic: Respiratory	-Sedation	Resolved (7)
3	B	Abnormal gait	1	Neurologic: Deficit: Abnormal Gait/Ataxia	-Surgical procedure -SLA	Ongoing
4	C	Wound dehiscence	22	Regional: Wound dehiscence	-Surgical procedure	Ongoing
5	D	Postoperative left hemineglect and hemiplegia (3/5 strength in left lower extremity, 0/5 in left lower extremity)	0	Neurologic: Deficit: Motor Neurologic: Deficit: Sensory	-Surgical procedure -SLA	Ongoing
6	E	Small subdural hematoma at operative site; postoperative right lower extremity mild weakness and paresthesia; mild expressive aphasia	1	Regional: Hemotoma Neurologic: Deficit: Ataxia Neurologic: Deficit: Sensory Neurologic: Deficit: Aphasia/Dysphasia	-Surgical procedure	Ongoing
7	F	New onset seizure associated with imaging findings of worsening cerebral edema	1	Neurologic: Seizure Regional: Edema/Swelling	-Surgical procedure -SLA	Ongoing
8	G	Postoperative wide complex tachycardia without hemodynamic instability. Condition managed medically	0	Systemic: Cardiac	-Pre-existing medical condition (arrhythmia)	Ongoing
9	H	MSSA bacteremia	8	Systemic: General systemic infection	-Surgical procedure	Resolved (9)
10	H	Intraparenchymal hemorrhage with surrounding edema affecting the left basal ganglia and left frontal lobe	29	Regional: Bleeding/Hemorrhage Regional: Edema/Swelling	-Surgical procedure -SLA -Disease progression	Ongoing
11	I	Intraventricular hemorrhage with ventriculomegaly	0	Regional: Bleeding/Hemorrhage	-Biopsy -Disease progression	Death (9)

suffered a complication. Nevertheless, only 2 patients in this series had multiple AEs, and the overall complication rate is not significantly changed using either calculation.

Our interim analysis also provides data pertaining to hospital resource utilization measures, including OR time, time in the ICU, and time in the hospital. The average total procedural time for stereotactic biopsy plus SLA was 188.2 ± 69.6 min, which is comparable to previously published series.[5,8,16,17] This time estimate for procedure completion is approximately 30 to 60 min longer than the reported average time required for stereotactic biopsy without laser ablation,[29,30] suggesting that the incorporation of SLA into a stereotactic procedure did not significantly increase anesthetic time.

The <24 h of ICU utilization in the majority of patients and the 61-h average overall hospital stay is consistent with the published literature for SLA (Tables 1 and 5),[3,6,8,9,16-18] and comparable or shorter than the ICU and hospital stays associated with open cranial surgery.[31-35] The observation that 1 quarter of patients did not require postoperative ICU care suggests future opportunities to de-escalate the level care for selected postablation patients. These results support the cost-effectiveness of SLA in the context of the documented benefits of shortened, less acute hospitalizations for both the patient[36] and the hospital system.[37]

Limitations

The disease progression within 30 d of SLA in patient H is a reminder that ablation should not be misrepresented as a "cure" for tumors with microscopic disease extension beyond what is visualized on MRI. Despite the >90% lesional ablation achieved in the majority of patients in the study, this situation is analogous to the high recurrence rates of gliomas even after a surgical gross total resection,[38,39] and is reflective of the

infiltrative nature of primary brain tumors. Accordingly, rapid disease progression adjacent to ablation sites has been previously reported in glioblastoma patients who underwent SLA but failed to respond to subsequent chemotherapy.[5] As such, it should be clearly communicated to patients in these settings that therapeutic efficacy is expected only if the tumor subsequently responds to chemotherapy and/or radiation.

The unusual cases of excessive blood loss (300 ccs) and prolonged ICU stays (>12 d) warrant further comment. These data points represent unusual outcomes for SLA, which is performed through a burr hole. Because of their unusual nature, these data points were confirmed before entry into the registry. Unfortunately, the clinical context surrounding these events were not collected in LAANTERN. In terms of blood loss, we speculate that if a Burr hole is placed such that a venous lacunae is violated, excessive blood loss can occur prior to hemostasis. As in most real-world surgical situations, the reported blood loss likely also includes a contribution from irrigation used during hemostasis. This blood loss was reviewed by independent reviewers and not considered an AE because of the following: (1) it did not trigger hemodynamic instability requiring transfusion or resuscitation, and (2) the patient emerged from surgery neurologically intact. In terms of prolonged ICU stays, we hypothesize these rare patients are likely related to the AEs described in the manuscript (see Table 6).

Generalizability

Despite the inherent shortcomings related to an interim analysis of a prospective registry (eg, limited clarifying details of data point outliers), the concordance of the data provided here with independent published series[3-7,13,15,24,25,40] suggests the robust nature of our observations. That said, continued assessments of safety and resource utilization data is warranted as the LAANTERN registry continues to accrue patients. Two other areas of assessment are needed in the future, including the following: (1) efficacy of impact on the underlying disease process, and (2) effects on the patient's quality of life. Both of these information sets are being actively collected as a part of the LAANTERN effort and will soon be available.

CONCLUSION

Analysis of the first 100 patients from the LAANTERN registry suggests that SLA is a safe, minimally invasive procedure for the treatment of intracranial pathologies. The morbidity and hospitalization time profiles compare favorably to those previously reported for conventional craniotomies.

Disclosures

The LAANTERN registry is supported by Monteris Medical. ClinicalTrials.gov study ID #NCT02392078. Drs Chen, Mohammadi, Sloan, Fecci, and Leuthardt are consultants for Monteris Medical Inc. Dr Smith is a consultant for Monteris Medical Inc, Medtronic Inc, and OsteoMed.

REFERENCES

1. McNichols RJ, Gowda A, Kangasniemi M, Bankson JA, Price RE, Hazle JD. MR thermometry-based feedback control of laser interstitial thermal therapy at 980 nm. *Lasers Surg Med*. 2004;34(1):564-576.
2. Hawasli AH, Kim AH, Dunn GP, Tran DD, Leuthardt EC. Stereotactic laser ablation of high-grade gliomas. *Neurosurg Focus*. 2014;37(6):E1.
3. Mohammadi AM, Hawasli AH, Rodriguez A, et al. The role of laser interstitial thermal therapy in enhancing progression-free survival of difficult-to-access high-grade gliomas: a multicenter study. *Cancer Med*. 2014;3(4):971-979.
4. Ali MA, Carroll KT, Rennert RC, et al. Stereotactic laser ablation as treatment for brain metastases that recur after stereotactic radiosurgery: a multiinstitutional experience. *Neurosurg Focus*. 2016;41(4):E11.
5. Rennert RC, Carroll KT, Ali MA, et al. Safety of stereotactic laser ablations performed as treatment for glioblastomas in a conventional magnetic resonance imaging suite. *Neurosurg Focus*. 2016;41(4):E7.
6. Hawasli AH, Bagade S, Shimony JS, Miller-Thomas M, Leuthardt EC. Magnetic resonance imaging-guided focused laser interstitial thermal therapy for intracranial lesions: single-institution series. *Neurosurgery*. 2013;73(6):1007-1017.
7. Carpentier A, Chauvet D, Reina V, et al. MR-guided laser-induced thermal therapy (LITT) for recurrent glioblastomas. *Lasers Surg Med*. 2012;44(5):361-368.
8. Rao MS, Hargreaves EL, Khan AJ, Haffty BG, Danish SF. Magnetic resonance-guided laser ablation improves local control for postradiosurgery recurrence and/or radiation necrosis. *Neurosurgery*. 2014;74(6):658-667; discussion 667.
9. Carpentier A, McNichols RJ, Stafford RJ, et al. Laser thermal therapy: real-time MRI-guided and computer-controlled procedures for metastatic brain tumors. *Lasers Surg Med*. 2011;43(10):943-950.
10. Carpentier A, McNichols RJ, Stafford RJ, et al. Real-time magnetic resonance-guided laser thermal therapy for focal metastatic brain tumors. *Neurosurgery*. 2008;63(1 Suppl 1):ONS21-28; discussion ONS28-29.
11. Donos C, Breier J, Friedman E, et al. Laser ablation for mesial temporal lobe epilepsy: surgical and cognitive outcomes with and without mesial temporal sclerosis. *Epilepsia*. 2018;59(7):1421-1432.
12. Grewal SS, Zimmerman RS, Worrell G, et al. Laser ablation for mesial temporal epilepsy: a multi-site, single institutional series. *J Neurosurg*. published online:July 1, 2018 (doi:10.3171/2018.2.JNS171873 .
13. Thomas JG, Rao G, Kew Y, Prabhu SS. Laser interstitial thermal therapy for newly diagnosed and recurrent glioblastoma. *Neurosurg Focus*. 2016;41(4):E12.
14. Sloan AE, Ahluwalia MS, Valerio-Pascua J, et al. Results of the NeuroBlate System first-in-humans Phase I clinical trial for recurrent glioblastoma: clinical article. *J Neurosurg*. 2013;118(6):1202-1219.
15. Kang JY, Wu C, Tracy J, et al. Laser interstitial thermal therapy for medically intractable mesial temporal lobe epilepsy. *Epilepsia*. 2016;57(2):325-334.
16. Kamath AA, Friedman DD, Hacker CD, et al. MRI-guided interstitial laser ablation for intracranial lesions: a large single-institution experience of 133 cases. *Stereotact Funct Neurosurg*. 2017;95(6):417-428.
17. Ahluwalia M, Barnett GH, Deng D, et al. Laser ablation after stereotactic radiosurgery: a multicenter prospective study in patients with metastatic brain tumors and radiation necrosis. *J Neurosurg*. published online: May 4, 2018 (doi:10.3171/2017.11.JNS171273).
18. Patel P, Patel NV, Danish SF. Intracranial MR-guided laser-induced thermal therapy: single-center experience with the visualase thermal therapy system. *J Neurosurg*. 2016;125(4):853-860.
19. Rennert RC, Khan U, Tatter SB, et al. Patterns of clinical use of stereotactic laser ablation: analysis of a multicenter prospective registry. *World Neurosurg*. 2018;116:e566-e570.
20. Kim WK, Hengstenberg C, Hilker M, et al. The SAVI-TF registry: 1-year outcomes of the european post-market registry using the ACURATE neo transcatheter heart valve under real-world conditions in 1,000 patients. *JACC Cardiovasc Interv*. 2018;11(14):1368-1374.
21. Larson PS, Starr PA, Bates G, Tansey L, Richardson RM, Martin AJ. An optimized system for interventional magnetic resonance imaging-guided stereotactic surgery: preliminary evaluation of targeting accuracy. *Neurosurgery*. 2012;70(1 Suppl Operative):95-103; discussion 103.
22. Sawaya R, Hammoud M, Schoppa D, et al. Neurosurgical outcomes in a modern series of 400 craniotomies for treatment of parenchymal tumors. *Neurosurgery*. 1998;42(5):1044-1055; discussion 1055-1046.
23. Brown DA, Himes BT, Major BT, et al. Cranial tumor surgical outcomes at a high-volume academic referral center. *Mayo Clin Proc*. 2018;93(1):16-24.

24. Waseem H, Vivas AC, Vale FL. MRI-guided laser interstitial thermal therapy for treatment of medically refractory non-lesional mesial temporal lobe epilepsy: outcomes, complications, and current limitations: a review. *J Clin Neurosci*. 2016;38:1-7.
25. Torcuator RG, Hulou MM, Chavakula V, Jolesz FA, Golby AJ. Intraoperative real-time MRI-guided stereotactic biopsy followed by laser thermal ablation for progressive brain metastases after radiosurgery. *J Clin Neurosci*. 2016;24:68-73.
26. Waters JD, Gonda DD, Reddy H, Kasper EM, Warnke PC, Chen CC. Diagnostic yield of stereotactic needle-biopsies of sub-cubic centimeter intracranial lesions. *Surg Neurol Int*. 2013;4(Suppl 3):S176-181.
27. Kreth FW, Muacevic A, Medele R, Bise K, Meyer T, Reulen HJ. The risk of haemorrhage after image guided stereotactic biopsy of intra-axial brain tumours–a prospective study. *Acta Neurochir (Wien)*. 2001;143(6):539-545; discussion 545-536.
28. Hall WA. The safety and efficacy of stereotactic biopsy for intracranial lesions. *Cancer*. 1998;82(9):1749-1755.
29. Smith JS, Quiñones-Hinojosa A, Barbaro NM, McDermott MW. Frame-based stereotactic biopsy remains an important diagnostic tool with distinct advantages over frameless stereotactic biopsy. *J Neurooncol*. 2005;73(2):173-179.
30. Satyarthee GD, Chandra PS, Sharma BS, Mehta VS. Comparison of stereotactic and ultrasound-guided biopsy of solid supratentorial tumor: a preliminary report. *Asian J Neurosurg*. 2017;12(4):664-669.
31. Dasenbrock HH, Liu KX, Devine CA, et al. Length of hospital stay after craniotomy for tumor: a national surgical quality improvement program analysis. *Neurosurg Focus*. 2015;39(6):E12.
32. Barker FG. Craniotomy for the resection of metastatic brain tumors in the U.S., 1988–2000: decreasing mortality and the effect of provider caseload. *Cancer*. 2004;100(5):999-1007.
33. Peruzzi P, Bergese SD, Viloria A, Puente EG, Abdel-Rasoul M, Chiocca EA. A retrospective cohort-matched comparison of conscious sedation versus general anesthesia for supratentorial glioma resection. Clinical article. *J Neurosurg*. 2011;114(3):633-639.
34. Gravesteijn BY, Keizer ME, Vincent AJPE, Schouten JW, Stolker RJ, Klimek M. Awake craniotomy versus craniotomy under general anesthesia for the surgical treatment of insular glioma: choices and outcomes. *Neurol Res*. 2018;40(2):87-96.
35. Sacko O, Lauwers-Cances V, Brauge D, Sesay M, Brenner A, Roux FE. Awake craniotomy vs surgery under general anesthesia for resection of supratentorial lesions. *Neurosurgery*. 2011;68(5):1192-1198; discussion 1198–1199.
36. Kossovsky MP, Sarasin FP, Chopard P, et al. Relationship between hospital length of stay and quality of care in patients with congestive heart failure. *Qual Saf Health Care*. 2002;11(3):219-223.
37. Leuthardt EC, Voigt J, Kim AH, Sylvester P. A single-center cost analysis of treating primary and metastatic brain cancers with either brain laser interstitial thermal therapy (LITT) or craniotomy. *Pharmacoecon Open*. 2017;1(1):53-63.
38. Shaw EG, Berkey B, Coons SW, et al. Recurrence following neurosurgeon-determined gross-total resection of adult supratentorial low-grade glioma: results of a prospective clinical trial. *J Neurosurg*. 2008;109(5):835-841.
39. Stummer W, Reulen HJ, Meinel T, et al. Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. *Neurosurgery*. 2008;62(3):564-576; discussion 564–576.
40. Iyer A, Halpern CH, Grant GA, Deb S, Li GH. Magnetic resonance-guided laser-induced thermal therapy for recurrent brain metastases in the motor strip after stereotactic radiosurgery. *Cureus*. 2016;8(12):e919.

Acknowledgments

The authors thank Luc Mongeon, PhD, and Beth Larson-DeBruzzi for editorial assistance in preparation of this manuscript.