Results of the NeuroBlate System first-in-humans Phase I clinical trial for recurrent glioblastoma

Clinical article

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Object. Laser interstitial thermal therapy has been used as an ablative treatment for glioma; however, its development was limited due to technical issues. The NeuroBlate System incorporates several technological advances to overcome these drawbacks. The authors report a Phase I, thermal dose–escalation trial assessing the safety and efficacy of NeuroBlate in recurrent glioblastoma multiforme (rGBM).

Methods. Adults with suspected supratentorial rGBM of 15- to 40-mm dimension and a Karnofsky Performance Status score of ≥ 60 were eligible. After confirmatory biopsy, treatment was delivered using a rigid, gas-cooled, side-firing laser probe. Treatment was monitored using real-time MRI thermometry, and proprietary software providing predictive thermal damage feedback was used by the surgeon, along with control of probe rotation and depth, to tailor tissue coagulation. An external data safety monitoring board determined if toxicity at lower levels justified dose escalation.

Results. Ten patients were treated at the Case Comprehensive Cancer Center (Cleveland Clinic and University Hospitals–Case Medical Center). Their average age was 55 years (range 34–69 years) and the median preoperative Karnofsky Performance Status score was 80 (range 70–90). The mean tumor volume was 6.8 ± 5 cm^3 (range 2.6–19 cm^3), the percentage of tumor treated was 78% ± 12% (range 57%–90%), and the conformality index was 1.21 ± 0.33 (range 1.00–2.04). Treatment-related necrosis was evident on MRI studies at 24 and 48 hours. The median survival was 316 days (range 62–767 days). Three patients improved neurologically, 6 remained stable, and 1 worsened. Steroid-responsive treatment-related edema occurred in all patients but one. Three had Grade 3 adverse events at the highest dose.

Conclusions. NeuroBlate represents new technology for delivering laser interstitial thermal therapy, allowing controlled thermal ablation of deep hemispheric rGBM. Clinical trial registration no.: NCT00747253 (ClinicalTrials.gov).
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KEY WORDS • laser interstitial thermal therapy • glioblastoma • coagulation • brain tumor • clinical trial • oncology

THE prognosis of patients with GBM remains dismal, with a median survival less than 15 months from the time of diagnosis.[29] The median survival of patients with rGBM is only 3–5 months. Resection increases survival by only 8 weeks,[1] but often is not feasible. Investigational treatments including systemic and local chemotherapy have not significantly improved survival and often have significant risks. Focal therapies such as brachytherapy[4,27] and SRS[27,30] have also had limited efficacy in selected patient populations.[10,18,27] However,

toxicity for brachytherapy has been high,[25] and the only randomized controlled study of radiosurgery (for newly diagnosed GBM) demonstrated no benefit, whereas the studies that did suggest benefit have been small, retrospective, single-institution studies providing level 4 evidence (http://www.cebm.net), which are marred by perceived selection bias.[18] Thus, the utility of these modalities for the treatment of GBM has been controversial and has not yet been incorporated into currently accepted multiinstitutional cancer center guidelines for care.[16]

Laser interstitial thermal therapy is a minimally invasive technique for treating tumors percutaneously and has been used as an ablative treatment for glioma and other tumors for more than 2 decades. It may offer the benefit of surgery to brain tumor patients who are otherwise unsuitable for craniotomy. Treatments use low-powered thermal energy[3,6–8,12,13,17,22–24] to create zones of coagulation (rather than vaporization) around the delivery fiber. Although complications such as hemiparesis and focal seizures have occasionally been described, other studies have demonstrated that strength and language function have occasionally improved,[13] and increases in survival have also been suggested.[22,23] However, several technical limitations of the devices have prevented widespread application of this technology.[7,8,22] The most daunting of these has been the inability to precisely monitor the "dose" of LITT delivered to individual patients in real time. Previous descriptions of thermal energy application have primarily been based on theoretical a priori calculations of the energy required to treat a tumor based on tumor volume, without real-time monitoring or control of energy deposition to match specific geometry and heat-conduction properties of the tumor.[23,24] Others have used MR images in real time, but rely on a technique that identifies only tissues that die during the procedure.[22] This underestimates the thermal damage in surrounding cells, which continues to develop for hours to days after lasing has been completed. An LITT technique using a 980-nm diode laser and real-time thermometry[3] was recently demonstrated for well-circumscribed brain metastases, but no such real-time approach has previously been demonstrated for primary brain tumors.

The NeuroBlate System (Monteris Medical, Inc.) incorporates several technological advances to overcome drawbacks seen with existing devices. NeuroBlate allows for conformal laser thermal coagulation of deep-seated brain tumors by using a side-firing laser probe equipped with software that predicts thermal tissue damage, in real time, by considering both temperature and duration of thermal exposure. The rotation and probe depth are controlled by the surgeon, allowing for "sculpting" of the thermal effect guided by real-time MRI thermography. We hypothesize that these technical advances to LITT will facilitate safer, more precise use of this technology to ablate GBMs and other lesions unsuitable for resection in a minimally invasive fashion. The goal of this Phase I trial was to evaluate the safety of NeuroBlate at 3 doses.

Methods

Study Design

This study was a prospective, multicenter, Phase I, sequential, thermal dose–escalation study conducted to evaluate the preliminary safety of, and techniques necessary for, the treatment of recurrent or progressive GBM using the NeuroBlate System. (The system was then called the AutoLITT system, but has since been rebranded as NeuroBlate by the company.) As in all Phase I studies, it was anticipated that toxicity might ensue—particularly at the highest dose. The main goal of the study was to evaluate the relationship between thermal dose, toxicity, and clinical efficacy. The study was approved by the institutional review board for the Case Comprehensive Cancer Center, the primary affiliate for clinical cancer research for both the Cleveland Clinic Foundation and University Hospitals–Case Medical Center. This study was performed under an investigational device exemption granted by the US FDA. This study was registered with the ClinicalTrials.gov database (http://www.clinicaltrials.gov/), and its registration no. is NCT00747253.

Adult patients with recurrent or progressive GBM in whom standard therapy (radiotherapy with or without chemotherapy) had failed were candidates for this study. A passive enrollment approach was used; study candidates were identified from the routine clinical populations present at the 2 sites. Participants were recruited after investigator review of the individual's clinical characteristics. Eligibility and exclusion criteria are summarized in Table 1. Informed consent was administered and patients were scheduled to receive the protocol treatments illustrated in Fig. 1.

The study design was a "k-in-a-row," modified up-and-down dose-escalation design, as described by Ivanova et al.[5] The goal of the design was to estimate the thermal dose that provides a 20%–30% probability of toxicity for an individual patient. It was anticipated that 3 thermal dose levels would probably be sufficient for the study. If any patient was unable to complete at least 14 days of follow-up for reasons not associated with the treatment or the procedure, then an additional patient would be recruited until at least 2 patients had been treated and had completed at least 14 days of follow-up at each dosing level. The intent-to-treat population was defined as those patients who had the laser probe inserted into the brain.

The 3 proposed thermal dosage levels were chosen based on preclinical data from in vivo porcine and canine models that included postprocedural histological analysis, using the approach discussed by Sapareto and Dewey.[20] Table 2 lists the definitions of the chosen thermal doses used in this study.

The primary study end point was to evaluate the feasibility and safety of NeuroBlate application in treatment of rGBM. Safety for NeuroBlate application was defined as the absence of severe clinical toxicity within 14 days after the procedure. Severe toxicity was defined as toxicity associated with a drop of 20 or more points in the KPS score. The maximum therapeutic dose was to be estimated in this study.

Secondary study end points included toxicity evaluation, as estimated by brain edema that was not controlled by pharmacological interventions such as steroids, and other radiographic evidence of toxicity (for example, hemorrhage attributable to LITT or tissue damage outside of LITT-treated regions). Other secondary end points in-

TABLE 1: Inclusion and exclusion criteria used in this study of patients with rGBMs*

Inclusion Criteria	Exclusion Criteria
age ≥18 yrs	previous Tx of target GBM w/ SRS, brachytherapy, or carmustine-impregnated wafers (Gliadel)
previous histopathological (biopsy) Dx of GBM treated w/ RT, w/ or w/o resection &/or chemo	symptoms due to mass effect of the tumor
clinical &/or radiographic suspicion of tumor recur/progression for which stereotactic biopsy is deemed necessary to differentiate btwn tumor or Tx toxicity	uncontrolled hypertension (systolic ≥180 mm Hg), angina pectoris, cardiac dysrhythmia, or recent intracranial hemorrhage
supratentorial GBM w/ 15–40 mm cross-sectional dimension across proposed axis of Tx as determined by MRI no more than 2 wks prior to NeuroBlate Tx; pts can have only 1 tumor in the treatable range—all other tumors must have a <1-cm cross-sectional dimension	serious infection, immunosuppression
resection of tumor is not immediately (w/in 30 days) indicated	pregnancy
KPS score ≥60	abnormal absolute neutrophil count (<1500/mm³) or coagulopathy
stable cardiovascular, neurovascular, & neurological status	inadequate bone marrow, liver, & renal function
pts must not be receiving concurrent antitumor therapy & must have recovered from toxicity of prior therapy; minimum intervals required: 1) >6 wks after receiving nitrosourea cytotoxic drug; 2) >4 wks after receiving any non-nitrosourea cytotoxic drug or any systemic investigational agent; 3) >2 wks after receiving any noncytotoxic antitumor drug; 4) >4 wks after receiving RT	pts whose physical dimensions cannot be accommodated in MRI scanner or pts w/ contraindications to MRI such as pacemakers, noncompatible aneurysm clips, shrapnel, & other internal ferromagnetic objects
pts must be competent to give informed consent	other concurrent medical or other condition (chronic or acute) that in the opinion of the investigator may prevent safe participation or otherwise render a patient ineligible for the study
	inability or unwillingness to provide informed consent
	posterior fossa neoplasms or those w/ anticipated Tx margins that will be w/in 5 mm of critical intracranial structures
	multiple GBMs in which >1 has a >15-mm cross-sectional dimension

* Chemo = chemotherapy; Dx = diagnosis; pts = patients; recur = recurrence; RT = radiation therapy; Tx = treatment.

cluded a change in treated and untreated tumor volumes, overall and progression-free survival, and any change in KPS score within 14 days of treatment.

Treated patients were followed for a minimum of 6 months or until death, whichever occurred first. Neurological examinations, adverse events, and MRI sequences were assessed at postprocedure Days 1, 2, 3, 7, 14, 28, 56, 84, and 168. All data were analyzed using SPSS Statistics software (IBM, Inc.). Toxicity was graded 1–5 according to the Cancer Therapy Evaluation Program's Common Terminology Criteria for Adverse Events (National Cancer Institute: Common Terminology Criteria for Adverse Events v3.0 [CTCAE]. Bethesda, MD, National Cancer Institute, 2006. [http://ctep.cancer.gov/forms/ctcaev3.pdf]). These are precisely defined by the Cancer Therapy Evaluation Program for various criteria, but in general the following simplification is usually accurate: Grade 1, mild; Grade 2, moderate; Grade 3, severe; Grade 4, life threatening; and Grade 5, death.

Patient accrual began in September 2008 and ended in October 2009.

The NeuroBlate System

An overview of the equipment and equipment layout is shown in Fig. 2. The laser probe is 3.3 mm in diameter and is internally cooled using CO_2 gas. The laser energy (1064 nm) exits the probe almost perpendicularly (side-firing probe) through a sapphire tip (Fig. 2, inset D). The laser source is a 12-W pulse mode diode laser (1064 nm, cycle of 1.6 seconds in on mode and 2.2 seconds in off mode).

The NeuroBlate System monitors and visually reports the temperature of tissue and the thermal dose—the biological effect function of time and tissue temperature initially described by Sapareto and Dewey.[20] By convention the temperature commonly used in reporting experimental thermal dosage equivalence is 43°C. Tissues exposed to temperatures of 43°C or higher for ≥ 60 minutes initiate apoptosis and die within 48 hours. Tissues exposed to 43°C for shorter periods of time have a decreased level of damage, which has been refined empirically through preclinical testing and canine and porcine models (unpublished data, Monteris Medical, Inc.). The NeuroBlate software determines the likelihood of eventual cell death across the monitored tissue following laser thermal therapy.

For this study, the software demarcated 3 different thermal dose volumes ("yellow," "blue," and "white") in the monitored tissue (Table 2, Fig. 3). The white region defined tissue exposed to the thermal equivalent of 43°C for 60 minutes. Preclinical studies indicated that all tissue within this boundary died in ≤ 48 hours. The yellow region represented tissue that had been exposed to the thermal equivalent of 43°C for 2 minutes. Preclinical
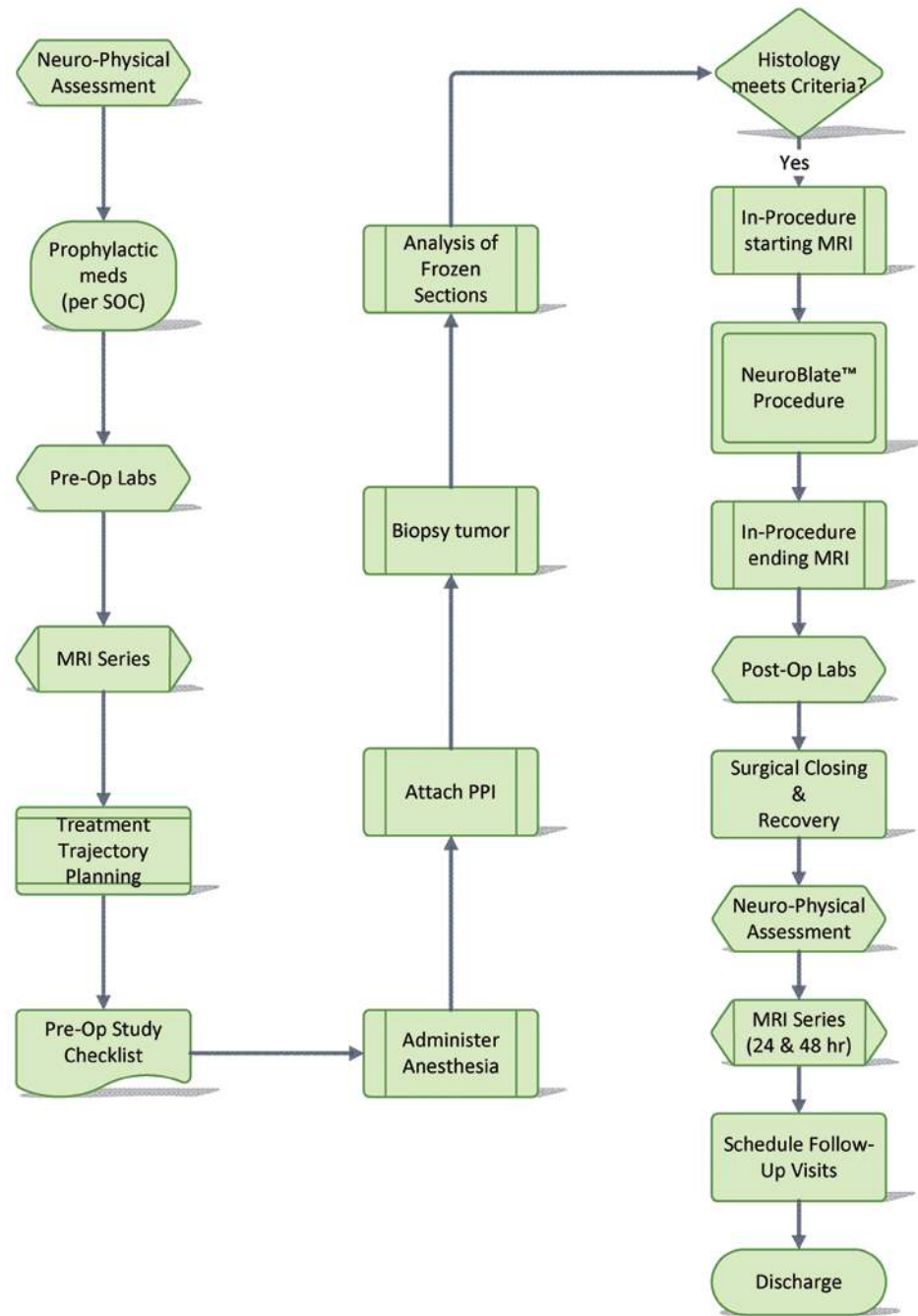
FIG. 1. Chart showing the workflow of the NeuroBlate first-in-humans study for rGBM. PPI = probe-patient interface; SOC = standard of care.

studies demonstrated that tissue outside of this yellow boundary line suffered no irreversible damage. The blue region defined tissue exposed to the thermal equivalent of 43°C for 10 minutes. This time period was selected based on empirical data suggesting that the degree of tissue damage after exposure to 43°C for 10 minutes was midway between that at exposures of 2 and 60 minutes. Tissue around this line may or may not undergo fatal thermal changes depending on a multitude of physiological factors. The MRI thermometry monitoring used a fast radiofrequency-spoiled gradient recalled echo sequence

(FOV 25.6 × 25.6 cm; matrix 128 × 128; TE 19.1 msec; TR 81 msec; flip angle 30°; bandwidth 100 Hz/pixel; and 3 slices of 5-mm thickness). This sequence required approximately 7.8 seconds for a single acquisition, and multiple acquisitions were obtained continuously during every laser firing.

Surgical Technique

The workflow as performed in the trial is shown in Fig. 1. Preoperative contrast-enhanced T1-weighted volu-

TABLE 2: Definition of thermal damage threshold dosages*

Line Color	TD Level	TD Equivalent
yellow	TD_{low}	2 min at 43°C
blue	TD_{medium}	10 min at 43°C
white	TD_{high}	60 min at 43°C

* TD = thermal dose.

metric images (isotropic 1-mm voxels—magnetization-prepared rapid acquisition gradient echo) were transferred to iPlan version 2.3 (Brainlab), and the probe trajectory and skull entry point were planned. In general trajectory planning was similar to that used for biopsy, except that an attempt was made to select a trajectory along the center of the long axis of the lesion to optimize NeuroBlate treatment. In some cases DTI-FT was also used during planning to identify nearby critical white matter tracts.

In the operating room, after induction of general anesthesia, a Mayfield 3-point fixation apparatus was attached to the patient's head and a trajectory guidance device (Navigus; Medtronic, Inc.) was secured to the skull. The Navigus had been previously modified to allow for securing the laser probe control mechanism. The patient underwent a brain biopsy directed by a Brainlab VectorVision surgical navigation system. Before proceeding with NeuroBlate treatment, confirmation of viable tumor was verified by histological analysis of frozen sections performed by a fellowship-trained neuropathologist.
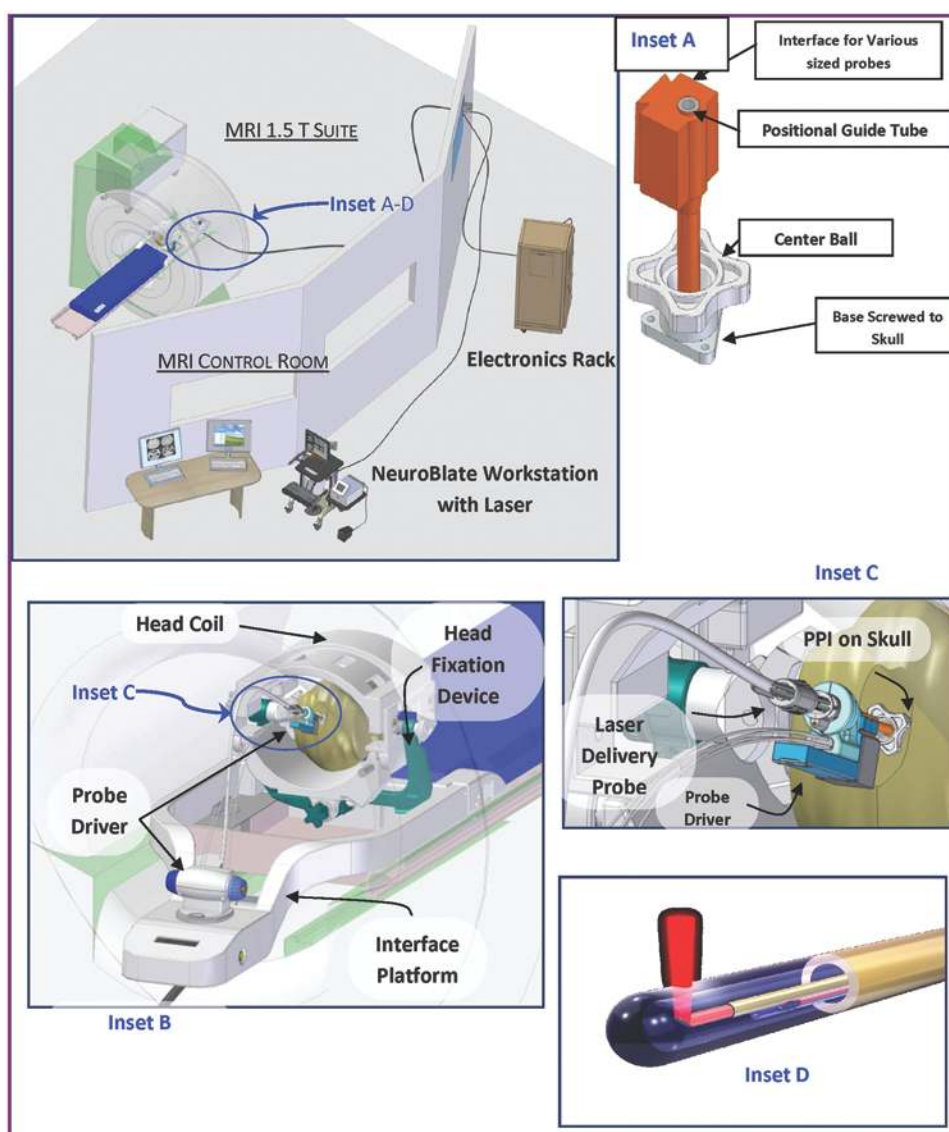

FIG. 2. Schematics showing layout of MRI suite adapted for the NeuroBlate procedure. The NeuroBlate electronics rack and workstation are situated in the MRI control room adjacent to the imaging suite. The cooling line, fiberoptic cable, and temperature probe cable are passed into the imaging suite through a wave guide. **Inset A:** Modified Navigus device. **Inset B:** Intraoperative MRI interface platform and probe driver. **Inset C:** Close-up of probe driver. **Inset D:** Tip of laser probe showing laser beam emerging out of the sapphire capsule.
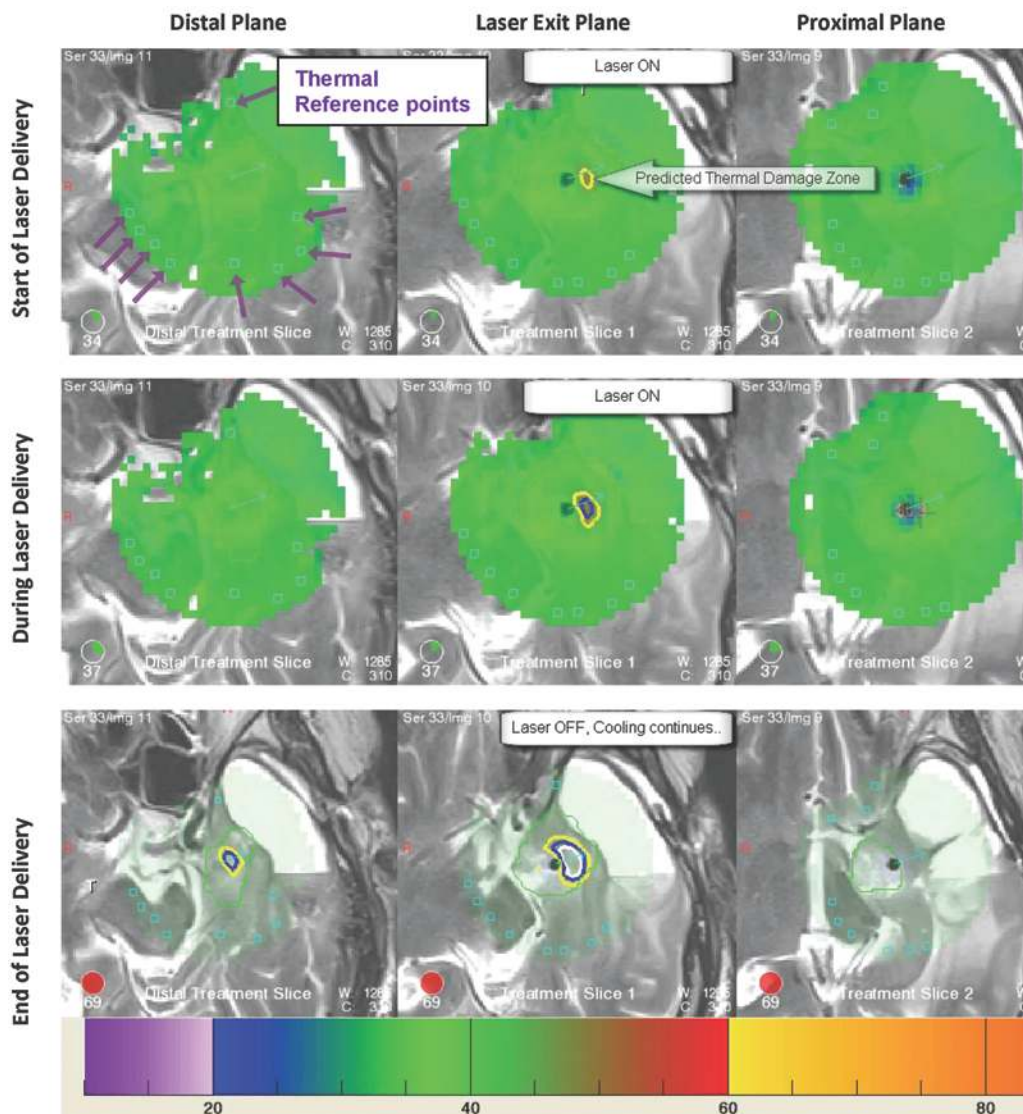
Fig. 3. NeuroBlate software generated predictive thermal dosage lines (damage threshold) used in this study; *yellow* (lowest dose), *blue* (intermediate dose), and *white* (highest dose). Illustrative time course of MRI thermometry presented by NeuroBlate software. Region of thermometry monitoring (*green area*; not shown in row 3), temperature reference points (*small light blue squares*, identified by *violet arrows* in the first panel), and thermal dosage lines (*yellow* and *blue*). The 3 panels in each row represent 3 successive "slices" perpendicular to the probe axis: the left panel is the most distal (nearest to the end of the sapphire capsule of the probe); the center panel is at the plane of laser exit from the probe; and the right panel is the slice proximal to the laser exit. A temperature (in °C) color key is shown at the bottom.

After biopsy, the Navigus device (Fig. 2, inset A) was left in place, additional sterile draping was applied, and the patient was transported, under anesthesia, to the MRI suite (1.5-T imager, Siemens AG) for NeuroBlate treatment. The laser probe fiberoptic cable, cooling system, and other lines passed through a wave guide into the control room to the NeuroBlate control system (Fig. 2). The MRI apparatus was then appropriately draped and the probe driver was securely affixed to the Navigus (Fig. 2, insets B and C). The probe driver gives the surgeon remote control of probe rotation and translation.

Pretreatment MR images included FLAIR, T2* diffusion-weighted, and T1-weighted volume spoiled gradient–recalled acquisition in the steady state. T1-weighted spin echo images that included an image volume containing the probe trajectory were acquired for NeuroBlate treatment target planning. Using the NeuroBlate software and the T1-weighted images, the surgeon then manually segmented the tumor. The surgeon also identified temperature reference points outside the tumor but within 2 cm of the tumor margin (Fig. 3). Confirmation of the trajectory set on the Navigus in the operating room was verified and, if necessary, adjusted by repositioning the Navigus and performing confirmatory imaging. The laser probe was introduced manually to within 40 mm of the final target point, then advanced to the target by using the probe driver.

During treatment, real-time thermometry data were

displayed by the software in 3 consecutive images (5-mm thick and 0.25-mm gap) in a plane perpendicular to the probe (Fig. 3). As illustrated in the upper row of MR images, as the laser is engaged, thermal deposition is typically first observed in the treatment "slice"—the plane containing the location of the laser exit (center row of images). The lowest thermal dose demarcation appears first and begins to enlarge with continued lasing (center and lower rows of images).

Each patient was assigned to a single dose level, and the surgeon attempted to optimize the delivery of the assigned dose to the tumor volume while minimizing dose to surrounding nonneoplastic tissue. Deposition of thermal energy outside the tumor into cisterns, ventricles, sulci, and subarachnoid space was permitted at the discretion of the surgeon. Depending on the size and geometry of the tumor, applications of laser energy at multiple angles and depths were required.

Laser treatment was initiated by the surgeon and stopped manually when it was thought that the predicted thermal ablation zone was sufficient or automatically if any monitored limits were exceeded. Typically, laser treatment occurred in an iterative process within a treatment plane until the thermal dose volume conformed to the tumor boundary. As additional laser applications were performed, previously calculated thermal doses were added to subsequent overlapping laser applications. The probe was either advanced or retracted to treat other planes within the tumor until maximum coverage of the prescribed thermal injury was achieved.

Timing of Subsequent Treatment Modalities

Following the 14th day after NeuroBlate treatment, the patient was eligible to engage in other treatment modalities (for example, chemotherapy). These additional treatments and any impacts were reported only as clinical observations (*Appendix* table).

Data and Calculations

Patient demographic data, the location of the tumor, and clinical data were compiled according to standard clinical criteria. The "eloquence" of the tumor was graded I–III by using the criteria of Sawaya et al.[21] (Table 3). The amount of edema on the 48-hour postoperative MRI was graded qualitatively with a score of 0 (no detectable edema), 1 (moderate edema without significant shift), or 2 (severe regional edema with mass effect or shift). The largest tumor dimension (D1) was defined as the widest dimension of the tumor in a plane perpendicular to the axis of the trajectory. The secondary dimension (D2) was defined as the widest dimension of the tumor perpendicular to both D1 and the axis of the trajectory (Fig. 4).

Before treatment, an initial tumor volume margin was defined by the surgeon and enclosed the intended target tissue (V_T). Subsequent to treatment, the treated volume (V_D) was identified. These 2 volumes help to define 3 distinct, nonoverlapping regions (Fig. 5): 1) an undosed volume (V_U)—the portion of the V_T that did not overlap with the V_D; 2) a volume (V_I)—where V_T and V_D overlap; and 3) a volume (V_A)—the portion of V_D that did not overlap with V_T.

The PTT was calculated as $V_I/V_T \times 100$ according to the intended dose for each treatment. The conformality index was calculated as $(V_A + V_I)/V_I$. The total energy, laser pulses, and lasing time were recorded automatically by the NeuroBlate software.

Results

Patient Demographic Data and History

Ten patients were treated between September 2008 and October 2009, and the median follow-up was 8 months. Demographic data for the patients in this study are given in Tables 4 and 5. The mean age was 55 years; 8 patients were male and 2 were female. The median preoperative KPS score was 80 (range 70–90). Tumors were located in various locations and relative to eloquent cortex, and were believed to be inoperable or "high risk" for open resection. Six tumors were on the left (dominant) side. Two tumors were in noneloquent cortex (Grade I), 5 were near eloquent cortex (Grade II), and 3 were located in eloquent regions of the brain (Grade III). The mean tumor dimensions were 28 ± 5 mm for D1 (range 22–36 mm) and 22 ± 6 mm for D2 (range 12–34 mm). The mean volume of the MR enhancing aspects of the tumor was 6.8 ± 5 cm³ (range 2.6–19 cm³). There was no statistical difference between the eloquence, D1, D2, or volume of the tumors treated at each of the 3 thermal dosages (Table 4). At the time of the procedure, the median time since diagnosis was 457 days (range 111–1726 days, mean 617.5 [SD 480.3] days; see Table 5). In addition, 1 patient was initially registered for the trial, but it was subsequently

TABLE 3: Classification of tumor eloquence*

Grade I: Noneloquent	Grade II: Near Eloquent	Grade III: Eloquent
frontal or temporal polar region	near motor or sensory cortex	primary motor or sensory cortex
rt parietooccipital lesions	near calcarine fissure	visual center
cerebellar hemisphere lesions	near speech center	speech center
	corpus callosum	internal capsule
	near dentate gyrus	basal ganglia
		hypothalamus/thalamus
		brainstem

* Reprinted with permission from Sawaya et al: Neurosurgical outcomes in a modern series of 400 craniotomies for treatment of parenchymal tumors. *Neurosurgery* 42:1044–1056, 1998.
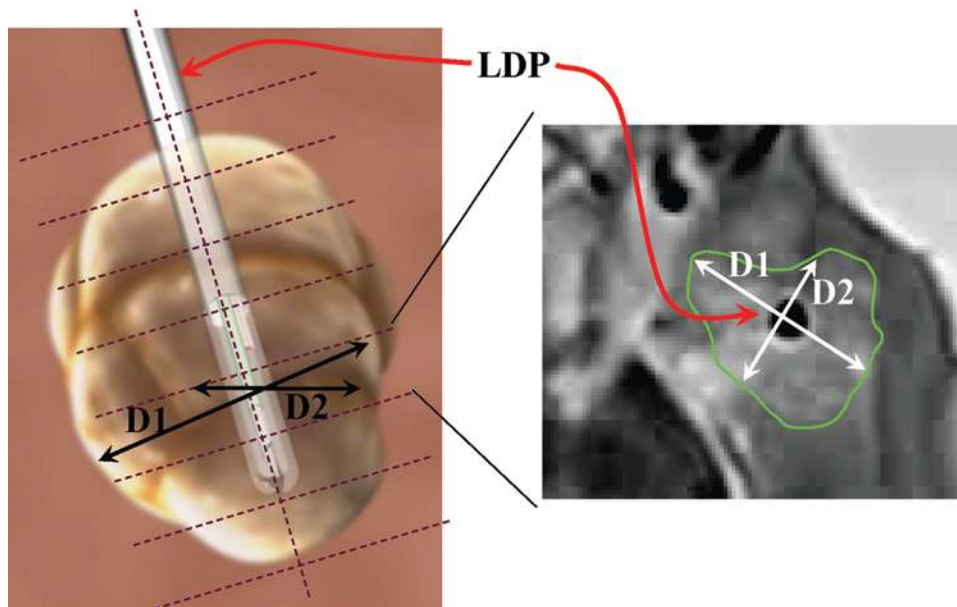
Fig. 4. Illustration demonstrating measurable parameters used to define treatment. **Left:** Volumetric representation of tumor. **Right:** Cross-sectional view. LDP = laser delivery probe.

determined that the depth of the tumor from the scalp was 106 mm. Because the longest probe available for the trial was 105 mm, the probe could not be positioned into the tumor, and treatment was not performed.

Delivery of Thermal Dose

The mean volume of tumor treated at the intended dose was 5 ± 3.2 cm^3 (range 1.98–11.03 cm^3). The mean PTT at the intended dose level was 78% (range 57%–90%), and the mean modified conformality index was 1.21 ± 0.33 (range 1–2.04). There were no significant dif-

ferences in V_D, V_T, PTT, or modified conformality index at the 3 thermal dose levels (Table 6).

In all cases, contrast-enhanced T1-weighted MRI studies performed at 24 and 48 hours after treatment showed necrosis at the treatment site. The NeuroBlate software accurately predicted the regions of treatment necrosis within the blue and white treatment zones; typically, these 2 regions were nearly concordant (Fig. 6).

Laser application times were 2–8 minutes per treatment slice. With prolonged lasing, the thermal energy spread beyond the treatment slice to the more distal moni-
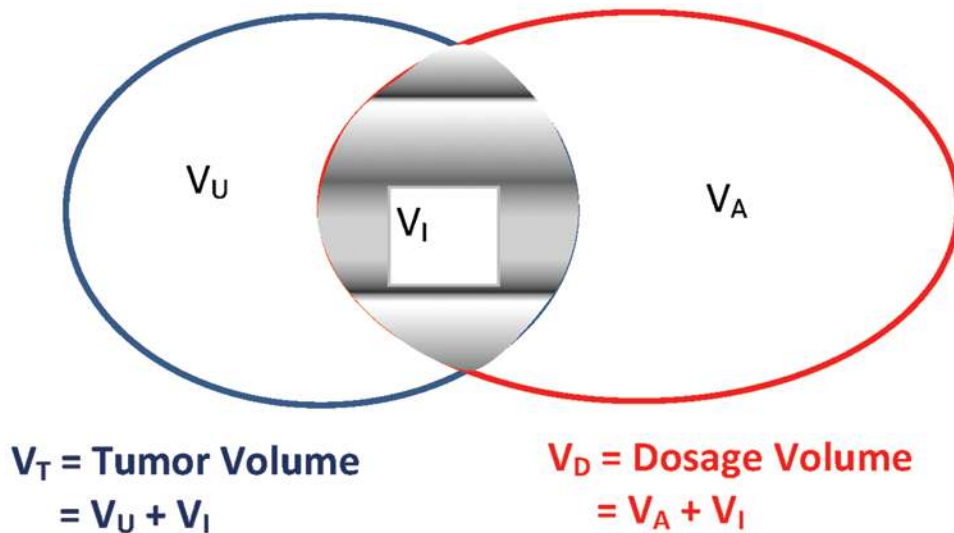

V_T = Tumor Volume
= $V_U + V_I$

V_D = Dosage Volume
= $V_A + V_I$

Fig. 5. Schematic showing surgeon-defined initial tumor margin enclosing the target tissue intended to be treated (labeled V_T). Following lasing, the delivered thermal dosage is designated as V_D. These regions define 3 distinct, nonoverlapping areas: an undosed region (V_U), which is the portion of the V_T that does not overlap with the V_D; V_I, where V_T and V_D overlap; and V_A, which is the portion of V_D that does not overlap with V_T.

TABLE 4: Characteristics in 10 patients with rGBMs at start of study

Case No.	Tx Date	Target Dosage Threshold	Age (yrs), Sex	Side	Location	Eloquence*	D1 (mm)	D2 (mm)	Vol of Lesion (cm³)	Preop KPS
1	9/24/08	yellow	47, M	lt	temporal	III	24	20	5.14	90
2	12/30/08	yellow	55, M	lt	temporoparietal	III	36	34	19.01	70
3	1/6/09	yellow	66, F	rt	parietal	I	28	27	9.88	80
4	1/27/09	blue	51, F	lt	temporooccipital	II	29	27	6.40	80
5	3/12/09	blue	55, M	rt	temporal	II	36	20	7.20	80
6	4/3/09	white	69, M	rt	parietal	I	31	12	2.60	70
7	4/7/09	white	63, M	lt	frontal	II	22	15	2.63	90
8	4/23/09	white	44, M	lt	parietal	II	27	25	12.81	90
9	5/28/09	white	55, M	rt	frontal	III	24	23	6.24	90
10	10/7/09	white	34, M	lt	frontal	II	26	22	9.96	90

* According to the scale proposed by Sawaya et al.

tored slice. Rarely was a significant thermal dose deposition seen in the more proximal monitored slice.

Dose deposition typically occurred in a controlled and predictable fashion. As illustrated in Fig. 7 upper, the surgeon selected the desired orientation of the laser (indicated by the light blue arrow at approximately the 11 o'clock position). After the appropriate thermal dose (yellow, in this case) reached the tumor margin (green area), lasing was stopped. In Fig. 7 lower, the probe has been rotated to approximately the 5 o'clock position at the same depth, and lasing resumed and was concordant with probe direction. When the surgeon stops lasing, the treatment zones stop enlarging within approximately 16 seconds (or approximately 2 MR thermometry images).

The surgeon was always able to observe laser deposition in real time. Occasionally the pattern of thermal deposition was counterintuitive. Figure 8 upper illustrates the treatment of the patient in Case 9. The laser was firing at approximately the 8 o'clock position (labeled treatment slice 4) with predicted thermal deposition orientation in both the treatment slice and the more distal slice (treatment slice 3). However, thermal deposition was also observed in the proximal slice (treatment slice 5) at approximately the 11 o'clock orientation and outside the region of the tumor segmentation. It was also observed that following lasing in a particular region, it was increasingly difficult to "push" additional thermal ablation past the damaged region in subsequent attempts (not illustrated). Figure 8 lower illustrates another example from the treatment of the patient in Case 8. While lasing at approximately the 2 o'clock position, in an effort to push the white dosage line to the tumor boundary, dose deposition occurred at the 5 o'clock and 10 o'clock positions, perpendicular to the expected direction of the laser and in the plane proximal to the laser exit.

Clinical Outcomes

The clinical outcomes of patients in the trial are summarized in Table 7. Overall the NeuroBlate procedure was well tolerated. All 10 patients were alert and responsive within 1–2 hours postoperatively, and 9 of the

10 were ambulatory within 4–12 hours. Although most patients were clinically stable (that is, without any pain in the surgical area, nausea, or headache) and suitable for discharge within 48 hours after the procedure, the study protocol mandated an MRI study and neurological assessment at 48 hours. Preoperative health status and investigator desire to observe any posttreatment effects (including delayed brain edema) resulted in longer hospital stays for some participants, especially those enrolled earliest. These factors resulted in a median hospital stay of 3 days, and this did not vary significantly by treatment dose. No probe entry site or CNS infections were reported within 2 months of follow-up; one entry-site infection was reported at 147 days postprocedure and was not attributed to the procedure or to the NeuroBlate device.

Treatment-related edema was evident on MR images at 48 hours postoperatively in nearly all patients. Edema was effectively managed with steroids. At the lowest thermal dose (yellow), no changes in postoperative KPS scores were observed. In the intermediate-dose (blue) and high-dose (white) groups, 3 patients had improved KPS scores at postoperative Day 14; improvements ranged from 10 points (2 patients) to 20 points (1 patient).

Direct Toxicity

Two patients developed temporary neurological deficits several days after the procedure; one patient reported dysphasia with mild upper-limb weakness contralateral to

TABLE 5: Prior treatment history in 10 patients with rGBMs

Parameter (days before NeuroBlate)	Mean (SD)	Minimum	Maximum
days after initial Dx	617.5 (480.3)	111	1726
days after recur	58.1 (61.2)	13	198
days since prior op	613.7 (482.0)	111	1726
days prior RT	538.8 (496.8)	44	1696
no. rounds of prior chemo	2.3 (0.9)	1	4
days since most recent chemo	210 (249.0)	4	572

TABLE 6: Treatment parameters in 10 patients with rGBMs*

Case No.	Dose Level	Total Pulses	Total Lasing Time (min)	Total Energy (J)	Volume (cm³)				PTT at Intended Dose	Conf Index ([V_A + V_I]/V_I)
					V_I	V_U	V_A	V_T		
1	yellow	336	9.0	6,410	2.93	2.21	0.00	5.14	57	1.00
2	yellow	630	16.8	11,940	11.03	7.98	0.00	19.01	58	1.00
3	blue	280	7.5	5,297	7.90	1.98	5.35	9.88	87	1.68
4	blue	1021	27.2	19,520	4.86	1.54	1.35	6.40	80	1.28
5	white	645	17.2	12,310	5.11	2.09	1.25	7.20	75	1.24
6	white	639	17.0	12,170	1.98	0.62	0.70	2.60	81	1.35
7	white	1884	50.2	36,040	2.13	0.50	2.22	2.63	90	2.04
8	white	933	27.4	19,410	10.63	2.18	1.38	12.81	85	1.13
9	white	416	10.5	7,971	4.56	1.68	0.59	6.24	75	1.13
10	white	1304	35.8	26,190	6.27	3.69	1.10	9.96	67	1.18
mean		642	17.1	12,240	4.99	2.04	1.18	6.80	78	1.21
SD		495	13.5	9,687	3.24	2.14	1.54	4.99	12	0.33

* Conf = conformality; V_A = volume of nontumor treated at intended dose; V_I = volume of initially defined tumor treated at intended dose; V_T = volume of initially defined tumor; V_U = volume of initially defined tumor outside intended dosage line.

the procedure, and another patient had mild contralateral weakness and homonymous hemianopia. Both deficits resolved after therapy with steroids.

Two patients suffered neurological deterioration due to the NeuroBlate procedure. The patient in Case 8 experienced a small intracerebral hemorrhage (arterial pseudoaneurysm) 6 weeks posttreatment. This was successfully treated by coil placement, and the patient did not suffer from any long-term neurological deficit. The patient in Case 9 suffered a white matter tract injury at the treatment site and experienced severe hemiparesis but eventually improved, regaining significant function in 6–8 weeks. This patient had not undergone preoperative DTI-FT (which was not required by the protocol); however, no patient undergoing preoperative DTI-FT suffered a direct white matter injury in this study.

All serious (Grades 3–5; severe, life threatening, death) adverse events observed in this study are shown in Table 8.

Other Adverse Events

Three patients developed DVT (2 severe and 1 moderate), and 1 patient each developed Grade 3 neutropenia and a Grade 4 PE. The treating physicians did not attribute the thromboembolic events to the device.

More than 9 months postprocedure, 1 patient developed an epicranial gliosarcoma on and in the skull at the probe entry site. This mass was removed surgically without complication. It is unclear whether this was attributable to the biopsy, laser probe, or both.

There was no correlation of any type of adverse event with the dosage level (either by ANOVA or direct examination of the raw data). Similarly, there was no correlation between dosage level and event severity. Two cases of hemiparesis were noted in patients whose tumors were in eloquent (Grade III) or near eloquent (Grade II) cortex, although only one of these was severe. In addition, the 2 serious complications (in Cases 8 and 9) were associated

with patterns of dose deposition that were counterintuitive.

All nonserious (Grades 1–2; mild and moderate) adverse events observed in this study are shown in Table 9. The median survival in this selected group of 10 patients was 316 days (range 62–767 days; Table 7, Fig. 9). Although the small study size makes statistical significance questionable, there was a trend for increased survival in the patients treated with the higher (white) thermal dose, including those with complications (Fig. 9 upper). There were only 2 deaths during the 6-month window of the study's prescribed follow-up period; one in a patient treated at the yellow thermal dose and another in one treated at the blue dose. Both patients suffered progression of the underlying disease and were entered into hospice rather than receiving additional treatment. No deaths were related to the treatment procedure or device. At least 3 patients entered into subsequent clinical trials after completing the mandated 14-day observation point.

Discussion

Technical Limitations and Characteristics

The mean percentage of treated tumor at the intent-to-treat dose in this trial was 78% ± 12% (range 57%–90%; Table 6). This is lower than other treatments using focused energy for tissue ablation and does not meet the goal of 98% resection, which correlated with improved survival in previous series of resected GBM.[11] However, it should be recognized that this limitation was due in part to the trial design as mandated by the FDA, which allowed only a single probe trajectory to be used. Additional technical challenges were related to the limited trajectories achievable with available cranial immobilization devices and the design of available MRI coils, which limited trajectories to the vertex of the skull. Nonetheless, the favorable clinical outcomes observed (discussed below) suggest that despite these limitations, NeuroBlate may
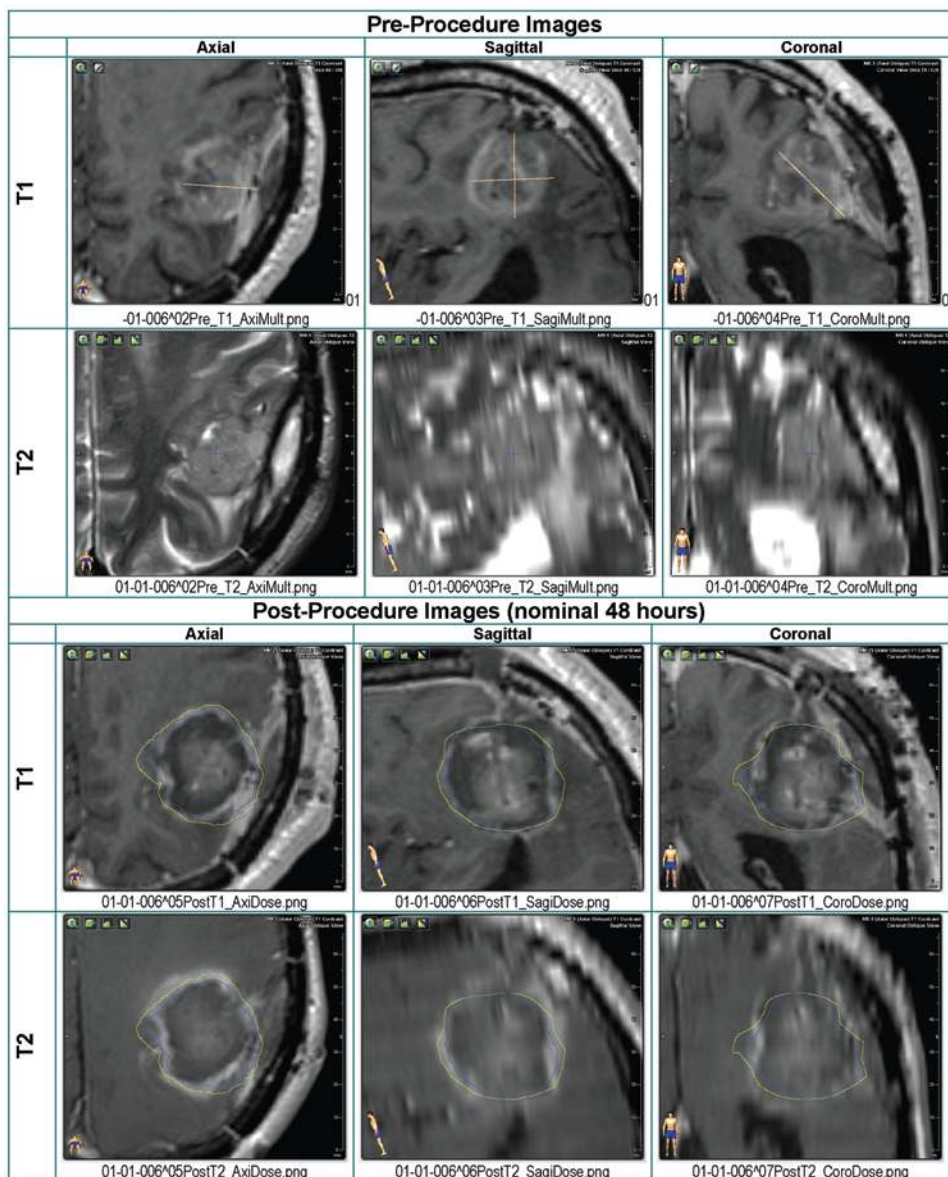
Fig. 6. Axial, sagittal, and coronal T1- and T2-weighted (as marked) MRI studies obtained before and 48 hours after a Neuro-Blate procedure. Note that the *yellow line* in the postprocedural images is the extent of predicted ablation by the blue (medium) target dosage threshold, and that this conforms very well with the extent of observed laser ablation at 48 hours.

be clinically beneficial. This observation is also consistent with a recent study demonstrating that resection of as little as 78% of a GBM conferred a survival benefit.[19] Furthermore, new technical innovations such as novel miniframes that permit increased trajectory angles as well as multiple trajectories using a single bur hole (S. Manjila, K. Knutson, A.E. Sloan, unpublished data) have recently become available. Novel MRI coil designs enabling improved access to the cranium from a variety of angles are currently under development. These should enable future surgeons to achieve greater coverage of tumor at the selected thermal dose.

Although resection of rGBM appears to be effective in up to one-third of patients,[1] many are not candidates for resection of rGBM for a variety of reasons. Previous at-

tempts in which less invasive approaches such as brachytherapy[4,27] and stereotactic radiosurgery[28,30] were used have proven ineffective in recent meta-analysis and randomized trials. However, unlike therapies using ionizing radiation, NeuroBlate therapy results in tumor death over a period of only a few days. In addition, the near real–time feedback of the thermal dose delivery enables the surgeon to precisely control the damage inflicted on the tumor.

A conformality index is a measure of the "precision" of the delivery of treatment energy to a tumor relative to the total volume of brain (tumor + nontumor) receiving this dose. In contrast to SRS, for which a conformality index of ≤ 2.0 is generally considered well tolerated,[26] conformality indices as low as 1.00 and 1.24 were associ-
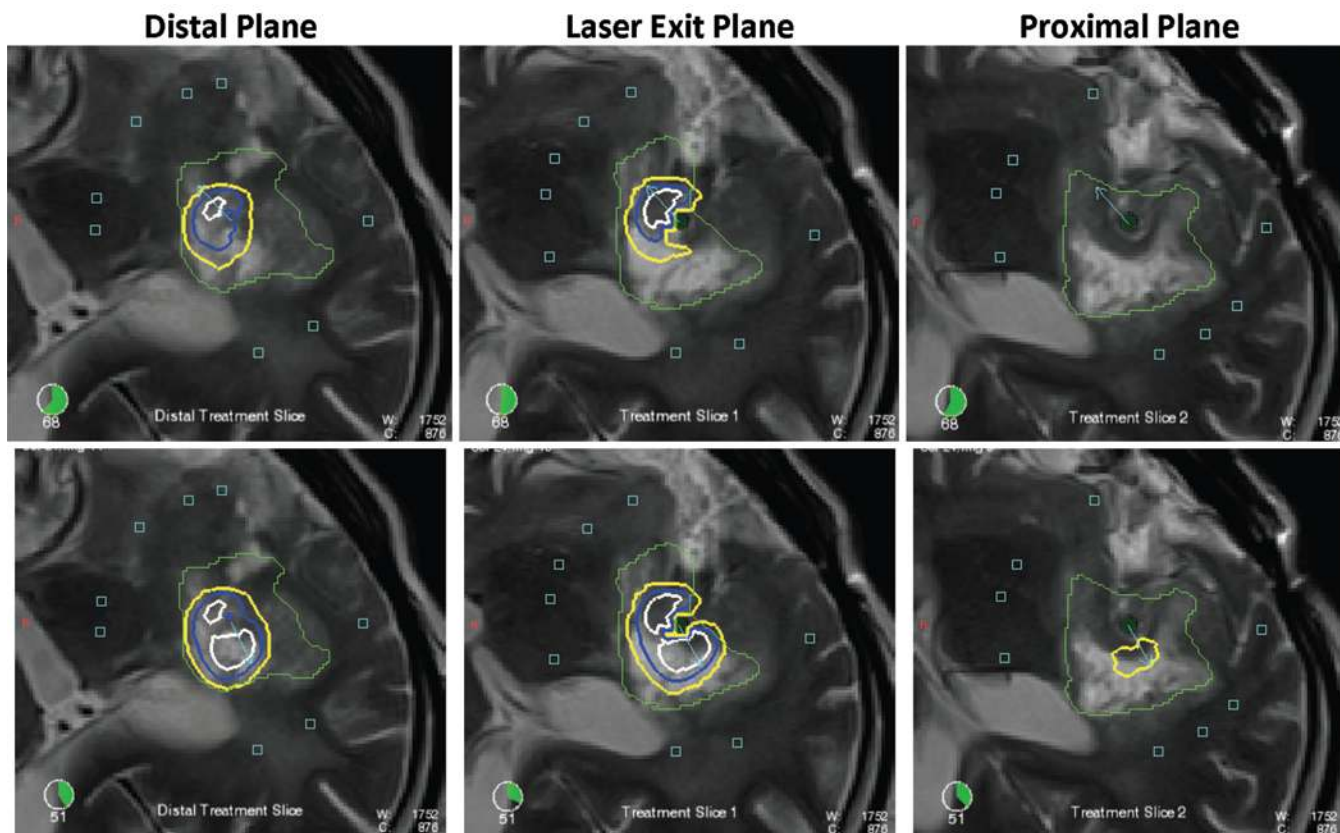
FIG. 7. Dose deposition was usually predictable. Illustration of thermal dose lines and directionality *(blue arrows)* of laser probe. **Upper:** Row of images showing the probe pointing to approximately 11 o'clock, with a corresponding deposition of thermal energy. **Lower:** Row of images showing the same coordination of energy deposition, with the probe firing at approximately 5 o'clock (including dosage from prior firings).

ated with transient mild motor and/or speech deficits in patients at the low and medium thermal doses, respectively, although both patients recovered fully after steroid treatment (Tables 6 and 7). In addition, treatments with a conformality index of 1.13 resulted in a ruptured pseudoaneurysm and significant damage to the primary motor tract, respectively, in 2 patients at the highest dose. Thus, whereas NeuroBlate is safe, the temporal dynamics and tissue damage induced by thermal ablation are clearly different from those associated with SRS, for which the MRI evidence of treatment effect often appears in 3–6 months rather than within 48 hours. Greater surgical precision and caution may be required for LITT than SRS. It should also be noted that both patients who sustained damage at the higher dose levels also had the probe adjacent to critical structures (vessels or eloquent fiber tracts). In addition, in both cases, dose deposition occurred in a counterintuitive fashion (Fig. 8). This suggests that perhaps a more careful preoperative imaging session including MR angiography and DTI-FT would probably help avoid damage. Indeed, although preoperative DTI-FT was not a requirement of the study, no patient in whom DTI-FT was used suffered a sustained tract injury. Also, because the surgeon can observe the thermal dose deposition in real time, damage may be preventable if the surgeon stops lasing when unexpected thermal deposition is observed because it suggests an unanticipated "heat sink" that may represent a vessel or a fiber tract. Improved understanding and prediction of tissue response to thermal therapy and additional metrics to describe this phenomenon are important topics for future study.

Patient Outcomes

The median time since diagnosis in this group of patients was 457 days (range 111–1726 days) at the time of the procedure. Hence this was a highly selected group of patients who had received a median of 2 previous therapies (range 1–4; see *Appendix* table). The median survival time seen in this small cohort of patients after NeuroBlate is encouraging at 316 days, as compared with the 90- to 150-day median survival typically observed for rGBM.[1] The median progression-free survival at 6 months in rGBM is 15%,[1] and in this study it was estimated to be greater than 30% (the small study size only allows for a lower-limit estimate). The favorable survival results may be due in part to selection bias because the entry criteria required patients with unifocal tumors 1–4 cm in maximum diameter. The mean tumor size in this group was 27.5×22.5 mm (range 22×15 mm to 36×34 mm), and the mean volume was 6.8 cm^3 (range 2.6–19 cm^3). The prolonged survival in this heavily pretreated group suggests that NeuroBlate may be an appropriate treatment for

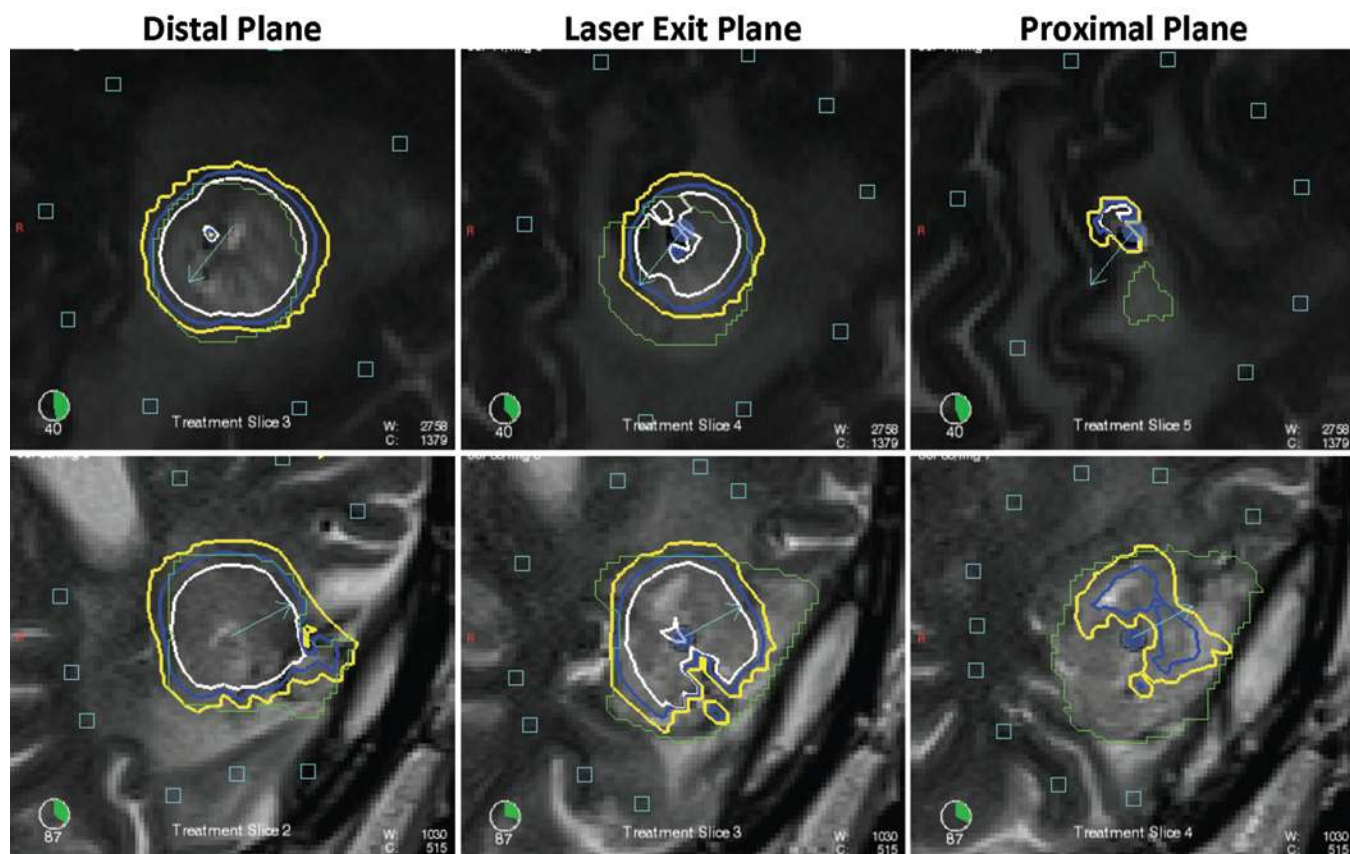**Distal Plane**   **Laser Exit Plane**   **Proximal Plane**

Fig. 8. Occasionally the pattern of thermal deposition was counterintuitive. **Upper:** Note that in the third treatment slice (image labeled treatment slice 5) the laser direction *(blue arrows)* is at 8 o'clock, whereas the thermal effect is seen at 11 o'clock and proximal to the plane of laser exit (laser exit is in plane with treatment slice 3). **Lower:** In the third treatment slice (image labeled treatment slice 4) the laser direction is set at 2 o'clock, whereas the thermal effect is seen at both 5 o'clock and 10 o'clock proximal to the plane of laser exit (treatment slice 3).

patients with rGBM. About one-third of this study cohort entered subsequent clinical trials, as is typical of this patient population. Furthermore, NeuroBlate can be easily combined with other treatment modalities because most patients can start additional therapies 2 weeks postprocedure, as in this trial. An intriguing possibility regarding this greater than expected survival is that the thermal effects of the NeuroBlate treatment extend beyond the region of coagulation, with a preferential toxic effect of hyperthermia on nearby tumor cells.

Overall, NeuroBlate was a well-tolerated treatment. The degree of postoperative edema was moderate and easily controlled with steroids. A possible explanation for this could be that procedure-generated edema was partially moderated by a reduction in the volume of surviving tumor cells. Nonetheless, 2 patients developed temporary neurological deficits several days after the procedure: one had dysphasia with arm weakness and the other had homonymous hemianopia. Both deficits were considered preoperative and resolved after therapy with steroids.

Two patients had serious neurological adverse events due to the NeuroBlate procedure, both at the highest dose level. The patient in Case 8 suffered a small intracerebral hemorrhage due to an arterial pseudoaneurysm 6 weeks after treatment. This was successfully managed by endo-vascular coil placement with no long-term neurological deficit. The vessel affected was in contact with the target tissue, and the damage to the vessel, in a retrospective review, was apparent on immediate postprocedural MRI studies. In the future, when there are vascular concerns near target tissues, pre- and posttreatment angiography (via CT and/or MRI modalities) may be considered to allow the surgeon to avoid thermal dosing of delicate vasculature and to assess the local vascular fidelity before a patient is discharged. The patient in Case 9 experienced severe hemiparesis on awakening from the procedure but eventually improved, regaining significant function in 6–8 weeks. This event was attributed to the proximity of a motor tract to the target tumor and to the fact that denser tissues like nerve bundles, pial surfaces, and vascular structures appear to absorb thermal energy better than normal parenchyma (unpublished preclinical observations).

In addition, the trial design specified that the maximal dose (white) be applied to the target tissue adjacent to this eloquent region. In the future, pretreatment fiber tract mapping using DT MRI should be incorporated into the procedure. This will facilitate appropriate caution and avoidance of thermal injury or application of a lower thermal dose (blue) to eloquent structures in the future.

TABLE 7: Clinical outcomes in 10 patients with rGBMs*

Dose Level & Case No.	Days of Hospital Stay	Edema at 48 Hrs†	Change in KPS Score at Day 14	Neurological Complications at Day 14	Neurological Complications at Day 84	Days of Survival Post-LITT
yellow						
1	2 (4.3)	2+ (3)	0 (0)	none	none	314 (225)
2	7	1	0	mild dysphasia	none	265
3	4	0	0	none	none	96
blue						
4	3 (3.5)	1+ (2)	+10 (5)	none	none	334 (198)
5	4	2+	0	mild hemiparesis, HH	none	62
white						
6	3 (3.4)	2+ (1+)	+20 (0)	none	none	485 (434)
7	3	2+	0	none	none	305
8	3	1–2+	0	none	pseudoaneurysm	319
9	6	1+	−30	severe hemiparesis	mod hemiparesis	434
10	2	1+	+10	none	none	767
overall median	3					316
CI	2–7					265

* Values in parentheses are medians at the indicated dose. Abbreviations: HH = homonymous hemianopia; mod = moderate.
† Edema scores: 0 = no detectable edema; 1 = moderate edema without significant shift; 2 = severe regional edema with mass effect or shift.

Also of note, both patients who suffered serious adverse consequences were noted to have unexpected patterns of thermal energy deposition (Fig. 4). This suggests the need for careful observation of the patterns of thermal deposition during LITT and that such unexpected patterns require additional intraoperative scrutiny and caution. Additional study of such unexpected patterns may yield further insight and should be the topic of future study.

Although the maximum tolerated dose was not reached even at the highest dose used in the study, the observation that the 2 most serious adverse consequences were unpredictable suggests that keeping the current highest dose (white; 43°C for 60 minutes) in use until the effects of LITT are better understood and more predictable appears to be prudent.

One patient developed an epicranial gliosarcoma

TABLE 8: Serious adverse events seen in the study, by dose level*

Toxicity	Yellow				Blue				White			
	Severe	LT	Fatal	Subtotal	Severe	LT	Fatal	Subtotal	Severe	LT	Fatal	Subtotal
neutropenia	1			1				0				0
postop WI				0	1			1				0
VPR				0				0	1			1
cerebral cyst	1			1				0				0
glioma				0	1			1				0
brain abscess	1			1				0				0
hematoma		1		1	1			1				0
hemiparesis				0				0	1			1
partial Sz				0	1			1				0
dysphasia	1			1				0				0
DVT	1			1				0	1			1
PE		1†		1				0				0
total	5	2	0	7	4	0	0	4	3	0	0	3

* LT = life threatening; Sz = seizure; VPR = vascular pseudoaneurysm rupture; WI = wound infection.
† Occurred when the patient was taken off study; this was not a serious adverse event as determined by the institutional review board.

TABLE 9: Nonserious adverse events seen in the study, by dose level

Toxicity	Yellow			Blue			White		
	Mild	Mod	Subtotal	Mild	Mod	Subtotal	Mild	Mod	Subtotal
balance disorder	1		1			0			0
dizziness	1		1			0			0
headache		2	2	2		2	1		1
confusional state							1		1
hemiparesis			0	1		1			0
partial Sz	1		1		1	1			0
speech disorder	1		1			0			0
vision blurred			0	1	1	2			0
DVT			0			0		1	1
total	4	2	6	4	2	6	2	1	3

at the probe entry site more than 9 months after LITT. This mass was removed surgically without complication. Although rare, there are previous reports of gliomas developing (progressing) both along surgical routes and epicranially.[2,14,15] It is not possible to predict or assess the future likelihood of such tumor seeding events as a direct result of the NeuroBlate procedure. However, prudence suggests that in future the patients treated with LITT be appropriately monitored for site-distant progression, especially along the probe trajectory, as is suggested for other needle-based interventions involving aggressive malignancies.[14] Whereas many of the cases were treated by lasing from the deep to the superficial aspect of the tumor, in the future it may be advantageous to perform the lasing from superficial to deep, thereby sterilizing cells in contact with the probe.

Deep vein thrombosis and PE were reported in 3 and 1 patients, respectively, and were not thought to be directly attributable to the procedure or device (the patients had risk factors or history of DVT). The patient in whom PE was diagnosed was off study at the time of the event, and this was deemed not to be a severe adverse event. Patients with rGBM are known to be at risk for DVT,[9] and because the postprocedure hospitalization from NeuroBlate is expected to be < 48 hours we do not believe that this should lead to any significant increase in venous thromboembolic disease. Prophylaxis for DVT (pneumatic compression stockings) was used in these cases; it is the standard of care at both participating institutions.

Observations Regarding the Procedure

In the present study, NeuroBlate appears to be a safe and a well-tolerated procedure. Unless complications occur, patients can be safely discharged after 24–48 hours without significant pain in the surgical area, nausea, or headache. No infections related to the procedure were seen in this study within 6 months of treatment. As with all surgical ablative procedures, NeuroBlate is limited to the margins of the treatment area defined by the surgeon. For highly infiltrative tumors, such as GBM, surgical intervention will not eliminate tumor cells that have diffused through the brain separate from the tumor mass itself. However, local control of the tumor mass is generally
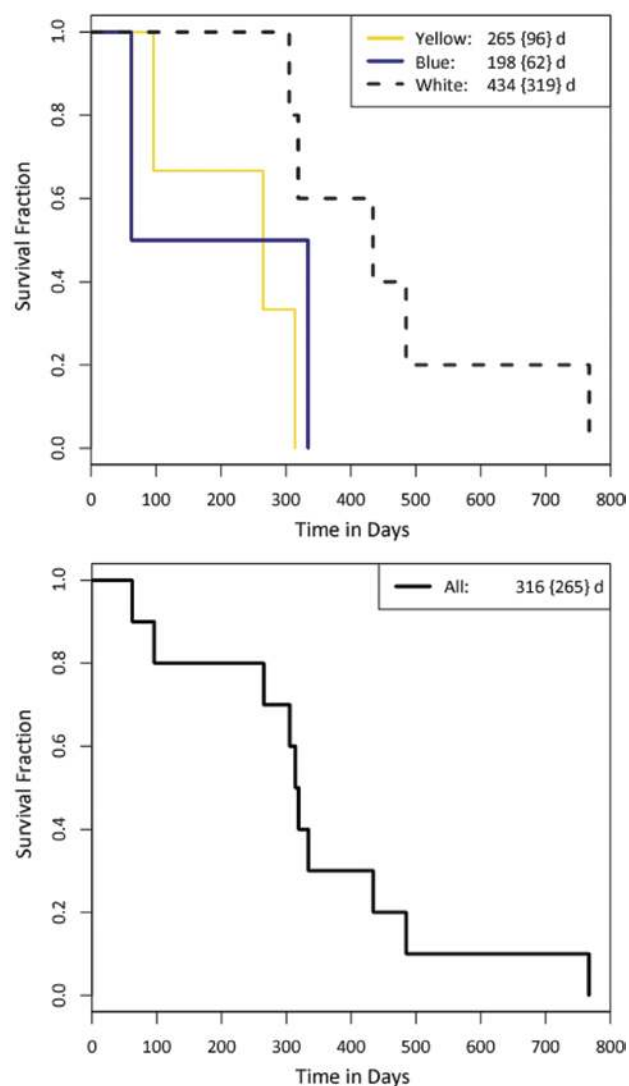

Fig. 9. Kaplan-Meier survival curves of NeuroBlate first-in-humans trial for rGBM, by thermal dose level **(upper)** and for all participants **(lower)**. The colors of the survival curves indicate the dosage levels, with corresponding median survival and lower limit of confidence interval for the curves indicated in the key (the upper confidence limit was not reached). d = days.

the first objective of treatment in a craniotomy as well as in a NeuroBlate case. NeuroBlate may be particularly helpful in controlling the edema, mass effect, and other deleterious effects of malignant brain tumors.

The minimally invasive nature and interactive surgical control of the NeuroBlate procedure, coupled with the advantages of real-time MRI monitoring, suggests utility in treating brain tumors in which margins are best determined by MRI or in which resection is preferred, but not completely feasible or practical. It may also be useful to treat certain patients who might otherwise be poor candidates for surgery or SRS due to tumor location or size limitations. Additionally, the nature of laser energy leads to extensive tumor cell death within 48 hours and may have benefit in specific cases for which the ionizing energy used in radiation and radiosurgery poses unacceptable risks or fails to rapidly reduce tumor mass effect.

Although this study was limited to patients with rGBMs, NeuroBlate offers a potentially important method of intervention in patients with some low- to high-grade gliomas, whether benign or malignant, as well as benign tumors such as meningiomas, brain metastases, and failures of SRS for brain metastases. The NeuroBlate System received FDA 510(k) clearance on May 1, 2009. Clinical studies are planned or underway to further evaluate NeuroBlate for rGBMs as well as other malignant tumors and for failed radiosurgery for brain metastases (recurrent tumor and radiation necrosis).

Conclusions

The NeuroBlate Thermal Therapy System appears to provide a novel and minimally invasive approach for treating deep hemispheric rGBM. This brain tumor therapy represents a significant advance over historical attempts at LITT and is facilitated by real-time thermography and software that accurately predict thermal damage. The regulatory issue that limited the number of trajectories is no longer active. Technical issues that limited the range

of motion of immobilization devices and also the MRI coil design that limited access in this trial are currently being addressed. Vascular studies and DTI tractography should be incorporated into the treatment process in selected cases. NeuroBlate holds the promise of enabling the delivery of thermal ablation in real time with surgical precision in some patients with brain tumors in whom safe, conventional surgery is impractical or impossible.

Appendix Table 1: Treatments undergone by study participants (10 patients with rGBM)*

Parameter	Case No.									
	1	2	3	4	5	6	7	8	9	10
prior Txs										
days btwn Dx & proc	454	1056	838	402	153	442	1726	472	521	111
days btwn recur & proc	30	21	26	13	43	29	2	198	59	23
days since prior op	433	1056	838	385	153	442	1726	472	521	111
days since prior RT	343	991	774	316	76	384	196	350	414	44
days since 1st course of chemo	343	991	774	316	76	382	187	198	414	44
days since 2nd course of chemo	32	525	680	270	39	NA	279	106	200	NA
days since 3rd course of chemo	NA	144	572	120	NA	NA	156	NA	NA	NA
days since 4th course of chemo	NA	NA	NA	43	NA	NA	53	NA	NA	NA
days btwn other Txs & 1st proc	NA	NA	NA	NA	NA	51	10	NA	NA	NA
prior other Tx						Celldex vaccine	chemo			
days since last chemo	32	144	572	43	39	382	53	106	200	44
subsequent Txs										
final info at or after exit	wd after 12-wk FU; consented for another clinical trial	wd after 12-wk FU; entered hospice care	ND	wd after 4-wk FU; entered hospice care	ND	ND	wd after 12-wk FU; consented for another clinical trial	wd after 4-wk FU; consented for another clinical trial	ND	2- & 4-wk FU visits not done; in Tx for SAE
final disposition info	wd after 12-wk FU; consented for another clinical trial; yellow line	wd after 12-wk FU; entered hospice care; yellow line	dead	wd after 4-wk FU; entered hospice care; died 62 days post-Tx; blue line	dead	dead	wd after 12-wk FU; consented for another clinical trial; white line	wd after 4-wk FU; consented for another clinical trial; died 96 days post-Tx; yellow line	dead	2- & 4-wk FU visits not done; white line
vital status (01 Nov 2011)	dead	dead	dead	dead	dead	dead	alive	dead	dead	dead

* FU = follow-up; NA = not applicable; ND = no data beyond study period (protocol followed for complete study period); proc = procedure; SAE = serious adverse event; wd = withdrew.

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