Atlas-based functional radiosurgery: Early results

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(Received 16 July 2008; revised 7 November 2008; accepted for publication 4 December 2008; published 14 January 2009)

Functional disorders of the brain, such as dystonia and neuropathic pain, may respond poorly to medical therapy. Deep brain stimulation (DBS) of the globus pallidus pars interna (GPi) and the centromedian nucleus of the thalamus (CMN) may alleviate dystonia and neuropathic pain, respectively. A noninvasive alternative to DBS is radiosurgical ablation [internal pallidotomy (IP) and medial thalamotomy (MT)]. The main technical limitation of radiosurgery is that targets are selected only on the basis of MRI anatomy, without electrophysiological confirmation. This means that, to be feasible, image-based targeting must be highly accurate and reproducible. Here, we report on the feasibility of an atlas-based approach to targeting for functional radiosurgery. In this method, masks of the GPi, CMN, and medio-dorsal nucleus were nonrigidly registered to patients' T1-weighted MRI (T1w-MRI) and superimposed on patients' T2-weighted MRI (T2w-MRI). Radiosurgical targets were identified on the T2w-MRI registered to the planning CT by an expert functional neurosurgeon. To assess its feasibility, two patients were treated with the CyberKnife using this method of targeting; a patient with dystonia received an IP (120 Gy prescribed to the 65% isodose) and a patient with neuropathic pain received a MT (120 Gy to the 77% isodose). Six months after treatment, T2w-MRIs and contrast-enhanced T1w-MRIs showed edematous regions around the lesions; target placements were reevaluated by DW-MRIs. At 12 months post-treatment steroids for radiation-induced edema and medications for dystonia and neuropathic pain were suppressed. Both patients experienced significant relief from pain and dystonia-related problems. Fifteen months after treatment edema had disappeared. Thus, this work shows promising feasibility of atlas-based functional radiosurgery to improve patient condition. Further investigations are indicated for optimizing treatment dose. © 2009 American Association of Physicists in Medicine. [DOI: 10.1118/1.3056460]

Key words: functional radiosurgery, internal pallidotomy, medial thalamotomy

I. INTRODUCTION

Lesioning or neuroprostethic stimulation¹ of selected targets in the thalamus and basal ganglia are widely accepted procedures aimed towards the symptomatic improvement of a variety of neurodegenerative brain disorders. The subthalamic nucleus (STN) is the region most commonly targeted today.² Deep brain stimulation (DBS) of the STN is a procedure commonly offered to patients with advanced Parkinson's disease (PD) who have developed motor complications related to dopaminergic replacement (on-off phenomena, dyskinesias, freezing, etc.). DBS is a safe procedure that can produce substantial motor benefit in patients undergoing chronic stimulation.³ The main advantages of STN DBS include a remarkable improvement of off-medication motor functioning scores, substantial reduction in the need for dopaminergic drugs, and abolition of drug-related side effects such as dyskinesias. On the other hand, several side

effects have been observed after STN DBS, including cognitive decline,⁴ apathy and other affective disorders,⁵ and hypophonia.⁶ While DBS rarely induces permanent brain damage, lesioning of the STN induces a permanent ablation of brain tissue. Nevertheless, the results of STN lesioning by radiofrequency thermal ablation or by radiosurgery appear to be equivalent to those induced by DBS.⁷⁻⁹ In addition, lesioning techniques are less expensive than DBS, and their use is spreading in countries where the cost of DBS is prohibitive. Gene therapy targeting the STN,¹⁰ which is functionally modified to produce a gabergic (instead than glutamatergic) output, is a novel therapy being currently investigated in clinical trials.¹¹ The globus pallidus is another common stereotactic target in the basal ganglia. The target lies in the postero-ventro-lateral part of the internal globus pallidus¹² (GPi) where the sensorimotor region is located. GPi DBS induces motor improvements in patients affected by PD which are grossly equivalent to those associated with

STN DBS, but to date has not resulted in substantial reduction of dopaminergic drugs.¹³ On the other hand, GPi DBS has a safer profile in terms of cognitive and psychiatric complications associated with chronic stimulation.¹⁴ GPi DBS is also used to treat dystonias, with remarkable improvement seen in primary dystonias such as those characterized by the presence of the gene DyT1.¹⁵ GPi lesioning has been widely used until recently, providing good symptomatic improvement in PD patients.¹⁶ The lesioning technique most widely used is microelectrode-guided postero-ventro-lateral pallidotomy, and reports of radiosurgical pallidotomy are also available.¹⁷ Another less common basal ganglia target is the putamen, where stem cells producing dopamine have been implanted.^{18,19} Other important stereotactic targets are located in the thalamus. The lateral region of the thalamus is part of the sensorimotor circuit which returns to the cortex the inputs originated from the sensorimotor cortex and transmitted to the thalamus by the basal ganglia. The nucleus ventralis intermedius (VIM) is an excellent target to control tremor,²⁰ while the nucleus ventralis oralis pars anterior and pars posterior are effective to control focal dystonias such as writer's cramp.²¹ Again, there is wide experience lesioning the VIM,²² and recently VIM DBS has gained acceptance to treat essential tremor.²⁰ DBS implantation of the nucleus ventralis posterolateralis of the thalamus has been used to treat neuropathic pain.²³ Another thalamic target used to treat neuropathic pain is the centromedian nucleus (CMN), which is part of the intralaminar complex.²⁴ A recent report suggests a promising effect of DBS implantation of the CMN and the anterior nucleus of the thalamus to treat selected cases of medically refractory epilepsy.²⁵

Correct target identification is crucial for the success of each of these procedures. Image guidance is essential and includes modalities such as MRI, CT, and ventriculography. MRI allows direct localization of several structures; STN and GPi can be easily identified on T2 FSE imaging.²⁶ 3 T MRI offers enhanced visualization of basal ganglia and thalamic targets, allowing identification of targets (such as the VIM) not otherwise visible using most 1.5 T MRI scanners.²⁷ Ventriculography is a long-practiced invasive technique that permits the targeting of specific nuclei on the basis of a fairly fixed relation with a line passing through the anterior and posterior commissure (AC-PC line).²⁸ For DBS implantation, microelectrode recording is frequently used to obtain final confirmation that a specific target is reached, a technique that is effective because the target nuclei have a characteristic electrophysiologic activity.²⁹⁻³¹ Nevertheless, volumetric reconstruction of basal ganglia and thalamic targets has been recently described as an additional tool to improve target localization.³²

Our recent efforts have been devoted to the development and validation of an accurate technique for threedimensionally mapping a few nuclei relevant in functional neurosurgery and radiosurgery, such as the STN, the GPi and globus pallidus pars externa (GPe), the CMN, and the red nucleus.³³ The technique has been developed and validation has been published;^{34,35} we believe three-dimensional atlasbased identification of such nuclei could significantly im-

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prove the accuracy of radiosurgery treatment. Until now, however, it had not been applied to real cases. The aim of this work was to demonstrate the clinical feasibility of functional radiosurgery using atlas-based target identification.

II. MATERIALS AND METHODS

Two patients affected by functional brain disorders were selected for functional radiosurgery. The first patient, 53 years old, suffered from facial neuropathic pain. He had undergone several surgeries to drain an infected right on the right maxillary sinus developing over time a lancinanting pain over the distribution of the second and third branch of the trigeminal nerve. This pain proved to be refractory to medical therapy and to several procedures including partial section of the right trigeminal nerve (which elicited a severe constant burning overlapping the original shooting pain). He underwent CyberKnife (Accuray Incorporated, Sunnyvale, CA) radiosurgery targeting the cisternal segment of the nerve (57 Gy prescribed to the 70% isodose volume) and left motor cortex stimulation. The second patient, 41 years old, developed post-anoxic focal dystonia secondary to prolonged cerebral hypoxia experienced during heart valve surgery. The patient was in an anoxic coma for about 72 hours after surgery and then in a barbiturate coma for about 15 days. He subsequently developed dysarthria, bilateral blepharospasm and severe and painful dystonia of the right arm and leg. Eventually, according to the pathologies, the two patients underwent medial thalamotomy (MT) and internal pallidotomy (IP), respectively, delivered by CyberKnife radiosurgery. Radiosurgical MT was offered due to the severity of pain, lack of response to any other non-destructive procedure and to CT-PET findings indicating bilateral hypermetabolism of the medial thalamus. Radiosurgical IP was offered to relieve dystonia because he was on anticoagulant therapy.

Targets were selected and spatially defined on the patients' MRIs by an expert functional neurosurgeon, aided by atlas-based computerized identification providing volumetric reconstruction of selected targets. For the neuropathic pain patient, ¹⁸F-FDG-PET (ECAT PET, Siemens Medical Solutions, Malvern, PA), using reconstructed transversal spatial resolution and slice thickness equal to 2 and 2.4 mm, respectively, was also considered as a primary source of information for target delineation in the nonselective MT, a lesioning technique involving many thalamic nuclei: this exam showed increased metabolism in the medial thalamus and intralaminar complex, including the CMN and centrolateral nucleus. The accuracy of target localization was aided by reference to Talairach and Tournoux and Montreal Neurological Institute (MNI) atlases. Medio-dorsal (MD) and CMN nuclei were conferred onto the images of the neuropathic pain patient, and GPi and GPe were conferred onto the dystonia patient's images. Both patients were scanned using T1-weighted-MRI (T1w-MRI) and T2-weighted-MRI (T2w-MRI), acquired with standard MRI at 1.5 T with a Genesis Signa (GE Medical Systems, Waukesha, WI) for the IP patient and at 3 T with a TrioTim (Siemens Medical Solutions, Malvern, PA) for the MT patient. Acquisition and reconstruction param-



FIG. 1. Superposition of the atlas-based identification of the GPi and CMN on the T1w-MRIs of the IP (upper panel) and MT (lower panel) patients, in axial, coronal, and sagittal views.

eters for T1w- and T2w-MRIs were the same as in Ref. 34. T1w-MRIs were used for automatic local non-rigid registrations of the MNI electronic atlas onto patient volumes, according to the method described in Ref. 33. T2w-MRIs were acquired for manual identification of the target nuclei by an expert functional neurosurgeon, whose delineation was aided by automatic atlas-based identification. MD, CMN, GPi, and GPe masks were nonrigidly registered³³ to the patient T2w-MRI (see Fig. 1) and integrated into the planning CT.

The target delineation for the MT was based on the hypermetabolic zone identifiable in the ¹⁸F-FDG-PET, which was registered to the patient CT. The CMN was superimposed on the ¹⁸F-FDG-PET-based target, to be sure it was entirely enclosed within the target limits. Additionally, the MD nucleus mask was superimposed on the ¹⁸F-FDG-PET-based target to determine that extent to which it was actually involved. In this case no modification was applied to the ¹⁸F-FDG-PET-based target because the CMN

and MD were judged by the functional neurosurgeon to be adequately within the ¹⁸F-FDG-PET-based target.

The coarse target delineation for the IP was initially based on anatomical landmarks. The GPi and GPe masks were then superimposed on the anatomical-landmark-based target, which was substantially refined using the three-dimensional information from the two masks in order to target the postero-ventro-lateral part of the GPi.

The MultiPlanTM treatment planning system was used to delineate the multimodality-imaging-based targets and create conformal treatment plans for the IP and MT (see Fig. 2). For the IP, the critical structure of the optic tract was delineated; it was much farther from the target than the reported error of the atlas-based identification method.³⁵ During the optimization of the treatment plan, the dose delivered to the optic tract was kept as low as possible. Additional artificial critical structures were delineated to limit the spread of the low percentage isodose curves, which given the high doses used in functional radiosurgery may still be associated with a high absolute dose. A strategy to minimize radiation delivery time for the dystonic patient was investigated due to severe dystonia and generally poor clinical condition. After comparing conformality and treatment time for IP treatment plans generated using the 5- and 7.5-mm collimators with the trigeminal path, we chose to accept the slightly lower plan conformality associated with the 7.5-mm collimator to reduce the amount of time the patient was under anesthesia during treatment delivery. Therefore, the plan using the trigeminal path with 7.5-mm collimator (i.e., 6.1 mm field size at 650 mm source-to-axis distance) was selected.

Six- and twelve-month follow-up exams consisted of contrast-enhanced (CE-) T1w- and T2w-MRIs (T1w-MRI and T2w-MRI reconstructed transversal spatial resolution and slice thickness equal to 0.47 and 1.33 mm, respectively; both of them acquired by the same 1.5 T scanner used for planning the IP). Additionally, MR diffusion-weighted images (DWIs) were acquired to distinguish the lesion from



FIG. 2. 3D beam distribution (upper-left), axial (upper-right), sagittal (lower-left), and coronal (lower-right) views of the IP (a) and MT (b) treatment plans visualized on the patients' T2w-MRIs.

TABLE I. Treatment parameters for MT and the IP.

Treatment parameter	MT	IP
Target volume (mm ³)	240.5	215.3
Path	Even	Trigeminal
Collimator(s)	5/7.5 mm	7.5 mm
No. of beams	207	164
MUs	67 946	35 423
Prescription dose (Gy)	120	120
Prescription isodose (%)	77	65
Coverage (%)	95	77
CI	1.3	1.49
nCI	1.37	1.94
HI	1.3	1.54
Treatment time (min)	156	102

radiation-induced edema (reconstructed transversal spatial resolution and slice thickness equal to 1 and 5 mm, respectively; *b* value equal to 1000 s/mm^2). For the neuropathic pain patient, a 6-month follow-up ¹⁸F-FDG-PET was acquired (reconstructed transversal spatial resolution and slice thickness equal to 2.34 and 3.27 mm, respectively, scanned by a Discovery ST scanner, GE Medical Systems, Waukesha, WI). All follow-up exams were registered on the pretreatment T1w-MRI.

III. RESULTS AND DISCUSSION

Table I summarizes the parameters of the treatment plans. In both cases target volumes as delineated by the expert functional neurosurgeon with the support of the automatic atlas-based method were relatively large: this limits the potential misidentification of the nuclei due to the 2-mm maximum error of the atlas-based method.³⁵ In fact, considering the cubic root of the volumes was about 6 mm in both cases, this length is significantly larger than the potential atlas-based localization maximum error. These cases therefore represent good practical examples for application of the atlas-based identification is not compromised by the potential error in the atlas-based identification of the nuclei.

The relatively small number of beams and total monitor units (MUs) in the dystonic patient was achieved using the trigeminal path.

Although the prescription radiation dose was equal for both patients, the prescription isodose was significantly different, generating a much higher absolute dose maximum in the IP. This higher dose was selected on the basis of the poor success rate reported in the literature,³⁶ combined with the clinical goal of alleviating dystonia-related problems in the patient. While the MT plan coverage with the prescription isodose was high (equal to 95%), the IP plan was significantly lower and resulted in a less homogenous treatment as quantified by the homogeneity index (defined as the ratio between the maximum dose value inside the target and the prescription dose). The small difference between the conformity index (CI) (defined as the ratio between the total volume enclosed by the prescription dose surface and the volume of tumor enclosed by the prescription dose surface) and the new conformity index³⁷ (nCI) indicates the prescription isodose closely encompasses the target in the MT plan. Conversely, in the IP plan both the nCI and the CI are much greater than 1.0, suggesting a lower target volume coverage by the prescription isodose. Compared to the results of Nakamura et al.,³⁷ in our cases the CI for the MT is lower than the 25th percentile of the CI obtained using the Gamma Knife (1.38) while the CI for the IP is lower than the median value (1.67); the nCI for the MT is lower than the 25th percentile (1.51) while the nCI for the IP is higher than the median value (1.78). This comparison shows again the high conformality achieved by using the CyberKnife in the MT, while suggesting that a more conformal solution could have been applied to the IP using the 5-mm collimator, which in this case was rejected in favor of a shorter treatment duration given the clinical condition of the patient. From a comparative perspective, because of its isocentric nature, the GammaKnife is likely to produce dose distributions with steeper gradients in the midlow isodose range than that obtainable by the CyberKnife (used in the nonisocentric mode) while producing less homogeneous dose distributions within the target. We attempted to limit the spread of the low-dose percentage curves by applying artificial critical structures during the treatment plan optimization. For the dose delivered in functional radiosurgery it is imperative to limit as much as possible the spread of low dose percentage curves. In fact, in radiosurgery the volume of normal tissue within or immediately adjacent to the prescribed isodose surface is generally highly correlated with the risk of complications.³⁸ This means that complication probability rises as CI and nCI increase above 1.0. This correlation was found in the study by Nakamura *et al.*,³⁷ where more serious complications (from mild side effects to those requiring corticosteroids or surgical resection for radionecrosis, to mortality) were associated with higher CIs and nCIs. On the other hand, in the same study no correlation was found when lesions were smaller than 1 mL, as were the IP and MT lesions described in this study. The fact that both cases experienced the same time course of corticosteroids independently of the CI and nCI values is in agreement with the results provided by Nakamura *et al.*³⁷

The maximum dose to the optic tract in the IP was about 15 Gy delivered to a small volume, and the minimum dose was about 2 Gy.

Treatments lasted longer than 100 min in both cases, even when using the trigeminal path. Thus, high-dose functional radiosurgery is a time-consuming technique, especially when dealing with patients in low tolerance conditions. The inevitable arrival of high dose-rate LINACs³⁹ will significantly increase the speed of functional radiosurgery (for example, the latest CyberKnife system version has a dose-rate of 800 MU/min).

Figure 3 shows the pretreatment T1w-MRI (a), the 6-month follow-up T2w-MRI (b) and DWI (c), and the atlasbased targets GPi (d) and GPe (e). The 6-month follow-up T2w-MRI shows a large area of radiation-induced edema which prevents the identification of the actual lesion. The



FIG. 3. Pretreatment patient T1w-MRI (a), 6 months follow-up T2w-MRI (b), 6 months follow-up DWI (c), and GPi (d) and GPe masks reported on the pretreatment T1w-MRI of the IP patient. All the other volumes apart from the masks were rigidly registered to the pretreatment patient T1w-MRI.

6-month follow-up DWI distinguishes lesion from edema, yet one cannot assess the accuracy of lesion location relative to GPi and GPe masks due to the edema-related geometric distortion. Edema internally deformed most of the anatomical region of the lesion in the 6-month follow up T2w-MRI. Given that the registration of the 6-month follow-up T2w-MRI to the pretreatment T1w-MRI is based on a global rigid transformation, the localized deformed part does not affect the parameter optimization. A registration based on a global affine transformation of the subvolumes containing the lesion in the two MRIs would probably improve the accuracy of the match, but would not be sufficient for an evaluation of the accuracy of the lesion placement compared to the GPi mask. On the other hand, a local nonrigid registration would fail due to the hyperintense signal related to the edematous area in the 6-month follow-up T2w-MRI not present in the pretreatment MRIs. However, the correspondence of the lesion to the deformed GPi mask suggests some level of agreement. The patient was scanned again 18 months after treatment and the edema was negligible (data not shown). The exam indicated an accurate location of the lesion in the postero-ventrolateral zone of the GPi.

Figure 4 shows the same analysis for the MT. The 6-month control MRI was a CE-T1w-MRI (b), where the lesion rim is clearly visible; the internal portion identifiable on the CE-T1w-MRI corresponds to the lesion highlighted in the 6-month follow-up DWI (c). Figures 4(d) and 4(e) show the deformed MD and CMN masks, respectively, inside the



FIG. 4. Pretreatment patient T1w-MRI (a), 6 months follow-up CE-T1w-MRI (b), 6 months follow-up DWI (c), MD (d) and CMN (e) masks reported on the pretreatment T1w-MRI of the MT patient. All the other volumes apart from the masks were rigidly registered to the pretreatment patient T1w-MRI.



FIG. 5. Pretreatment patient ¹⁸F-FDG-PET (a), 6 months follow-up ¹⁸F-FDG-PET (b), 12 months follow-up DWI (c), 12 months follow-up CE-T1w-MRI (d), CMN (e) and MD (f) masks reported on the pretreatment T1w-MRI of the MT patient. All the other volumes apart from the masks were rigidly registered to the pretreatment patient T1w-MRI.





FIG. 6. Time course of medication reduction for pain- and dystonia-related problems for the IP (left) and MT (right) patients before, 6 and 12 months after the treatment.

lesion. However, direct evaluation of the accuracy of the lesion location is not possible because the actual target was chosen primarily based on the ¹⁸F-FDG-PET-based hypermetabolic zone (incorporating other nuclei as well) and, as in the IP case, edema severely limited evaluation of clinical accuracy.

Figure 5 shows, for the MT patient, the pre-treatment ¹⁸F-FDG-PET (a), the 6-month follow-up ¹⁸F-FDG-PET (b), the 12-month follow-up DWI (c), the 12-month follow-up CE-T1w-MRI (d), and the deformed MD (e) and CMN (f) masks. All these volumes were registered to the pretreatment T1w-MRI. Radiosurgical MT resulted in a clear suppression of hypermetabolism, as visible on the follow-up ¹⁸F-FDG-PET (crosshair region). Still, radiation-induced edema was present 6 months after treatment; 12 months after treatment, edema was negligible.

Figure 6 shows the time course of the reduction in painand dystonia-related medications for the IP (a) and the MT (b) patients. For the IP case, all medication was terminated 12 months post-treatment; for the MT patient, all medications save neurontin were terminated 6 months posttreatment, and neurontin was terminated 12 months posttreatment. In both cases high doses of steroids, especially at 3 and 6 months post-treatment, were necessary for edema mitigation.

Pain relief after the IP was evaluated using a visual analog scale (VAS) and dystonia was evaluated by means of the unified dystonia rating scale (UDRS). The pretreatment VAS value was 10/10, and decreased to 0/10 in the 12-month post-treatment evaluation; the pretreatment UDRS value of 42.5/44 fell to 29/44 in the 12-month post-treatment evaluation. Quality of life was evaluated in this patient with the activities of daily living (ADL) index, specifically assessing the need for help in the daily activities, and using the functional independence measure (FIM) to assess motor and cognitive activities. The pretreatment ADL was 0/6 and in-

creased to 1/6 in the 12-month post-treatment evaluation; the pretreatment FIM was 29/91 and rose to 32/91 in the 12-month post-treatment evaluation. Only pain relief was evaluated in the MT patient. The pretreatment VAS was 10/10, and 12 months post-treatment it had decreased to 0/10. All these evaluations showed significant improvements in pain and dystonia and slight improvement in independence for activities of daily living. Of course, further clinical investigations are needed for optimizing dose assessing the success of treatment, and detecting complications.

medications before and after MT

IV. CONCLUSIONS

This proposed approach for functional radiosurgery resulted in lesions being accurately located and improvements in quality of life in the first two treated patients. Additionally, this work shows how atlas-based identification can be used not only in preoperative scenarios, but also in combination with post-therapeutic follow-up exams such as DWIs, for comprehensive correlation between lesion position on threedimensional atlas-based reconstructions and patient outcomes. Further investigations are needed to understand if dose reduction is possible without compromising treatment efficacy.

ACKNOWLEDGMENTS

Dr. Himanshu Shukla, Dr. David Schaal, Dr. Warren Kilby, and Dr. Francesco Lena are gratefully acknowledged for their help with the development of the manuscript.

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