Visualization of nerve fibers and their relationship to peripheral nerve tumors by diffusion tensor imaging

Tene A. Cage, MD,¹ Esther L. Yuh, MD, PhD,² Stephanie W. Hou, MD,² Harjus Birk, BS,³
Neil G. Simon, MBBS, FRACP,⁴ Roger Noss, PhD, DABNM,¹ Anuradha Rao, MD,²
*Cynthia T. Chin, MD,² and Michel Kliot, MD⁵

Departments of ¹Neurological Surgery and ²Radiology, ³School of Medicine, University of California, San Francisco, California;
⁴Prince of Wales Clinical School, University of New South Wales Australia, Sydney, Australia; and ⁵Department of Neurological
Surgery, Northwestern University Feinberg School of Medicine, Chicago, Illinois

OBJECT The majority of growing and/or symptomatic peripheral nerve tumors are schwannomas and neurofibromas. They are almost always benign and can usually be resected while minimizing motor and sensory deficits if approached with the proper expertise and techniques. Intraoperative electrophysiological stimulation and recording techniques allow the surgeon to map the surface of the tumor in an effort to identify and thus avoid damaging functioning nerve fibers. Recently, MR diffusion tensor imaging (DTI) techniques have permitted the visualization of axons, because of their anisotropic properties, in peripheral nerves. The object of this study was to compare the distribution of nerve fibers as revealed by direct electrical stimulation with that seen on preoperative MR DTI.

METHODS The authors conducted a retrospective chart review of patients with a peripheral nerve or nerve root tumor between March 2012 and January 2014. Diffusion tensor imaging and intraoperative data had been prospectively collected for patients with peripheral nerve tumors that were resected. Preoperative identification of the nerve fiber location in relation to the nerve tumor surface as seen on DTI studies was compared with the nerve fiber's intraoperative localization using electrophysiological stimulation and recordings.

RESULTS In 23 patients eligible for study there was good correlation between nerve fiber location on DTI and its anatomical location seen intraoperatively. Diffusion tensor imaging demonstrated the relationship of nerve fibers relative to the tumor with 95.7% sensitivity, 66.7% specificity, 75% positive predictive value, and 93.8% negative predictive value.

CONCLUSIONS Preoperative DTI techniques are useful in helping the peripheral nerve surgeon to both determine the risks involved in resecting a nerve tumor and plan the safest surgical approach.

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KEY WORDS MRI; tractography; nerve tumor; diffusion tensor imaging

PERIPHERAL nerve tumors are rare, and on average 6 people out of 1 million undergo surgery for these tumors each year.^{4,10} The majority of these masses are slow-growing schwannomas and neurofibromas.^{3,5} Though these tumors may be symptomatic, most are benign.^{3,10} Intraneural tumors may involve 1 or multiple nerve fascicles and may originate from deep within the nerve subsequently splaying apart fascicles as the tumor expands, or they may be attached to a superficial fascicle and thereby displacing the remainder of the nerve to one direction.

To gain a better preoperative understanding of peripheral nerve tumors and their relationship to adjacent struc-

tures, high-resolution ultrasound and MRI have been used to visualize the size, density, and location of these masses as related to their associated nerves.¹⁰ Though high-resolution ultrasound is a powerful, safe, and rapid diagnostic tool that can detect peripheral fascicles in schwannomas, no data have revealed whether the resolution is sufficient to identify relations between tumor and individual nerve fascicles in neurofibroma cases or when there are internal tumor fascicles.⁷ Likewise, though standard MRI offers good resolution of soft tissues, it is not sensitive enough to map the precise relation of tumor to associated nerve fascicles.

Not all peripheral nerve tumors require surgical remov-

ABBREVIATIONS DTI = diffusion tensor imaging; FA = fractional anisotropy; GTR = gross-total resection; IDEAL = iterative decomposition of water and fat with echo asymmetry and least-squares estimation; MRN = MR neurography; NPV = negative predictive value; PPV = positive predictive value.

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* Drs. Chin and Kliot share senior authorship.

al. However, for tumors that grow in size or are symptomatic, surgery with the goal of gross-total resection (GTR) is recommended.⁴ Most peripheral nerve tumors can be fully resected while sparing motor and sensory function if approached with the proper expertise and techniques.^{1,5} Intraoperative electrical stimulation of motor nerve fascicles and direct recording allow the surgeon to identify involved and nearby functional nerves and avoid damaging them during tumor resection.³ With a negative electrical map over the surface of the mass, the tumor capsule can be safely entered and the tumor resected without violating or damaging functional nerve fibers.

Magnetic resonance diffusion tensor imaging (DTI) with tractography has been successfully performed and proven to be clinically useful in the brain. However, only recently, DTI has been applied in the peripheral nervous system to permit the visualization of axons and fascicles in peripheral nerves.^{2,8,9} The challenges of applying DTI with tractography to nerves include the relatively small size and complex course of these nerves, as well as the heterogeneity of tissues along the course of the nerves (such as muscle, bone, and vasculature), which can cause an obscured background signal. We have recently shown that it is feasible to employ high-resolution ultrasound and DTI to visualize schwannomas and their relationship to associated nerves.⁷ Here, we extend this technique to the surgical management of peripheral nerve tumors. With preoperative DTI, the relationship of the nerve tumor to the axons and nerve fascicles can be visualized and studied. In that context, DTI proves to be a reliable and useful technique in helping the peripheral nerve surgeon to determine the risks involved in resecting a nerve tumor and plan the safest surgical approach. Here, we report our clinical experience using DTI to preoperatively determine the relationship of nerve fibers to their associated peripheral nerve tumors. We correlate these imaging findings with intraoperative direct nerve stimulation, thereby validating preoperative DTI as a valuable and accurate tool to assist in the resection of peripheral nerve tumors with the goal of preserving nerve function.

Methods

Patient Selection

We performed a retrospective chart review of patients treated at the University of California, San Francisco, with a diagnosis of peripheral nerve or nerve root tumor between March 2012 and January 2014. All patients were treated in the Department of Neurosurgery and underwent preoperative MR neurography (MRN), which includes MR DTI with tractography to visualize the nerve fibers and associated nerve tumor. A single attending surgeon in the Department of Neurosurgery performed all operations, except one; a separate attending neurosurgeon in the department performed that one surgery.

Patients were identified through a search of all radiographic MR neurograms ordered at the University of California, San Francisco, during the study period. This search returned 47 patients. Patients were excluded if they had not undergone surgical intervention or if they had a tumor biopsy only. Patients were also excluded if they had not undergone DTI with tractography prior to surgery or if

there was no detailed description of where the nerve fibers were in relation to tumor in the operative notes.

Preoperative Imaging

All patients underwent DTI and tractography of the tumor and associated nerve or nerves. Magnetic resonance imaging sequences included pre-Gd T1-weighted, fat-saturated post-Gd T1-weighted, and iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL). Imaging was performed on a 3-T scanner (MR750, GE Healthcare) as part of the preoperative workup. Diffusion tensor imaging was performed using FOCUS, a reduced field-of-view diffusion method that applies a 2D spatially selective radiofrequency excitation in a single-shot echoplanar imaging sequence, as described elsewhere⁹ (FOCUS 28 directions, TR 3200 msec, TE 55 msec, FOV 18 × 9 cm, acquisition matrix 256 × 144, slice thickness 3.0 mm, voxel size 1.31 mm³, b value 600 sec/mm²).^{6,11} Tractography was performed to reconstruct the nerve fiber tracts with fractional anisotropy (FA) using FiberTrak software (GE Healthcare).⁹ The T1-weighted MRI sequence was used to calculate FA maps, which involved tracing the outline of the affected nerve proximal to the tumor, at the region of the tumor, and distal to the tumor. The orientation of nerve fibers in relation to nerve tumor was standardized and agreed on by both the neurosurgeon and the neuroradiologist. The orientation of fibers to the tumor was based on the patient's orientation in the anatomical position. No distinction could be made between motor and sensory nerve fibers on DTI and tractography. Possible fiber locations were anterior, posterior, lateral, or medial to the tumor. All locations were based on the patient's orientation in the anatomical position. Two attending neuroradiologists interpreted the MRN results. Preoperative tumor volume was calculated on MRI using the following formula: (length × width × height)/2.

Operative Technique and Intraoperative Localization of Nerve Fibers

Patients underwent tumor resection with comprehensive electrophysiological monitoring including preoperative and intraoperative somatosensory evoked potentials and motor evoked potentials. In addition, the surgeon performed intraoperative direct electrical stimulation recordings for motor fiber stimulation of the surgical field, tumor capsule, and involved nerve fibers before, during, and after tumor resection. However, the direct electrophysiological stimulation technique along the tumor surface can only identify motor nerve fibers, not sensory fibers.

Location and orientation of motor nerve fibers in relation to nerve tumors were confirmed with electrical stimulation. The same terms used in the preoperative MRN descriptions were used to describe the intraoperative orientation of nerve fibers in relation to tumor (anterior, posterior, lateral, medial; Fig. 1). Both intraoperative and MRI locations of nerve fibers were described relative to the patient's orientation in the anatomical position to eliminate nomenclature differences between surgical positioning and the supine position required for MRI. The presence or absence of motor nerve fibers along the tumor surface was determined by applying electrical stimulation along

the entire tumor surface in a systematic fashion using a monopolar electrode at a stimulus threshold just above that sufficient to elicit a muscle response when stimulating the nerve entering or exiting the tumor. We then created a map of the tumor surface, containing zones where motor responses were or were not present. This map was then compared to the distribution of fibers seen on preoperative MR DTI studies. All resected tumor tissue was sent to pathology for final diagnosis.

Data Analysis

The motor and sensory nerve fiber locations were identified on preoperative DTI studies as described above. These data were compared with the position of the motor nerve fibers confirmed by direct motor stimulation of the tumor capsule and the associated nerve. Sensory fibers could not be localized using intraoperative stimulation. We calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of DTI in detecting the presence of nerve fibers in each of the 4 directional anatomical locations (anterior, medial, posterior, lateral) in relation to the tumor as shown by intraoperative electrical stimulation.

Clinical Outcome

Patients were followed up in the outpatient neurosurgery clinic after resection of the nerve tumor. Detailed motor, sensory, and reflex exams were performed in and documented for all patients.

Results

Characteristics of Patients and Tumors

Of the 47 patients initially revealed by our search, 17 were excluded because they had not undergone surgical intervention or they only had a tumor biopsy, 5 were excluded because they had not undergone DTI and tractography before surgery, and 2 were excluded because there was no detailed description in the operative notes of where the nerve fibers were located in relation to tumor. Thus, 23 patients met the inclusion criteria and were included in our study. Sixty-five percent of the patients were female ($n = 15$), and the median age at the time of surgery was 36 years (range 19–69 years; Table 1). No patient had undergone prior resection of the affected nerve or tumor. Tumor volumes as calculated on preoperative MRI ranged from 0.1 to 2016 cm³. The surgeon was able to achieve GTR in 18 cases (78%), whereas 5 cases (22%) required some tumor to be left behind.

All patients underwent preoperative MRI with DTI of the affected nerve, and an attending neuroradiologist interpreted all MR images. All patients underwent resection of their peripheral nerve tumor with intraoperative electrophysiological monitoring (Fig. 2).

A specimen was sent for definitive pathological diagnosis in all surgical cases, and the majority of tumors (14 [60.9%]) were diagnosed as schwannomas. Seventeen percent of tumors ($n = 4$) were neurofibromas (Table 1). Hemangioma, fibromatosis, sarcoma, neuroma, and myxoma were diagnosed in 1 patient each. Tumors varied greatly in size, and volume ranged from 0.1 to 2016 cm³ with a median value of 9.3 cm³. Most commonly, the tumor arose

FIG. 1. Intraoperative orientation of peripheral nerve tumor surfaces. Intraoperative direct electrophysiological stimulation of anterior (A), posterior (B), medial (C), and lateral (D) surfaces of the tumor.

from the brachial or lumbar plexus from a distal nerve branch ($n = 14$), with the radial nerve most frequently affected ($n = 4$). However, a spinal nerve root was involved in 21.7% of the cases.

After resection, patients were followed up in the outpatient neurosurgery clinic with follow-up times ranging from 1 to 21 months (median 1 month, mean 3 months). After surgery, 91.3% of patients had either an improved or stable motor exam and 65.2% had an improved or stable sensory exam (Table 2). Two patients (8.7%) had a documented worsened motor exam, and 8 patients (34.8%) had a worsened sensory exam. Only 2 patients reported new dysesthesias or pain following the operation.

Location of Nerve Fibers

Across all patients, motor nerve fibers were identified in all 4 possible locations with respect to the tumor. Direct electrical stimulation of the tumor capsule in a systematic manner revealed motor fibers anterior ($n = 12$), medial ($n = 14$), posterior ($n = 12$), and lateral ($n = 9$; Fig. 1) along the tumor surface. Likewise, all 4 possible locations of nerve fibers were seen on DTI. Magnetic resonance imaging demonstrated nerve fibers anterior ($n = 19$), medial ($n = 18$), posterior ($n = 16$), and lateral ($n = 11$) to the tumor.

Sensitivity, Specificity, PPV, and NPV of DTI in Determining the Location of Nerve Fibers in Relation to the Tumor

We calculated the sensitivity, specificity, PPV, and NPV of preoperative MR DTI as a diagnostic procedure to predict the presence or absence of nerve fibers along the tumor surface as confirmed by direct electrical stimulation of motor nerve fibers. These results demonstrated that for all patients, DTI's sensitivity, or its ability to predict the location of nerve fibers, was 95.7% (Table 3); that is, 95.7%

TABLE 1. Characteristics of patients with peripheral nerve tumors preoperatively demonstrated on DTI

Variable	No. (%)
Age at surgery in yrs	
Median	36
Range	19–69
Sex	
Male	8 (34.8)
Female	15 (65.2)
Diagnosis	
Schwannoma	14 (60.9)
Neurofibroma	4 (17.4)
Fibromatosis	1 (4.3)
Hemangioma	1 (4.3)
Myxoma	1 (4.3)
Neuroma	1 (4.3)
Sarcoma	1 (4.3)
Nerve involved	
Spinal nerve root	5 (21.7)
Trunk	1 (4.3)
Cord	2 (8.7)
Nerve branch	14 (60.9)
Radial n.	4
Common peroneal n.	3
Sciatic n.	3
Ulnar n.	2
Femoral n.	1
Median n.	1
Unable to distinguish	1 (4.3)
Tumor vol in cm ³ (measured on MRI)	
Mean	174.8
Median	9.3
Range	0.1–2016
Extent of resection (%)	
STR	5 (21.7)
GTR	18 (78.3)

n. = nerve; STR = subtotal resection.

of the time, tractography identified fibers in a location that was confirmed via direct intraoperative motor nerve stimulation. The specificity of DTI was only 66.7%. That is, in 33.3% of the patients, DTI identified nerve fibers that were not confirmed on intraoperative electrical stimulation. In addition, we found that the percentage of patients in whom a positive tractography signal mapped correctly to the anatomical fiber location in patients with nerve tumor, or PPV, was 75%. The probability of DTI detecting an area without nerve fibers that was confirmed on intraoperative electrical stimulation was 93.8%. This represents the NPV.

We further analyzed the accuracy of DTI to predict nerve fiber location by tumor size, pathological diagnosis, and tumor location (Table 3). Tumors larger than 100 cm³ in volume (n = 6) reached a 100% sensitivity and NPV. Peripheral nerve tumors that carried a pathological diag-

nosis other than schwannoma or neurofibroma (n = 5) also reached 100% for both sensitivity and NPV calculations. Tumors arising from nerve branches also carried a value of 100% for sensitivity and NPV.

Discussion

High-resolution MR DTI with tractography can offer detailed imaging of peripheral nerves and nerve tumors preoperatively. Because peripheral nerve tumors are often commonly slow-growing benign masses that cause symptoms attributable to mass effect on the associated nerve, the primary goal in resective surgery is debulking the mass and preserving neurological function. To do this, the surgeon must carefully identify nerve fibers and isolate them from the tumor. Using intraoperative electrophysiological monitoring, the location of the nerve can be mapped along the surface of the lesion throughout the resection. However, MR DTI with tractography allows for preoperative nerve fiber localization and mapping. This technique can provide surgeons with a 3D-like map of the tumor in relation to the associated nerve from which it is arising before starting the operation. Having access to this information preoperatively can aid the surgeon in understanding the nerve's relationship to and possible involvement in the tumor. For example, tractography can help elucidate whether the nerve is running along the surface of the tumor capsule or through the bulk of the mass. Although MR DTI with tractography alone should not replace a meticulous surgical technique and careful attention to the anatomy, having tractography information preoperatively allows the surgeon to counsel the patient on the predicted extent of resection and the possible compromise of nerve function and to better plan out the operative approach to safely and effectively proceed with the resection. Having this information in complex cases in which nerve fibers take tortuous courses around multiple surfaces of the tumor may help to spare injury of the nerve through preoperative planning of a safe corridor to begin tumor debulking.

As with any medical procedure, the utility of MR DTI with tractography for nerve tumor resection must be validated (Table 3). The most robust way to compare the anatomical location of nerve fibers with their location as seen on MR tractography would be to resect the tumor en bloc along with its associated nerve fibers and confirm fiber location via formal histological staining techniques. Then this fiber-to-tumor relationship could be directly compared with MR DTI results. However, because the goal of surgery is to preserve function by leaving nerve fibers intact whenever possible, en bloc resection is not a practical option. Intraoperative electrophysiological stimulation can be used to confirm the presence of motor nerve fibers by recording from muscle. We demonstrated that MR DTI carries a high sensitivity (95.7%) for positively detecting motor nerve fibers confirmed by direct electrical stimulation of the tumor capsule. As compared with its sensitivity, DTI's specificity was not as robust (66.7%). The relatively low specificity (and PPV) may relate to the inability of intraoperative electrical stimulation to detect sensory nerve fibers. Specifically, tractography may identify sensory nerve fibers that could not be detected intraoperatively, thus resulting in an apparent false-positive result.

FIG. 2. Magnetic resonance imaging with DTI tractography provides accurate and high-resolution imaging of anatomical nerve fibers in relation to associated nerve tumors. Three representative cases (A–C, D–F, G–I) comparing conventional MRI, DTI, and intraoperative findings in patients with nerve tumors. Conventional structural MRI (short-tau inversion recovery [STIR] sequence, **A**; post-Gd T1-weighted with fat saturation, **D**; IDEAL sequence, **G**) demonstrates the location of the nerve tumor along the length of the nerve fiber. DTI tractography (**B**, **E**, **H**) provides high-resolution images identifying small and larger nerve fascicles in approximation with and entering the tumor. Intraoperative exploration for tumor resection (**C**, **F**, **I**) confirms the location of nerve fibers identified with tractography (arrows and corresponding arrows in **B**, **E**, and **H**).

Further, the fact that our intraoperative stimulation paradigm only accounted for motor and not sensory fibers probably accounts for the 8 cases of worsened sensory exam and the 2 cases of new dysesthesias reported postoperatively (Table 2). Only 2 patients had a worsened motor exam postoperatively, suggesting that the intraoperative identification of motor fibers with electrical stimulation was beneficial. Additionally, the NPV of DTI—that is, the probability that there were no nerve fascicles in a location where the MRI had indicated negative fibers—was high (93.8%), suggesting that tractography may be suitable to identify a “window” from which to approach the tumor resection preoperatively.

We further investigated the utility of MR DTI in detecting nerve fibers in association with a nerve tumor by determining whether tumor size, pathology, or location along the peripheral nerve alters the accuracy of the test (Table 3). If a tumor arises from a distal nerve branch rather than a more proximal nerve root, trunk, division, or cord, the sensitivity, PPV, and NPV improve slightly. Like-

wise, for tumors larger than 100 cm³, sensitivity and NPV improve to 100%; however, specificity and PPV decrease. A diagnosis of a nerve tumor other than schwannoma or neurofibroma results in a slight increase in the robustness of all 4 modalities of accuracy measurements (Tables 1

TABLE 2. Clinical outcomes of nerve tumor resections

Parameter	No. (%)
Motor exam	
Improved	2 (8.7)
No change	19 (82.6)
Worsened	2 (8.7)
Sensory exam	
Improved	7 (30.4)
No change	8 (34.8)
Worsened	8 (34.8)
New dysesthesias or pain	2 (8.7)

TABLE 3. Sensitivity, specificity, PPV, and NPV of MRI DTI in detecting nerve fibers associated with peripheral nerve tumors

Parameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Overall	95.7	66.7	75.0	93.8
Tumor vol				
<100 cm ³	94.9	68.0	82.2	89.5
>100 cm ³	100.0	58.8	50.0	100.0
Diagnosis				
Schwannoma or neurofibroma	94.6	58.1	72.9	90.0
Other	100.0	81.8	81.8	100.0
Location				
Nerve branch	100.0	65.2	80.5	100.0
Other	85.7	68.2	63.2	88.2

and 3). The fact that MR DTI with tractography performs well when detecting nerve fibers where they are present (sensitivity) and when constructing a negative map (NPV; that is, it does not detect motor nerve fibers where they are not located) makes it a potentially useful clinical tool in planning and executing resections of peripheral nerve tumors. Advances in MR DTI combined with studies mapping both sensory and motor nerve fibers will further define its clinical utility and potential.

Conclusions

Using MR DTI with tractography to better characterize nerve tumors offers more information than conventional MRI. Our data suggested that MR DTI with tractography is a useful preoperative tool to identify the location of nerve fascicles when planning and performing nerve tumor resective surgery. Intracranial MR DTI with tractography has become a standard tool in planning and safely resecting brain tumors while preserving the function of deep white matter tracts involved in motor, sensory, or language function. Here, we employed similar principles in the peripheral nervous system to provide better preoperative planning for nerve tumor resection to better understand the relationship of nerve tumors with their associated nerve fascicles and fibers and to better counsel patients on the risks of suffering functional deficits.

Future studies involving other tumor types, such as plexiform neurofibromas and malignant nerve tumors, would be useful to determine whether the infiltrative nature of these tumors causes more distortion of the DTI signal, thereby altering the accuracy of the procedure as a preoperative test.

Magnetic resonance DTI with tractography is an evolving technique that should be used in combination with a meticulous surgical technique and intraoperative electrophysiological monitoring.

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Kliot, Cage, Yuh, Hou, Chin. Acquisition of data: Cage, Yuh, Hou, Birk, Rao, Chin. Analysis and interpretation of data: Kliot, Cage, Yuh, Hou, Chin. Drafting the article: Kliot, Cage. Critically revising the article: Kliot, Cage, Yuh, Simon, Chin. Reviewed submitted version of manuscript: Kliot, Cage, Simon, Chin. Approved the final version of the manuscript on behalf of all authors: Kliot. Statistical analysis: Cage, Yuh. Administrative/technical/material support: Noss. Study supervision: Kliot.

Correspondence

Michel Kliot, Northwestern University Feinberg School of Medicine, NMH/Arkes Family Pavilion Ste. 2210, 676 N. Saint Clair, Chicago, IL 60611. email: michel.kliot@northwestern.edu.