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Diffusion Tensor Imaging of the Ankle as a Possible Predictor of Chemotherapy Induced Peripheral Neuropathy: Pilot Study

Lana Hirai Gimber, MD, MPH[a,*], Linda Garland, MD[b], Elizabeth A. Krupinski, PhD, FSIIM, FSPIE, FATA, FAIMBE[c], Tyson S. Chadaz, MD[d], Michael Schwenk, PhD[e], Bijan Najafi, PhD[f,1], Mihra S. Taljanovic, MD, PhD, FACR[g]

[a] Department of Medical Imaging, The University of Arizona, College of Medicine, Banner—University Medical Center, Tucson, AZ
[b] University of Arizona Cancer Center, Tucson, AZ
[c] Department of Radiology & Imaging Sciences, Emory University, Atlanta, GA
[d] Department of Medical Imaging, The University of Arizona, College of Medicing, Banner—University Medical Center, Tucson, AZ
[e] Heidelberg University, Network Aging Research, Heidelberg, Germany
[f] Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, TX
[g] Department of Medical Imaging, The University of Arizona, College of Medicine, Banner—University Medical Center, Tucson, AZ

Purpose: Chemotherapy induced peripheral neuropathy (CIPN) is seen in up to 75% of treated cancer patients and can drastically limit their medical management and affect quality of life. Clinical and electrodiagnostic testing for CIPN have many pitfalls. Magnetic resonance neurography (MRN) is being increasingly used in the evaluation of peripheral nerves. Diffusion tensor imaging (DTI) shows promise in the workup of peripheral nerves. In this prospective pilot study, we investigated a possible relationship between DTI and peripheral neuropathy of the ankle and foot in cancer patients treated with chemotherapy.

Methods: Nine cancer patients with and without CIPN were clinically evaluated using vibratory perception threshold (VPT) testing. VPT score of >25 Volts defined presence of CIPN. The posterior tibial nerve and branches in both feet were imaged using MRN and DTI. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values were measured at the posterior tibial, medial plantar, and lateral plantar nerves. Measurements for the CIPN group were compared to without CIPN by VPT cutoff. Correlations and possible relationships between DTI parameters and CIPN were analyzed.

Results: A total of 16 feet of 9 enrolled patients were imaged (9 feet with CIPN and 7 feet without CIPN). Average age was 60.6 ± 13.4 years (range: 33-74). Posterior tibial nerve ADC values were significantly lower than the medial plantar nerve ADC values in all feet ($F = 3.50$, $P = 0.04$). We found a correlation with FA and ADC values at specific nerve locations with CIPN, with the left medial plantar nerve FA value and left lateral plantar nerve ADC value demonstrating the strongest positive correlations (0.73 and 0.62, respectively).

Conclusions: The use of DTI for assessing CIPN is challenging but promising. This pilot study provides preliminary data showing correlations between FA and ADC measurements with CIPN and potential utility of DTI as a predictive marker of onset and severity of CIPN in the ankle and foot, which could aid in preventive strategies. Larger, prospective DTI studies are needed to draw definitive conclusions.

Clinical Relevance: MRN with DTI shows promising results as a potential predictive marker of CIPN in the ankle and foot.

Introduction

Chemotherapy induced peripheral neuropathy (CIPN) can occur in up to a third of all patients undergoing systemic anti-cancer therapy and up to 75% of patients undergoing paclitaxel-containing regimens.[1] CIPN often occurs with the use of common chemotherapy agents such as taxanes, vinca alkaloids, and platinum-based alkylating agents. CIPN is caused by drug-induced damage to the peripheral nervous system, although the exact pathophysiology behind CIPN is incompletely understood. The symptoms vary and may include fear of falling and pain with ultimate decrease in quality of life. In patients where these symptoms are moderate to severe in intensity, the chemotherapy regimen is often delayed, reduced, or discontinued, which can adversely affect cancer-related outcomes.

Currently, assessment of peripheral neuropathy relies on electrodiagnostic testing and clinical examination. Vibratory perception threshold (VPT) testing can be performed using a biothesiometer, which is a noninvasive way to accurately measure the threshold of vibration perception. The biothesiometer is commonly used in clinical studies of peripheral neuropathy of all causes and has been shown to be predictive of foot ulceration in

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* Reprint requests: Lana Hirai Gimber, MD, MPH, The University of Arizona, College of Medicine, Banner—University Medical Center, 1501 N Campbell Ave, P.O. Box 245067, Tucson, AZ 85724.

E-mail address: lgimber@radiology.arizona.edu (L.H. Gimber).

[1] Mailing address: 1501 N Campbell Ave, P.O. Box 245067, Tucson, AZ 85724.

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diabetic patients.[2-4] This device is essentially a tuning fork controlled by electricity, where the amplitude of vibration can be set by changing the voltage on the dial. During assessment, the vibrating end of the biothesiometer is held against the sole of the foot for the measurements. There is minimal to no discomfort associated with this procedure. If the patient is unable to sense 25 volts (V) by the biothesiometer, they are deemed to be at risk for foot ulceration.[3]

Routine magnetic resonance imaging (MRI) and magnetic resonance neurography (MRN) are being increasingly used in the evaluation of peripheral nerves. Diffusion tensor imaging (DTI) is a subtype of diffusion-weighted imaging (DWI), which provides functional data and uses the movement of water molecules to reveal nerve microarchitecture and function in addition to providing information on fiber trajectory.[5-10] DTI allows nerve tractography and calculation of quantitative parameters such as the apparent diffusion coefficient (ADC) and fractional anisotropy (FA). ADC describes the mean diffusivity while FA measures the directional preference of free water proton diffusion.[8-10] Recent literature suggests increased ADC values and decreased FA values in peripheral neuropathy cases.[9]

Multiple studies have shown that DTI has the potential to help detect peripheral nerve injury and even reinnervation.[11-13] Naraghi et al[7] reviewed the applications of DTI in the peripheral nervous system in dealing with cervical and lumbar nerve roots, nerve entrapment syndromes, acute nerve injuries, and tumors. A recent study showed that FA values of the tibial and common peroneal nerves near the knee demonstrate moderate diagnostic accuracy and excellent interobserver performance in detecting diabetic peripheral neuropathy.[14] However, only a handful of studies have explored the DTI measurements of nerves at the level of the ankle, with even scarcer studies looking at these measurements in patients with CIPN. These techniques showed promise as a potential predictive marker of CIPN and an aid in evaluating preventive strategies. In our pilot study, we investigated the effect of CIPN on quantitative DTI measurements at the level of the ankle and hindfoot.

Methods

The study was funded by the institution's Graduate Medical Education (GME) Resident Excellence and Leadership Scholarship. Institutional review board approval was obtained. Given the limited funding provided by the scholarship, only 9 cancer patients on chemotherapy without and with subjective CIPN were recruited. There were 4 women and 5 men subjects, with overall mean age of the patients 60.6 years (age range: 33-74 years). Each subject underwent VPT testing to determine the presence or absence of peripheral neuropathy in each ankle and foot. The subjects then underwent MRI of each foot. DTI measurements for the CIPN group were compared to the group without CIPN, with the presence of CIPN defined by VPT. Correlations and possible relationships between DTI parameters and CIPN were analyzed.

Patients

All patients were treated and recruited at the Cancer Center at our institution between September 2014 and January 2015. The medical oncologists recruited patients they saw in clinic who were on chemotherapy and did not complain of peripheral neuropathy before treatment. In addition, a recruitment table was periodically set up in the lobby of the Cancer Center with information regarding the study. Our subjects had several different types of cancers, including pancreatic, colorectal, acute myeloid leukemia, diffuse large B-cell lymphoma, carcinoid, ductal carcinoma in situ, multiple myeloma, and 2 lung adenocarinoma. Five of the subjects had metastatic disease. Inclusion criteria were (1) adult patients with cancer currently on chemotherapy that did or did not have subjective CIPN and (2) patients who did not have subjective peripheral neuropathy before the onset of chemotherapy treatment. Exclusion criteria were patients who were status post lower extremity amputation, had preexisting peripheral neuropathy before chemotherapy, had a diagnosis of diabetes, or could not undergo MRI for reasons such as hardware, claustrophobia, or inability to lay on their backs. Patients less than 18 years old and pregnant patients were not included in this study.

VPT Testing

Each subject in the study underwent VPT testing within a week of the MRI. The plantar aspect of the heel was used for measurement. A VPT reading of less than 25 V was considered normal, whereas a VPT reading of ≥25 V defined CIPN.

MRI Protocol

MR images were acquired with a 16-channel send or receive foot-ankle coil (Siemens, Erlangen, Germany) on a 3T Siemens Skyra Magnetom system (Siemens). All scans were performed of the bilateral ankles with the exception of 2 subjects who could not tolerate completing the examination and therefore had only 1 ankle imaged.

The MRI protocol consisted of the following sequences:

(1) *For anatomy*: 3D sagittal T2-weighted turbo spin echo sampling perfection with application optimized contrasts using different flip angle evolution (SPACE) with inversion pulse of 220 ms. TR/TE 3200/213 ms, turbo factor 100, bandwidth 651 Hz/Px, integrated parallel imaging techniques (IPAT) factor 2, field of view (FOV) 225 × 225 mm^2, matrix size 256 × 256, slice thickness 1.2 mm, no interslice gap, voxel size 0.9 × 0.9 × 1.2 mm^3, 1.4 averages, and 72 slices. Scan time 6 minutes, 21 seconds.
(2) *For increased nerve visualization*: 3D sagittal T2-weighted enhanced steady-state gradient echo reverse fast imaging with steady-state precession (PSIF) DWI with uniform fat suppression achieved using a water-selective excitation technique applied in all 3 directions (slice, read, and phase). TR/TE 9.69/3.45 ms, flip angle 25°, *b* value 50, bandwidth 296 Hz/Px, IPAT factor 2, FOV 160 × 160 mm^2, matrix size 192 × 192, slice thickness 0.80 mm, no interslice gap, voxel size 0.4 × 0.4 × 0.8 mm^3, 1 average, and 88 slices. Scan time 7 minutes, 54 seconds (Fig 1).
(3) *For DTI data*: We customized a 2D axial DWI-weighted echo-planar imaging with manual shimming to optimize homogeneity over the volume of interest, with a strong fat suppression pulse. TR/TE 7100/77 ms, $b0 = 50$ s/mm^2 and nex = 2, $b1 = 600$ s/mm^2 and nex = 5, directions 6, bandwidth 1552 Hz/Px, IPAT factor 2, FOV 180 × 180 mm^2, matrix size 70 × 70, slice thickness 2.0 mm, no interslice gap, voxel size 1.3 × 1.3 × 2.0 mm^3, and 47 slices. Scan time 4 minutes, 41 seconds.

DTI Postprocessing

Postprocessing and analysis was performed on the Siemen's Neuro 3D software. The SPACE and PSIF sequences were reviewed to confirm the location of the nerves in each subject. The PSIF images were used for image fusion and to draw the region of interest within the nerve boundaries and exclude the other

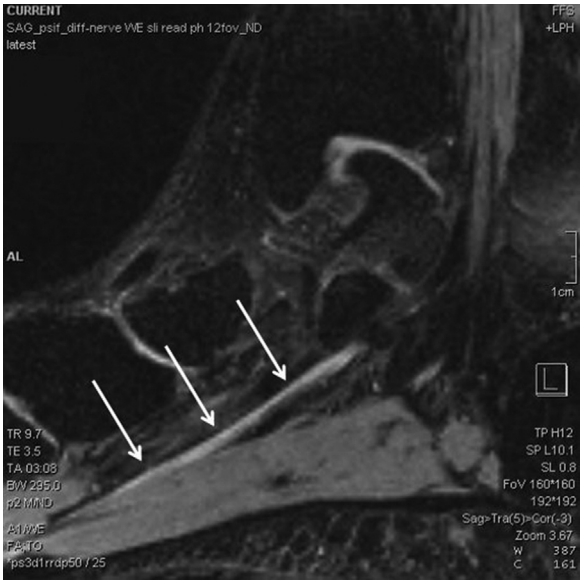

FIG 1. 3D sagittal PSIF MR image of the medial aspect of the ankle. Note normal anatomic appearance of the medial plantar nerve (arrows) showing intermediate signal intensity.

surrounding soft tissue structures (Fig 2). All images were reviewed. Mean FA and mean ADC values were obtained by consensus read by 2 musculoskeletal trained radiologists. The radiologists were blinded to the VPT results during interpretation.

Each ankle or foot measurement were obtained in 3 different locations. For FA and ADC data sampling, the region of interests (ROIs) manually drawn in the transverse or axial plane perpendicular to the long axis of the examined nerve. This was achieved by custom reformation of 3D images in the desired plane to enable optimal visualization of the examined nerve in the short axis while avoiding obliquity. The posterior tibial nerve was outlined at the level of the distal tibial epiphysis. Both the medial and lateral plantar nerves were outlined at the level of the tarsal navicular.

Statistical Analysis

Descriptive statistical analyses were performed. Associations between CIPN, FA and ADC, and nerve location were investigated using 2-way analysis of variance (ANOVA) (where ADC and FA values were dependent variables and CIPN status, nerve and right or left independent variables) and unpaired *t*-tests (StatView v5.0, SAS Institute Inc, Cary, NC). Correlations between VPT measurements with FA and ADC values were identified using Pearson correlation coefficient.

Results

Nine patients were enrolled in the study and a total of 16 feet were imaged, including 9 feet with CIPN and 7 feet without CIPN. Two subjects with CIPN could not tolerate completion of the examination and therefore only 1 feet was imaged in each subject. A VPT measurement of 25V or greater defined the presence of CIPN. Table 1 shows the VPT results in all 16 feet imaged. Mean VPT reading in the 9 feet with CIPN was 60 (range: 35.8-102.5) whereas the mean VPT reading in the 7 feet without CIPN was 6.9 (range: 2.2-15.3) ($t = 6.878$, $P < 0.001$). There was no significant difference in VPT value as a function of right vs left foot ($t = 0.664$, $P = 0.516$), with the mean VPT measurement in the right foot 35.69 (standard deviation = 32.56) and in the left foot 46.16 (standard deviation = 36.87).

The mean FA and ADC values were obtained of the posterior tibial nerve, medial plantar nerve, and lateral plantar nerve in the bilateral feet except for in 2 subjects who could not complete imaging of their left feet. Table 2 shows the results of the FA and ADC values obtained at each nerve location in all subjects.

Given the fact that there were 16 feet and there were no significant differences between right and left feet, in addition to the analyses performed above on the individual level, we combined the feet to increase statistical power. There was no significant difference in FA or ADC values between subjects without CIPN versus subjects with CIPN as defined by VPT testing when both

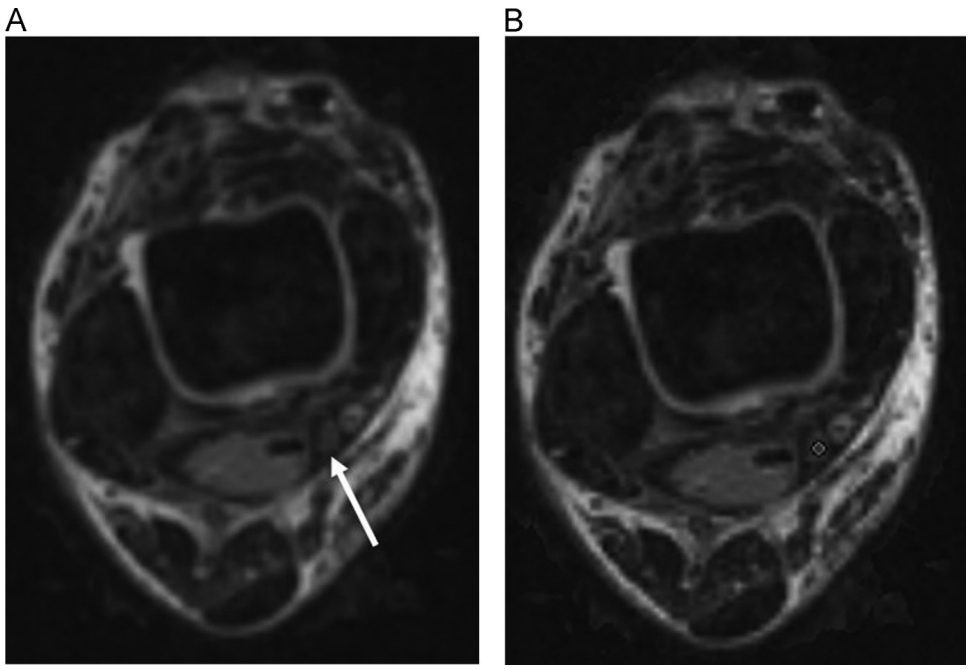

FIG 2. Fused axial DTI and PSIF MR images of the ankle obtained for posterior tibial nerve FA and ADC measurements. In (A), note the normal appearing posterior tibial nerve in short axis (arrow). (B) An ROI (circle) was placed within the posterior tibial nerve boundaries to measure FA and ADC values.

TABLE 1
VPT results in the right and left foot for each subject. A VPT of 25V or more defines CIPN

Subject	Right foot VPT (volts)	Left foot VPT (volts)
1	41.1	46.4*
2	102.5	102.4*
3	6.1	8.5
4	4.8	6.4
5	15.3	46.4
6	57.7	64.7
7	4.8	2.2
8	53.1	69.2
9	35.8	69.5

* Inability to complete study.

feet were combined. The mean FA and ADC values at each nerve level are summarized in Table 3 as a function of CIPN.

Using 2-way ANOVA, there was a significant difference ($F = 3.497$, $P = 0.04$) in ADC as a function of nerve location, with the medial plantar nerve ADC overall being significantly higher than the posterior tibial nerve. In addition, the FA of the posterior tibial nerve in the right foot was significantly higher ($F = 16.07$, $P < 0.0001$) when compared to both the medial plantar nerve and lateral plantar nerve.

Table 4 shows the correlation of VPT measurements with FA and ADC values using Pearson correlation coefficient. The left foot medial plantar nerve FA value and left foot lateral plantar nerve ADC value had the highest correlations with VPT measurements ($P < 0.05$).

Discussion

CIPN occurs frequently in the setting of chemotherapy, often decreasing quality of life and at times necessitating a change in or cessation of chemotherapy regimen. A predictive marker of CIPN would greatly aid clinical treatment, possibly identifying individuals before development of peripheral neuropathy symptoms and initiating early physical therapy, particularly balance training,[15] to decrease the onset and severity of neuropathy symptoms while retaining function. In this study, we evaluated DTI of the tibial nerve branches including the medial and lateral plantar nerves at the level of the ankle and hindfoot in subjects with CIPN.

Previous studies show that DTI already plays a role in detecting and predicting many other diseases. Baumer et al.[11] demonstrated that FA maps can depict mild peripheral neuropathy when compared with nerve conduction studies, diagnosing even subclinical lesions of the ulnar nerve at the elbow. Poretti et al.[16] explored current literature regarding Krabbe's disease, and found that DTI in the brain may serve as a sensitive in vivo biomarker of white matter microstructural damage, predict function after stem cell transplantation, and monitor effects of transplantation on white matter development. Another recent study revealed that DTI, especially FA and radial diffusivity, may yield valid quantitative markers in chronic inflammatory demyelinating polyneuropathy and demonstrated high diagnostic accuracy.[17]

Although there is not much data exploring DTI values of the ankle and foot nerves in those with CIPN, there have been prior studies evaluating DTI of the tibial nerve in other pathologies more proximally in the leg. Many of the studies show a decreasing FA value and increasing ADC value in those with diabetic peripheral neuropathy when measured at the tibial nerve.[14,18] A recent study[19] in patients with diabetic neuropathy demonstrated close

TABLE 2
FA and ADC values obtained at each nerve level in the right and left foot in each subject

	Right foot			Left foot		
	Posterior tibial	Medial plantar	Lateral plantar	Posterior tibial	Medial plantar	Lateral plantar
Subject 1						
FA	0.45	0.43	0.41			
ADC	1.2	1.13	1.15			
Subject 2						
FA	0.37	0.3	0.31			
ADC	1.23	1.48	1.59			
Subject 3						
FA	0.62	0.2	0.33	0.55	0.3	0.33
ADC	1.12	0.91	1.5	0.53	1.52	1.35
Subject 4						
FA	0.41	0.33	0.35	0.44	0.35	0.3
ADC	1.12	1.29	1.26	1.45	1.51	1.4
Subject 5						
FA	0.57	0.29	0.40	0.32	0.31	0.34
ADC	0.74	0.85	1.65	1.21	1.4	1.25
Subject 6						
FA	0.66	0.25	0.24	0.56	0.23	0.28
ADC	0.74	0.93	1.49	1.31	2.46	1.65
Subject 7						
FA	0.57	0.24	0.24	0.40	0.28	3.48
ADC	1.50	1.31	1.31	1.43	1.71	1.4
Subject 8						
FA	0.51	0.25	0.3	0.29	0.25	0.21
ADC	1.30	1.36	1.28	1.26	1.32	1.52
Subject 9						
FA	0.31	0.21	0.19	0.31	0.25	2.17
ADC	1.80	1.79	1.83	1.22	1.41	1.59

TABLE 3
Mean FA and ADC values at each nerve level in each foot compared to VPT measurements

	DTI mean (SD)	VPT mean (SD)	*P* value
Right FA		35.7 (32.6)	
Posterior tibial	0.50 (0.12)*		0.33
Medial plantar	0.28 (0.07)*		0.66
Lateral plantar	0.31 (0.07)*		0.46
Left FA		46.2 (36.9)	
Posterior tibial	0.41 (0.11)		0.32
Medial plantar	0.28 (0.04)		0.12
Lateral plantar	1.02 (1.29)		0.58
Right ADC		35.69 (32.56)	
Posterior tibial	1.19 (0.34)**		0.59
Medial plantar	1.23 (0.31)**		0.25
Lateral plantar	1.45 (0.22)		0.81
Left ADC		46.16 (36.87)	
Posterior tibial	1.20 (0.31)***		0.68
Medial plantar	1.62 (0.39)***		0.84
Lateral plantar	1.45 (0.14)		0.31

* Values with significant differences in the right foot.
** Values with significant differences in the right foot.
*** Values with significant differences in the left foot.

Table 4
Correlation of VPT measurements with FA and ADC values

	Right foot VPT	Left foot VPT
FA		
Posterior tibial	0.31	0.40
Medial plantar	0.15	0.73*
Lateral plantar	0.14	0.244
ADC		
Posterior tibial	0.02	0.16
Medial plantar	0.31	0.11
Lateral plantar	0.18	0.62*

* Values with highest correlations between VPT measurements and DTI values.

associations between the severity of neuropathy and FA values measured in the tibial nerve in addition to good associations with some measurements of motor nerve conduction studies with FA and ADC values.

Our study did not find a significant difference in FA or ADC values between subjects without CIPN versus subjects with CIPN, although there were some correlations with VPT measurements. However, our study did find a significant difference in FA and ADC values as a function of nerve location. We showed that ADC increased distally, with the medial plantar nerve values higher than the posterior tibial nerve values in both feet. In addition, we demonstrated in the right foot that the FA value was significantly higher proximally in the tibial nerve when compared to more distally in the medial and lateral plantar nerves. These findings are in agreement with previous studies suggesting that FA and ADC do change based on location, with FA decreasing distally and ADC increasing distally.[20,21] In contrast, other studies have shown variable results with no change in ADC[22] or no change in FA values.[23]

There were many limitations to this small pilot study, however, the insights into performing DTI in the evaluation of CIPN have been invaluable, particularly dealing with feasibility, time, cost, and statistical variability. These limitations and insights are outlined below, and should be addressed before carrying out a larger study.

First, adequate funding needs to be obtained. The funding for this study only allowed recruitment of 9 patients, making significant differences difficult to statistically assess. Given the high cost of MRI scanner time, a new prospective study with an adequate larger sample size would require a substantial amount of funding. In addition, a portion of the scans will likely be nondiagnostic due to issues such as patient motion, scanner failure, and inability of patients to complete scans. This would have to be calculated into the total funding cost.

Patient recruitment is another issue of importance. For this study, an announcement was made to all oncologists at the cancer center to recruit patients during clinic. Recruitment would likely have been more successful had we instead worked closely with just 1 or 2 oncologists, building a stronger and more personal interdepartmental relationship. In addition, our study population was not ideal, consisting of many very old and sick subjects who were unable to keep still which frequently resulted in motion artifact leading to difficult evaluation of small nerves in the hindfoot. Recruiting a more middle aged and sturdier population, such as with early stage breast cancer, would likely have yielded better results.

One of the more crucial factors when developing a larger study to evaluate DTI should strive to decrease as much statistical variability as possible. A more homogeneous study population is needed. The patient population in our study was very heterogeneous, with various types of cancers and chemotherapy regimens. Working closely with 1 or 2 medical oncologists who deal with a single type of cancer would lead to a more homogeneous subject group. Also, imaging patients before and after administration of chemotherapy to assess changes in the nerve would allow for matched pairs. Additionally, when dealing with the very small nerves in the ankle and foot, we noticed high variability in DTI measurements in different nerves and within the same nerve at different locations. A suggestion for a follow-up study would be to include nerve DTI measurements more proximally in the distal leg to reduce this variability.

As with many studies requiring some type of postprocessing, there is the question of whether the time spent to postprocess is feasible in clinical practice. Even with only 9 patients in this study, the postprocessing was quite cumbersome. The Siemen's Neuro 3D software, which we used for our postprocessing analyses, has a steep learning curve. In addition, it is inefficient to have to switch to a completely different station, which is not always available, for postprocessing. Having the capability to link the postprocessing software to the institution's PACS and have it available at the same reading work station would be essential for this to be implemented in clinical practice.

In conclusion, although our pilot study has several limitations, it is one of the first to evaluate DTI of the tibial nerve branches at the level of the ankle and hindfoot in subjects with CIPN. The differences found in quantitative DTI values with nerve location and mild correlations with VPT measurements in our study suggest that stronger associations may be seen if a larger more robust and homogenous study was performed. Given the differences we observed in ADC and FA as a function of nerve location and using the ADC difference as it was associated with a lower (but significant) *P* value, doubling the sample size would likely yield power greater than 0.80. With the high prevalence and such debilitating effects that CIPN can produce, this area warrants further exploration. Development of an accurate predictive marker of CIPN would greatly improve quality of life and treatment outcomes. The use of DTI for assessing CIPN is challenging but promising. The next steps would include a larger prospective study evaluating larger nerves in the distal leg in a more homogeneous, younger population before and after chemotherapy treatment in addition to correlating DTI findings with pain ratings and nerve conduction studies.

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