Tumor Segmentation of Whole-Body Magnetic Resonance Imaging in Neurofibromatosis Type 1 Patients: Tumor Burden Correlates

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BACKGROUND

Neurofibromatosis Type 1 (NF1) is an autosomal dominant genetic disorder resulting from a defect in the NF1 gene on chromosome 17.[1] The NF1 gene is thought to be a tumor suppressor gene, and its inactivation results in over-activation of the Ras signaling cascade.[2] About 1 in 2000 to 5000 individuals are affected by NF1, predisposing to multiple benign nerve sheath tumors, termed neurofibromas.[1-3] In addition to morbidity caused by mass effects of large benign neurofibromas, NF1 patients also have an approximately 5 to 13% life-time risk of developing malignant peripheral nerve sheath tumors (MPNSTs), which are the main cause of their early mortality, resulting in a decreased life expectancy for NF1 patients versus the general population.[2,4]

Whole-body magnetic resonance imaging (WBMRI) has been used in the surveillance of NF1 patients to detect neurofibromas and screen for MPNSTs.[5] The lack of ionizing radiation allows relatively safe serial use to detect changes in tumor size and potentially identify early MPNSTs.[5] Recently, computerized methods of image processing in this domain have been used to calculate the total body tumor volume (tumor burden),[6] but these methods remain cumbersome. One such technique was limited to only larger internal tumors in the initial studies.[2,6] Additionally, images used in these studies had large slice thicknesses (1 cm) and were performed on 1.[5] Tesla scanners in different centers. These methods could result in missed tumors and/or non-uniform protocolling.

Objective:

The objectives of this study were to: (1) utilize a new method of software-assisted segmentation to determine tumor burden from WBMRIs, (2) examine whether significant relationships exist between tumor burden and clinical and demographic data, and (3) obtain higher resolution WBMRI images on one scanner using a uniform imaging protocol.

METHODS

Subjects

A consecutive series of adults with NF1 who underwent WBMRI for NF1 surveillance between April 2014 and March 2016 were enrolled. Patients were referred as a convenience sample from the Neurofibromatosis clinic at the University of Texas Southwestern Medical Center in Dallas, TX.

Whole-body MRI

All patients underwent imaging using a uniform protocol on a 3 Tesla scanner (Ingenia, Philips, Best, the Netherlands). Three XL torso array coils digitally linked to the posterior spine coils were used to obtain coronal STIR imaging of the head, upper torso, abdomen, and lower extremities (repetition time = 4483 ms, echo time = 40 ms, inversion time = 230 ms, echo train length = 18, slice thickness = 5 mm, interslice gap = 1.5 mm, matrix = 476 x 298, acquisition time per station = 6 minutes 48 seconds).

Image Analysis

WBMRIs were then assessed for motion, breathing, suboptimal fat suppression, and pulsation artifacts for identification of any suboptimal or non-diagnostic sets. All WBMRIs were reviewed for hyperintense soft tissue neurofibromas by consensus between a trained reader and experienced radiologist **(Figure 1)**. Each tumor was classified as superficial (in the skin or subcutaneous tissues) or internal. Additionally, tumors were classified as discrete or plexiform. The trained reader then segmented all identified tumors using a semi-automated mathematical morphology tool from SliceOMatic software (TomoVision, Québec, Canada).

The tool analyzed each slice and used the gradient of intensity between groups of pixels to automatically define borders between hyperintense and hypointense areas. This allowed automated outlining (region growing) of each hyperintense tumor from its relatively hypointense background, which could then be manually tagged **(Figure 2, a-c).** Tagging the same tumor on multiple slices allowed calculation of the tumor volume by the software. Any color bleed-through induced by the automated region growing was scaled back to the tumor margins by the trained reader to ensure accurate representation of the tumor boundary. The segmented WBMRI was then reviewed by the radiologist and trained reader for missed tumors and correct inclusion of the tumor boundaries.

Segmentation yielded the following data for each patient WBMRI: number of total, superficial, internal, and plexiform tumors; total body tumor volume; and total body volume of superficial, internal, and plexiform tumors. Segmentation times were also recorded to assess the length of time required for evaluation.

Statistical analysis

Spearman correlations were used to determine associations between measurement data and continuous demographic data. Such parameters included age, height, weight, and body mass index (BMI). Non-parametric Mann-Whitney U tests were used to examine associations between measurement data and categorical demographic and disease-related data. Such parameters included sex, family history of NF1, history of MPNST, history of NF1-related surgery, and presence of plexiform tumors. All statistical calculations were designed and performed post-hoc using SAS software (SAS Institute Inc., NC, USA).

Figure 1: *Flowchart depicting imaging and segmentation protocol.*

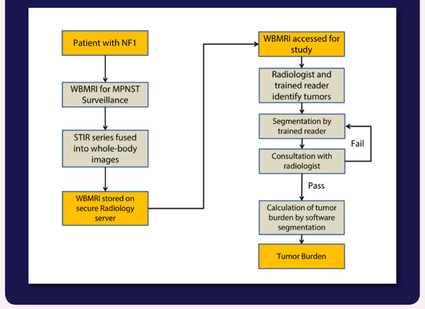
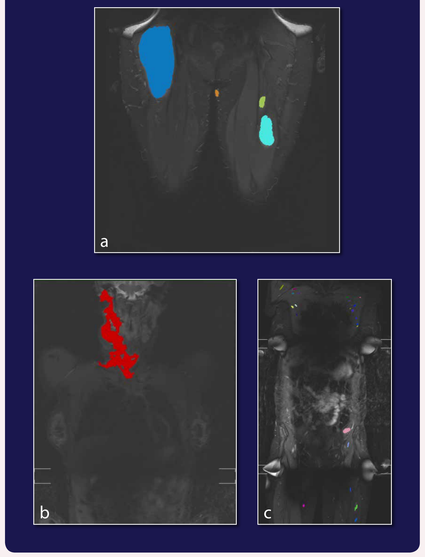


Figure 2: *Segmentation of WBMRI showing: (a) a superficial, discrete neurofibroma (orange) as well as multiple internal, discrete tumors; (b) an internal, plexiform neurofibroma; and (c) multiple internal, discrete neurofibromas.*



RESULTS

Patients

15 patients (42.3 ± 13.6 years, 10 female, 5 male) underwent WBMRI and were studied **(Tables 1 and 2)**. All patients had complete imaging. Only one patient had metal in the lumbar spine from prior surgery, somewhat limiting the evaluation in that region. However, a large MPNST in that area could be easily identified and all other patients had excellent diagnostic imaging without artifacts.

Segmentation times

Segmentation time per patient ranged from 15 to 120 minutes, with an average time of 44.3 minutes and median of 30 minutes. Analysis of segmentation times revealed a significant relationship between number of tumors identified and segmentation time (Spearman's $\rho = 0.9311$, $p < 0.0001$).

Tumor types and volumes

Review of the imaging yielded 2328 tumors. 1582 tumors (68.0%) were determined to be superficial, 746 (32.0%) internal, and 23 (0.988%) plexiform. Only one tumor (0.0430%) was found to be malignant. Tumor counts ranged from 14 to 397 tumors per patient (average 155.2, median 136, **Figure 3)**. Total tumor volume ranged from 6.95 mL to 571 mL (average 153 mL, median 94.6 mL, **Figure 4**). Individual tumor volume ranged from 0.0120 mL to 298 mL (average 0.986 mL, median 0.116 mL). 9 patients (60%) were found to have one or more plexiform neurofibromas (range 1-6 plexiform neurofibromas per patient, average 2.56, median 1).

Statistical correlations

Significant relationships were found between height and total body volume of superficial tumors ($\rho = 0.5966$, $p < 0.02$, **Table 3, Figure 5**), male gender and higher total body tumor volumes ($p < 0.05$, **Table 4, Figure 6**) as well as higher total body volumes of superficial tumors ($p < 0.03$, **Table 4, Figure 7**), and positive family history of NF1 and fewer tumors ($p < 0.05$, **Table 4, Figure 8**). Other factors tested did not reveal significant relationships.

Table 1: Demographics of study population, with percentages in parentheses.

Demographic Factor	NF1 Patients (N = 15)
Mean age (years)	42.3 ± 13.6
Mean height (inches)	64.6 ± 3.4
Mean weight (pounds)	170.7 ± 37.0
BMI	28.5 ± 4.6
Sex	
Female	10 (66.7)
Male	5 (33.3)

Table 2: Clinical factors of study population, with percentages in parentheses.

Clinical Factor	NF1 Patients (N = 15)
NF1 Inheritance	
Familial	7 (46.7)
Sporadic	8 (53.3)
History of MPNST	
Yes	1 (6.7)
No	14 (93.3)
History of NF1 surgery	
Yes	8 (53.3)
No	7 (46.7)
Plexiform Neurofibroma	
Yes	9 (60)
No	6 (40)

Table 3: Results of Spearman correlation between segmentation data and continuous demographic factors.

Measurement	Age	Height	Weight	BMI
# Total Lesions (ρ)	0.17189	0.3831	-0.00806	-0.13238
p value	0.5402	0.1587	0.9772	0.6381
# Superficial (ρ)	0.23256	0.37557	-0.02149	-0.18945
p value	0.4042	0.1677	0.9394	0.4989
# Internal (ρ)	-0.25873	0.08453	0.12545	0.13775
p value	0.3518	0.7645	0.656	0.6245
# Plexiform (ρ)	0.11231	-0.13841	-0.37974	-0.36963
p value	0.6903	0.6228	0.1627	0.1751
Total Volume (ρ)	0.27728	0.49237	0.00716	-0.17694
p value	0.317	0.0622	0.9798	0.5281
Superficial Volume (ρ)	0.23077	0.5966	0.37959	0.24844
p value	0.408	0.0189	0.1629	0.3719
Internal Volume (ρ)	0.34526	0.34861	-0.2274	-0.40393
p value	0.2075	0.2029	0.415	0.1354

Table 4: Results of Mann-Whitney U tests between segmentation data and categorical demographic and clinical factors.

Measurement	Sex	Family History	MPNST History	NF1 Surgery	Plexiform Lesion
# Total Lesions	0.16	0.04	0.13	0.38	1
# Superficial	0.13	0.15	0.13	0.77	0.86
# Internal	1	0.25	0.91	0.69	0.86
# Plexiform	1	0.67	0.33	1	-
Total Volume	0.04	0.12	0.13	0.22	0.26
Superficial Volume	0.02	0.27	0.3	0.45	0.52
Internal Volume	0.24	0.15	0.13	0.39	0.68

Figure 3: *Tumor counts by patient.*

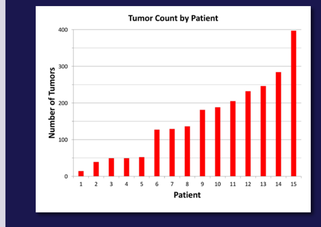


Figure 4: *Tumor burden by patient.*

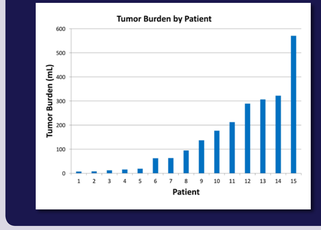


Figure 5: *Scatter plot of superficial tumor volume and height with Spearman correlation line.*

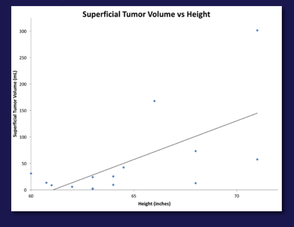


Figure 6: *Categorical scatter plot of tumor burden with sex.*

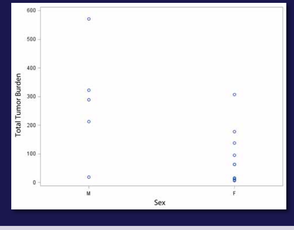


Figure 7: *Categorical scatter plot of superficial tumor volume with sex.*

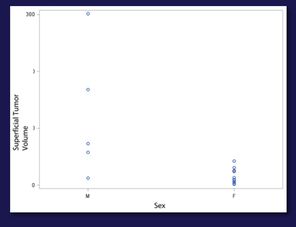
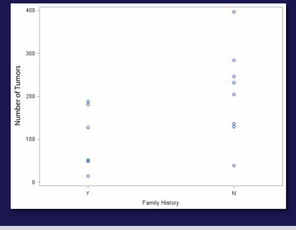


Figure 8: *Categorical scatter plot of tumor counts with NF1 family history.*



DISCUSSION

In this study we used a unique software segmentation technique to analyze WMBRI and determine total body tumor burden in a uniform population. This procedure was shown to be simple and feasible, allowing segmentation in a reasonable time. Several relationships are elucidated by analysis of this data. A possible confounder for the male gender relationship could be that males tend to have more body volume in general, and would therefore be expected to have larger tumors. A possible explanation for observed relationship in patients with a family history of NF1 is that patients aware of their genetic risk may seek medical attention at an earlier age. This may allow more frequent surveillance and earlier detection of internal tumors, allowing intervention if necessary. Additionally, the positive correlation between height and superficial tumor volume may be due to a taller person's larger surface area, which might be expected to give rise to more tumors.

Software aided analysis of WBMRI has been used to measure tumor volumes and quantitate tumor burden previously.[2,6] However, the current study involved 3T imaging with superior signal to noise ratio and thinner slice scanning (3.5mm), which allowed easy capture of the tumors. The segmentation method presented here allows the ability to analyze both smaller (down to 3 mm) tumors and large quantities of the individual tumors. The increase in detailed measurement that this allows is of unclear importance at this stage. However it is apparent that data obtained in this fashion does significantly correlate with certain factors, and further study with larger populations and additional demographic and clinical factors must be pursued.

Limitations of this study lie in the small sample size, preventing representation of NF1 patients as a whole with regards to NF1 inheritance, gender, presence of plexiform neurofibromas, and other factors. Further studies should utilize large, prospectively recruited patient populations. Additionally, this method should be investigated using double reader and repeat studies to ascertain inter- and intra-observer reliability in order to increase confidence in the accuracy and consistency of future applications of this method.

CONCLUSION

To conclude, this study showcases the utility of software segmentation of whole-body MRI in determining tumor burden in patients with Neurofibromatosis Type 1 and provides insight into demographic and clinical correlates. More widespread utilization of segmentation will further increase the usefulness of detailed tumor burden analysis as an imaging biomarker in neurofibromatosis research.

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