Research Square

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Application of 3D slicer three-dimensional reconstruction volume Analysis in Volume Measurement of Type I neurofibromatosis with plexiform neurofibromatosis

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Abstract

Background

Patients with neurofibromatosis type 1 (NF1) accompanied by plexiform neurofibromas have long been regarded as incurable. With disease progression, some patients develop severe limb dysfunction, impaired quality of life, and even malignant transformation into malignant peripheral nerve sheath tumors. In 2023, MEK inhibitor-targeted therapies were introduced in China, and an increasing number of patients have received systemic targeted treatment. Nevertheless, how to accurately evaluate tumor size changes following treatment has become a major focus for clinicians and patients'families.

Objective

3D Slicer software was initially adopted and systematically utilized for volumetric assessment of plexiform neurofibromas.

Methods

A retrospective multicenter analysis was performed on clinical and imaging data from NF1 patients with PNF who received targeted therapy. 3D Slicer software was used for three-dimensional reconstruction and volumetric measurement of PNF lesions. The reproducibility of this method was verified, and a correlation analysis was conducted between tumor volume change rates and the improvement of clinical symptoms.

Results

PNF is characterized by highly irregular morphology and diffuse growth along nerve fascicles, which renders traditional 1D-RECIST and 2D-WHO assessment criteria inadequate for quantitative evaluation due to inherent limitations. In this study, we developed and validated a 3D Slicer-based volumetric measurement protocol for PNF, with standardized operational procedures established. Although the measurement process is relatively time-consuming, the results exhibit excellent reproducibility with a low coefficient of variation for the measured data.

Conclusion

Owing to the rarity of NF1 with PNF, the small patient population, and the recent clinical recognition of this disease over the past three years, the present study has a relatively small sample size, which may have introduced bias in the correlation analysis between tumor volume change rate and clinical symptom improvement. Nevertheless, we successfully established and validated a set of 3D volumetric measurement tools and standardized workflows for PNF that can support clinical decision-making. Most importantly, this study lays a solid foundation for quantitative assessment in subsequent large-sample and long-term follow-up studies of PNF.

Introduction

Plexiform neurofibroma (PNF) is a major and clinically challenging manifestation of neurofibromatosis type 1 (NF1), a rare genetic disorder, and it affects approximately 30% to 50% of NF1 patients [1]. Characterized by diffuse, invasive growth along nerve trunks and their branches, PNF can involve nearly all nerve sheath structures throughout the body, including the paravertebral nerves, brachial plexus, lumbosacral plexus, sciatic nerves, and the neural structures of the chest wall and neck. This unique "tree root-like" growth pattern leads to a progressive increase in the number and volume of tumor lesions, which in turn causes severe morphological deformities, multi-system organ and limb dysfunction, and even carries a risk of malignant transformation into malignant peripheral nerve sheath tumors (MPNST) [2–4]. For decades, NF1 patients with inoperable PNF were considered to have no effective therapeutic options, resulting in poor quality of life and adverse long-term prognosis for affected individuals, predominantly pediatric patients.

The clinical landscape for NF1-PNF has changed dramatically since the introduction of MEK inhibitor-targeted therapy in China in 2023, with selumetinib emerging as the first-line oral targeted drug for inoperable PNF in pediatric and adolescent NF1 patients. Administered at a recommended dose of 25 mg/m² twice daily, selumetinib has been proven to induce significant tumor volume reduction and clinical symptom improvement in clinical trials [10], and it has become the standard systemic treatment for NF1-PNF in clinical practice. However, the accurate evaluation of therapeutic efficacy for PNF remains a critical unmet clinical need, as the irregular morphology and diffuse growth of PNF make conventional tumor assessment criteria—including the one-dimensional Response Evaluation Criteria in Solid Tumors (1D-RECIST 1.1) and two-dimensional World Health Organization (2D-WHO) standards—largely inadequate for quantitative volume measurement [5, 6]. These traditional methods, designed for regular, well-circumscribed solid tumors, often lead to underestimation of actual tumor burden and failure to detect subtle volume changes or internal structural alterations (e.g., cystic necrosis) induced by targeted therapy in PNF lesions.

In response to this clinical challenge, the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) international guidelines have identified volumetric measurement as the recommended gold standard for quantitative efficacy assessment of PNF [7, 8]. Despite this

recommendation, the clinical application of volumetric measurement for PNF is still in the exploratory stage worldwide, with a lack of standardized, reproducible operational protocols suitable for routine clinical practice—especially in the context of Chinese clinical settings, where targeted therapy for NF1-PNF has only been available for a short period. 3D Slicer, an open-source medical image post-processing software, has been widely and successfully applied in thoracic surgery, neurosurgery, and orthopedics for three-dimensional (3D) reconstruction and volumetric analysis [19–21], yet its application for the standardized volumetric measurement of PNF in NF1 patients has not been systematically reported. In this study, we aimed to establish and validate a 3D Slicer-based volumetric measurement protocol for PNF, verify the reproducibility of this method, and explore the correlation between tumor volume change rates induced by selumetinib therapy and the improvement of clinical symptoms in pediatric NF1-PNF patients.

Methods

1. **Clinical data**

Neurofibromatosis type 1 with plexiform neurofibroma (NF1-PNF) is a rare pediatric genetic disorder with a low incidence rate. This retrospective multicenter study enrolled 14 pediatric patients who met the established diagnostic criteria for NF1 and were complicated with inoperable PNF, all of whom received first-line targeted therapy with oral selumetinib in accordance with clinical practice guidelines. The standardized selumetinib dosing regimen was strictly followed for all patients: 25 mg/m² per dose, administered twice daily with regular clinical follow-up to monitor treatment response and adverse events.

Clinical demographic and therapeutic data were systematically collected, including age, gender, tumor anatomical location, selumetinib treatment duration, surgical history (if any), and the degree of clinical symptom improvement post-treatment. A total of 20 tumor sites were included in the final volumetric analysis, as some patients presented with multiple PNF lesions in distinct anatomical regions, and each lesion was measured independently to ensure data accuracy. Given the rarity of NF1-PNF and the short clinical application time of selumetinib in China, the inherent limitation of a small sample size was acknowledged, with the primary research focus on establishing and validating the 3D Slicer-based volumetric measurement protocol for PNF.

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of the Affiliated Hospital of Qingdao University(QYFYWZLL30725).Written informed consent for participation in the study was obtained from the patient's legal guardian.

2. Image data

Magnetic resonance imaging (MRI) scans were performed on all enrolled patients at the baseline (pre-treatment) and scheduled follow-up time points (post-treatment) to obtain serial imaging data for volumetric comparison. All MRI examinations were conducted on a Siemens MAGNETOM Altea scanner with a standardized axial slice thickness of 3 mm; T2-weighted imaging (T2WI) and short tau inversion recovery/flexible (STIR/FLEX) sequences were uniformly used for all scans to ensure high signal contrast between PNF lesions and normal surrounding tissues. All imaging data were exported and stored in Digital Imaging and Communications in Medicine (DICOM) format, the universal standard for medical image post-processing, to ensure compatibility with 3D Slicer software and eliminate format-related analysis errors.

3. Three-dimensional reconstruction methods and volume measurement

Three-dimensional image post-processing and volumetric measurement were performed using 3D Slicer software (Version 5.8.1), an open-source, cross-platform medical image analysis tool. To ensure operational consistency and minimize inter-observer variability (a key consideration for rare disease research with limited experienced operators), all 3D reconstruction and volumetric segmentation procedures were completed by a single senior radiologist with more than 10 years of experience in pediatric neuroradiology and medical image post-processing.

To evaluate the intra-observer reproducibility of the established protocol, the same radiologist repeated the tumor segmentation and volumetric measurement of all 20 PNF lesions at two separate time points with a 2-week interval, with no access to the initial measurement results during the repeat assessment to avoid bias. The coefficient of variation (CV) was calculated to quantify measurement reproducibility using the standard formula: CV = (standard deviation / mean volume) × 100%, with a lower CV value indicating higher measurement reliability.

A standardized, step-by-step operational protocol for PNF 3D reconstruction and volumetric measurement was established and strictly followed, with the detailed steps as follows:

1）DICOM data import: The baseline and follow-up MRI DICOM datasets of the target PNF lesion(s) were imported into the 3D Slicer platform, with image series aligned and normalized to eliminate spatial distortion;

2）Target tumor segmentation and extraction: The Segment Editor module was opened, and a dedicated segmentation layer was created and renamed for each target PNF lesion to distinguish multiple lesions in the same patient. T2WI and STIR/FLEX sequences were co-referenced for segmentation to

optimize lesion boundary identification. The Threshold tool was first used to perform semi-automatic labeling of PNF tissues based on MRI signal intensity thresholds (optimized for each anatomical site); the Paint, Draw, and Level Tracing tools were then used for manual fine-tuning of the tumor boundary to exclude normal surrounding tissues (e.g., nerves, muscles, blood vessels) and ensure accurate delineation of the entire PNF lesion, including diffuse micro-lesions along nerve fascicles;

3、3D model visualization: The visualization parameters (e.g., opacity, color, surface smoothness) of the segmented 3D model were adjusted to clearly display the spatial morphology and anatomical location of the PNF lesion, with multi-lesion models labeled with distinct colors for easy identification;

4、Volumetric calculation: The 3D Slicer software automatically calculated the volume of the accurately segmented PNF tissue in cubic centimeters (cm^3), with all quantitative volume data exported in a tabular format for subsequent statistical analysis and comparison.

4. Therapeutic Efficacy Evaluation Criteria

For objective, quantitative, and standardized assessment of PNF therapeutic efficacy, we referenced the clinical trial consensus statement for selumetinib sulfate and the **Response Evaluation Criteria in Solid Tumors (RECIST)** [9]. Efficacy was classified into four grades based on tumor volume change relative to baseline:

- **Complete Response (CR)**: Complete disappearance of the target tumor lesion;
- **Partial Response (PR)**: A ≥ 20% reduction in target tumor volume compared with baseline. Initial PR findings are unconfirmed and require reconfirmation by follow-up imaging within 3–6 months; PR maintained for ≥ 6 months is defined as sustained PR;
- **Progressive Disease (PD)**: A ≥ 20% increase in target tumor volume compared with baseline or the time of best response after PR confirmation. The appearance of new lesions or unequivocal progression of existing non-target lesions is also classified as PD;
- **Stable Disease (SD)**: Tumor volume changes that do not meet the criteria for PR or PD.

5. Clinical Correlation Analysis

- All enrolled patients underwent regular clinical follow-up in parallel with imaging assessments, with clinical symptom improvement systematically evaluated using a panel of validated, standardized assessment scales tailored to the main clinical manifestations of PNF (pain, motor dysfunction, morphological deformities, and quality of life). The specific scales used for each clinical outcome were as follows:
- 11-point Numerical Rating Scale (NRS-11) [10]: For the quantitative assessment of pain intensity associated with PNF lesions (0 = no pain, 11 = worst imaginable pain);
- Likert Satisfaction Scale (1932) [11]: For the evaluation of patient/caregiver-reported quality of life related to PNF symptoms and treatment (5-point scale, with higher scores indicating better quality of life);
- Society of Fetal Urology (SFU) classification [12]: For the assessment of hydronephrosis severity in patients with PNF involving the urinary system;
- Quick Disabilities of the Arm, Shoulder and Hand (QuickDASH) Scale [13]: For the quantitative evaluation of upper limb motor function in patients with PNF affecting the upper extremities;
- American Orthopaedic Foot & Ankle Society (AOFAS) Ankle-Hindfoot Scale [14]: For the assessment of lower limb motor function in patients with PNF involving the lower extremities (ankle/hindfoot).

All scale score data were collected at the baseline and the same follow-up time points as the MRI assessments, with raw scores collated and standardized for subsequent statistical analysis. To unify the scoring criteria and ensure directional consistency across different scales (higher scores indicating better clinical outcomes for all scales), all raw scale scores were converted to a uniform 10-point system prior to analysis. This standardization step eliminated the bias caused by different original scoring ranges and enabled an accurate and objective exploration of the correlation between the percentage change in PNF volume and the improvement in clinical symptoms.

6. Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics 26.0 software (IBM Corp., Armonk, NY, USA), with all statistical tests two-tailed. A normality test (Shapiro-Wilk test) was first performed on all continuous measurement data (e.g., tumor volume, scale scores); the results confirmed a non-normal distribution of all data, which is consistent with the characteristics of rare disease research with small sample sizes.

The Spearman rank correlation analysis was therefore used to assess the correlation between the percentage change in PNF volume and the improvement in clinical symptom scores (pain, quality of life, motor function). A Bonferroni correction was applied for multiple comparisons to adjust the P value and reduce the risk of type I error, a critical statistical step for small sample size studies. A corrected P value < 0.05 was considered statistically significant for all analyses, with the 95% confidence interval (95% CI) reported for all correlation coefficients to quantify the precision of the correlation estimates.

Results

1、Clinical data statistical results

A total of 14 pediatric NF1-PNF patients (20 tumor sites) who received standardized selumetinib targeted therapy were included in the final analysis, with their baseline demographic, clinical and therapeutic characteristics summarized in Table 1. The study cohort had a median age of 8 years (range: 3–15 years) and a male-to-female ratio of 6:8 (42.9%:57.1%). All patients strictly adhered to the recommended selumetinib dosing regimen (25 mg/m² twice daily) for a median treatment duration of 14 months (range: 3–26 months), with only 2 patients (18.2%) having a prior surgical history for PNF.

The baseline tumor burden was heterogeneous across the cohort, with a median tumor volume of 101.831 cm³ (range: 4.046–644.92 cm³) for all 20 measured PNF lesions; the tumors were distributed across multiple anatomical sites, with the head and neck being the most common (7 sites), followed by the limbs (5 sites), spine (2 sites), pelvic cavity (2 sites), and single lesions in the retroperitoneum, hip and sacrococcygeal region, respectively.

All patients experienced treatment-related adverse events of varying degrees during selumetinib therapy, with cutaneous acne being the most frequent (78.6%, 11/14), followed by diarrhea and constipation (28.6% each, 4/14) and alopecia (21.4%, 2/14). All adverse events were mild to moderate and were effectively managed with symptomatic supportive treatment, with no treatment discontinuation due to severe adverse events observed in the cohort.

Based on the 20 measured tumor sites, clinical symptoms associated with PNF were categorized by manifestation: pain was the most prevalent symptom (65.0%, 13/20), followed by morphological deformities (30.0%, 6/20) and organ/limb dysfunction (25.0%, 5/20). The dysfunctional lesions included 1 gastrointestinal, 1 urinary, 1 finger, and 2 ankle lesions, consistent with the anatomical distribution of the measured PNF sites.

Table 1
Baseline Demographic and Clinical Characteristics of Enrolled Patients (*n* = 14)

Characteristic Category	Index	Value (Median, Range) / Proportion (%)
Demographic data	Male/Female, n (%)	6 (42.9)/8 (57.1)
	Age, years	8 (3–15)
Tumor location, n	Head and neck (brain/tongue/maxillofacial/neck)	7
	Spine (paravertebral/intraspinal)	2
	Retroperitoneal	2
	Pelvic cavity	2
	Limbs	5
	Hip	1
	Sacrococcygeal region	1
Therapeutic characteristics	Targeted drug (selumetinib), n (%)	14 (100)
	Treatment duration, months	14 (3–26)
	Surgical history, n (%)	2 (18.2)
Baseline tumor burden	Median tumor volume, cm³	101.831 (4.046–644.92)
Clinical symptoms (n = 20 sites), n (%)	Pain	13 (54.2)
	Dysfunction	5 (20.8)
	Morphological deformities	6 (25.0)

Footnotes:

a Tumor sites: 20 lesions from 14 patients.

b Prior surgical history: surgical resection or biopsy for PNF before selumetinib treatment.

c Adverse events: all were grade 1–2 and manageable with symptomatic treatment.

2、3D Slicer 3D reconstruction results

All 20 PNF lesions were successfully reconstructed and volumetrically measured using the standardized 3D Slicer protocol established in this study. Radiological imaging in Fig. 1(A, B, C)confirmed the typical morphological characteristics of PNF: diffuse, irregular growth along nerve fascicles with

ill-defined boundaries, and post-selumetinib therapy, cystic changes and necrotic foci were clearly identified within the parenchyma of multiple PNF lesions (Fig. 2)—morphological alterations that cannot be accurately captured or quantified by conventional 1D/2D assessment methods.

The 3D Slicer software enabled accurate delineation of the entire PNF lesion, including diffuse micro-lesions along nerve trunks, via the combined use of semi-automatic Threshold labeling (based on site-optimized MRI signal intensity thresholds) and manual fine-tuning with Paint, Draw and Level Tracing tools. For large-volume PNF lesions with satellite foci and intratumoral cystic necrosis, the software allowed for separate segmentation and volumetric measurement of the necrotic/cystic areas (Fig. 2), providing detailed structural information beyond total volume quantification. For patients with multiple PNF lesions (Fig. 3), independent segmentation layers were created for each lesion with distinct color labeling, and the 3D models were fused for integrated volumetric analysis; the software automatically generated quantitative volume tables for each target lesion, enabling site-specific efficacy assessment.

The primary practical limitation of the 3D Slicer-based protocol was the time required for manual segmentation and fine-tuning: the average processing time for a single PNF lesion was 30–60 minutes, while lesions with complex anatomical locations and severe diffuse growth required more than 90 minutes of post-processing time.

Intra-observer reproducibility analysis confirmed the high reliability of the established protocol: the coefficient of variation (CV) for repeated volumetric measurements of all 20 PNF lesions by the coefficient of variation ranged from 0.1636% to 8.8114%, indicating minimal measurement variability and excellent consistency of results obtained at two time points with a 2-week interval.

Each PNF lesion was independently reconstructed with distinct color labeling; fused 3D models enable comprehensive whole-body volumetric analysis of tumor burden. The software-generated quantitative volume tables provide site-specific volume data, supporting individualized efficacy assessment of selumetinib therapy for multi-focal PNF.

3. Comparison of Traditional Assessment and 3D Slicer-Based Volumetric Measurement

A direct comparative analysis of 1D-RECIST (longest diameter) and 2D-WHO (perpendicular diameter product) criteria with the 3D Slicer-based volumetric measurement was performed for all 20 PNF lesions, with key findings summarized in Table 2. Traditional 1D/2D methods, designed for regular, well-circumscribed solid tumors (e.g., nephroblastoma, hepatoblastoma), were found to be inherently inadequate for PNF assessment due to the tumor’s unique "tree root-like" diffuse growth pattern and therapy-induced intratumoral structural changes.

Only one PNF lesion (pelvic cavity of Patient P10) exhibited a relatively regular morphology that allowed for measurement by traditional methods at baseline; however, post-selumetinib cystic necrosis rendered traditional methods unable to reflect the actual volume and structural changes of this lesion. In contrast, the 3D Slicer-based method accurately captured both the total volume change and the development of intra-tumoral cystic/necrotic foci for all lesions, providing a true reflection of the actual tumor burden.

Compared with traditional methods, the 3D Slicer-based volumetric measurement demonstrated superior performance in all key assessment dimensions: it effectively eliminated the severe underestimation of actual tumor volume caused by 1D/2D methods, exhibited high sensitivity for detecting subtle, heterogeneous volume changes induced by targeted therapy, and provided rich quantitative and qualitative data (total volume, partial structural volume, 3D morphological models, internal structural characteristics). Most importantly, the traditional methods showed marked subjective variability in the selection of the "longest diameter", while the 3D Slicer-based method achieved high reproducibility with a unified segmentation protocol and a low intra-observer CV with the coefficient of variation ranged from 0.1636% to 8.8114%

Table 2
Comparison of Plexiform Neurofibroma Volumetric Measurement: Traditional Methods vs. 3D Slicer-Based Reconstruction

Comparison Index	Traditional Methods (1D-RECIST/2D-WHO)	3D Slicer-Based Three-Dimensional Reconstruction	Key Notes
Measurement principle	1D (longest diameter) / 2D (perpendicular diameter product)	3D total volumetric measurement	PNF's "tree root-like" morphology makes single diameter unable to reflect true tumor burden; volume is the most direct geometric parameter for this complex tumor form
Capture of diffuse/irregular features	Poor; severe underestimation of actual tumor volume	Excellent; layer-by-layer segmentation delineates all scattered lesions along nerve fascicles	Only 3D volumetric measurement truly reflects actual PNF tumor burden
Efficacy assessment sensitivity	Low; only detects significant volume changes	High; sensitively detects subtle, heterogeneous volume changes	Targeted therapy-induced necrosis/cystic changes alter total volume but not always longest diameter—3D Slicer enables earlier, more sensitive efficacy identification
Measurement data richness	Single linear/2D area values only	Total volume, partial volume changes, 3D morphological models, internal structural characteristics	Intuitively reflects tumor-induced compression of surrounding tissues—key clinical information unavailable from linear data
Reproducibility and objectivity	Marked subjective variability in "longest diameter" selection	High reproducibility via unified segmentation protocol; stable intra-observer CV	3D Slicer CV(0.1636% to 8.8114%) in this study, confirming stable, reliable measurements

Footnotes:

a 1D-RECIST: longest diameter measurement.

b 2D-WHO: product of the longest perpendicular diameters.

c Intra-observer CV: coefficient of variation from two repeated measurements at 2-week interval.

d Only 1/20 lesions could be measured by traditional methods at baseline.

4. Correlation Between Tumor Volume Change Rate and Clinical Symptom Improvement

Volumetric measurements of the 20 PNF lesions at baseline and two scheduled follow-up time points were completed using 3D Slicer, with the percentage change in tumor volume calculated for each lesion (Table 3); the results showed significant heterogeneity in volume change rates across anatomical sites, with volume reduction ranging from − 86.47% to a slight increase of + 42.67% (Patient P14, maxillofacial region). All patients in the cohort exhibited clinical symptom improvement to varying degrees during follow-up, with standardized scale scores converted to a uniform 10-point system for correlation analysis.

Descriptive statistical analysis of the cohort suggested a qualitative positive trend between the percentage reduction in PNF tumor volume and the improvement in clinical symptoms (pain, quality of life, organ/limb function). However, formal Spearman rank correlation analysis (with Bonferroni correction for multiple comparisons) revealed no statistically significant correlations between the tumor volume change rate and any of the clinical symptom improvement outcomes (Table 4). Specifically:

Pain score improvement: $\rho = 0.386$, 95% CI: -0.30 ~ 0.82, $P = 0.270$ (corrected $P = 0.810$);

Quality of life (QoL) satisfaction score improvement: $\rho = 0.289$, 95% CI: -0.968 ~ 1.000, $P = 0.638$ (corrected $P = 0.900$);

Organ/limb function score improvement: $\rho = 0.000$, 95% CI: -1.000 ~ 1.000, $P = 1.000$ (corrected $P = 1.000$).

All correlation coefficients were low, and all corrected P values were > 0.05, indicating no statistically significant linear correlation between tumor volume change rate and the degree of clinical symptom improvement in this study cohort.

Table 3
3D Slicer-Based Tumor Volumetric Measurement and Clinical Symptom Improvement Scores (*n* = 14)

Patient	Lesions	Baseline Volume (cm^3)	Follow-up 1 Volume (cm^3)	Volume Change 1 (%)	Follow-up 2 Volume (cm^3)	Volume Change 2 (%)	Pain Score (Baseline/Follow-up/Change)	QoL Satisfaction Score (Baseline/Follow-up/Change)	Function Score (Baseline/Follow-up/Change)
P1	Maxillofacial region	67.775	43.181	-36.28	45.231	-33.26	-/-/-	4/2/-2	-/-/-
P2	Pelvic cavity	365.872	121.306	-66.84	117.284	-67.94	-/-/-	-/-/-	2/0/-2
	Hip	101.831	26.392	-74.10	26.331	-74.14	-/-/-	3/2/-1	-/-/-
P3	Paravertebral	29.716	14.112	-52.51	14.022	-52.81	4/0/-4	-/-/-	-/-/-
	Intraspinal	4.046	2.170	-46.37	2.03	-49.83	4/0/-4	-/-/-	-/-/-
P4	Hand	12.548	6.322	-49.62	5.877	-53.16	-/-/-	-/-/-	1/2/+1
	Ankle	54.926	25.822	-52.99	22.793	-58.50	6/1/-5	-/-/-	63/91/+28
P5	Brain	11.042	8.312	-24.72	7.992	-27.62	4/0/-4	-/-/-	-/-/-
P6	Brain	4.995	3.251	-34.91	3.011	-39.72	3/0/-4	-/-/-	-/-/-
P7	Neck	292.039	144.731	-50.44	148.374	-49.19	6/0/-6	4/3/-1	-/-/-
P8	Calf	133.861	84.371	-36.97	80.761	-39.67	3/1/-2	-/-/-	-/-/-
	Ankle	40.599	26.024	-35.91	26.145	-35.60	-/-/-	-/-/-	48/79/+31
P9	Neck	254.087	180.382	-29.01	185.382	-27.04	7/2/-5	4/3/-1	-/-/-
P10	Retroperitoneal	112.995	57.238	-49.34	57.012	-49.54	-/-/-	-/-/-	3/0/-3
	Pelvic cavity	552.940	273.381	-45.13	265.273	-52.02	3/0/-3	-/-/-	-/-/-
	Hip	277.645	48.723	-82.45	47.501	-82.89	-/-/-	2/0/-2	-/-/-
P11	Thigh	644.920	206.034	-68.05	198.852	-69.17	8/3/-5	-/-/-	-/-/-
P12	Tongue	11.166	11.089	-0.69	9.870	-11.61	6/0/-6	-/-/-	-/-/-
P13	Calf	8.910	5.967	-33.03	5.680	-36.25	4/0/-4	-/-/-	-/-/-
P14	Maxillofacial region	254.087	443.190	+ 42.67	427.880	+ 40.62	7/3/-4	2/4/+2	-/-/-

Footnotes:
a Volume change rate (%) = [(Follow-up volume − Baseline Volume) /Baseline Volume] × 100%.

Negative value = volume reduction; positive value = volume increase.

b Lesions from the same patient are marked with the same patient ID.

Table 4
Spearman Rank Correlation Analysis: Tumor Volume Change Rate vs. Clinical Symptom Improvement Scores (*n* = 14)

Clinical Assessment Scale	Correlation Coefficient (ρ)	P Value	Bonferroni Corrected P Value	95% Confidence Interval (CI)
Pain Score	0.386	0.270	0.810	-0.300 ~ 0.820
Quality of Life Satisfaction Score	0.289	0.638	0.900	-0.968 ~ 1.000
Organ/Limb Function Score	0.000	1.000	1.000	-1.000 ~ 1.000

Footnotes:

a Correlation analysis: Spearman's rank correlation coefficient (ρ).

b P-value: two-sided; corrected P-value with Bonferroni adjustment for multiple comparisons.

c Statistical significance: corrected $P < 0.05$.

d Clinical scores were standardized to a uniform 10-point system.

5. Analysis of Tumor Volume Changes Across Different Lesion Sites

Analysis of tumor volume change rates across different lesion sites revealed significant heterogeneity (Fig. 4). The hip lesions exhibited the most pronounced volume reduction, with a median change rate of approximately − 80%. Maxillofacial lesions showed the widest range of volume changes (-35% to 42%), encompassing both tumor growth and shrinkage. Distal extremity sites (e.g., ankle, calf) demonstrated a relatively consistent trend of volume reduction, with median rates ranging from − 40% to -30%.

Boxplots display the median (red line) and data variability of PNF volume change rates (%), with scatter points representing individual lesion measurements. Negative values indicate tumor volume reduction, and positive values indicate volume increase. Hip lesions exhibited the most significant volumetric shrinkage, tongue lesions the minimal change, and maxillofacial lesions the highest inter-lesion variability (including the only observed volume increase in this cohort).

Discussion

Plexiform neurofibromas (PNF) represent one of the most debilitating manifestations of neurofibromatosis type 1 (NF1), a rare genetic disorder that disproportionately affects pediatric patients. The diffuse, invasive growth of PNF along nerve fascicles not only leads to progressive morphological deformities and multi-system dysfunction but also carries a risk of malignant transformation, severely compromising patient quality of life and long-term prognosis [1, 15–17]. For decades, surgical resection was the only available intervention for PNF, yet it is often unfeasible for diffuse or deep-seated lesions, leaving most patients with no effective treatment options until the introduction of MEK inhibitor-targeted therapy. The clinical application of selumetinib in China in 2023 has revolutionized the management of inoperable NF1-PNF, but it has also highlighted an urgent clinical need for accurate, reproducible methods to assess therapeutic efficacy—one that conventional 1D-RECIST and 2D-WHO criteria are unable to meet due to their inherent limitations for irregular, diffuse tumors.

This study addressed this unmet need by establishing and validating a standardized 3D Slicer-based volumetric measurement protocol for PNF in pediatric patients receiving selumetinib therapy, and it is the first systematic report of this open-source software's application for PNF volumetric assessment in a Chinese clinical setting. Consistent with the recommendations of the REiNS international guidelines [7, 8, 18], our findings confirm that volumetric measurement is far superior to traditional 1D/2D methods for evaluating PNF, a tumor type characterized by a "tree root-like" growth pattern and therapy-induced intra-tumoral structural changes (e.g., cystic necrosis). While 3D Slicer has been widely used for volumetric analysis in thoracic surgery, neurosurgery, and orthopedics [19–21], its application for PNF had not been formally validated prior to this study; our results fill this gap by demonstrating that the software can accurately delineate diffuse PNF lesions—including micro-lesions along nerve trunks—and capture both total volume changes and internal structural alterations that are invisible to traditional diameter-based measurements. Notably, the coefficient of variation ranged from 0.1636% to 8.8114%, which falls within the 0.6%–6.8% range of CV values reported in international studies for tumor volumetric measurement [23], confirming the method's high reproducibility and reliability for PNF efficacy assessment in clinical practice and research.

In the course of establishing this protocol, we identified key practical insights for 3D Slicer's application in PNF volumetric measurement that are critical for standardization in routine clinical use. First, site-optimized MRI signal intensity thresholds, combined with semi-automatic segmentation and manual fine-tuning, enable complete, blind-spot-free delineation of PNF lesions in all anatomical sites—an essential step for avoiding under-measurement of diffuse disease. Second, the software's ability to segment and measure intra-tumoral cystic/necrotic areas independently provides a novel auxiliary method for efficacy evaluation, particularly for large-volume PNF where total volumetric measurement is time-consuming; this structural analysis may even capture therapeutic changes that total volume alone cannot reflect. Third, leveraging the typical "target sign" of PNF on MRI to extract only the peripheral high-signal tumor area for modeling can optimize measurement efficiency without compromising accuracy, a key adaptation for clinical settings with limited post-processing time. These insights not only validate 3D Slicer as a robust tool for PNF but also provide a practical, actionable workflow for clinicians and radiologists new to this technology.

A key finding of our study was the absence of a statistically significant correlation between PNF tumor volume change rate and the improvement of clinical symptoms (pain, quality of life, organ/limb function), despite a qualitative positive trend observed in descriptive analysis. This result, which contradicts the initial clinical hypothesis, can be attributed to four interrelated factors, all of which are closely tied to the inherent characteristics of NF1-PNF and the exploratory nature of this study. First, the small sample size (14 patients, 20 tumor sites) is the most significant limitation; NF1-PNF is a rare disease, and selumetinib has only been available in China for a short period, limiting the number of eligible patients for this retrospective multicenter analysis. Small sample sizes are inherently underpowered to detect weak linear correlations, and it is highly likely that a real but subtle positive correlation between volume reduction and symptom improvement exists, which would only be identified with a larger cohort of patients. Second, there is a clear asynchrony between tumor volume change and clinical symptom improvement: selumetinib induces rapid intra-tumoral necrosis and volume reduction, but the reversal of long-term nerve and muscle compression caused by PNF requires an extended follow-up period—meaning clinical symptoms may improve with a lag relative to radiological changes. Third, insufficient sensitivity of existing clinical assessment scales may have masked subtle improvements; a 20% reduction in PNF volume can significantly alleviate patient discomfort, but the scales used in this study (e.g., NRS-11, QuickDASH) were not specifically validated for NF1-PNF and may lack the resolution to detect these nuanced clinical changes. Fourth, PNF's response to selumetinib is multidimensional, extending far beyond simple volume reduction: intra-tumoral solid-to-cystic transformation and softening may alleviate nerve compression more effectively than volume change alone, and these structural alterations—rather than total volume—may have a closer correlation with clinical symptom improvement.

It is important to acknowledge the other inherent limitations of this study, which are primarily related to its retrospective design and the early stage of selumetinib's clinical application in China. The short follow-up duration (median 14 months) limits our ability to assess the long-term correlation between volume change and clinical outcomes, and the lack of inter-observer reproducibility analysis—due to the limited number of radiologists with experience in PNF post-processing—prevents us from validating the protocol's consistency across different operators. Additionally, the manual segmentation required for 3D Slicer is time-consuming (30–90 minutes per lesion), which may limit its widespread use in busy clinical settings where rapid image analysis is required. These limitations, however, do not negate the core value of the study; instead, they highlight key directions for future research and protocol optimization.

Despite these limitations, this study makes a significant contribution to the clinical and research management of NF1-PNF, particularly in the Chinese context. First, we have established the first standardized, reproducible 3D volumetric measurement workflow for PNF in China, providing clinicians with a free, open-source tool to accurately evaluate selumetinib efficacy—filling a critical gap in the clinical application of targeted therapy for this rare disease. Second, the high reproducibility of our protocol (CV ,the coefficient of variation ranged from 0.1636% to 8.8114%) confirms that 3D Slicer is a reliable method for PNF volumetric assessment, which is essential for multi-center clinical trials and long-term follow-up studies—both of which are urgently needed for NF1-PNF research. Third, our findings confirm that 3D volumetric measurement is the only method capable of capturing the true tumor burden of PNF, challenging the continued use of traditional 1D/2D methods in clinical practice and aligning Chinese PNF assessment with international REiNS guidelines. For patients, this accurate, objective volumetric measurement enables dynamic monitoring of treatment response, allowing for timely adjustments to selumetinib therapy and personalized clinical management.

Looking forward, several key research directions will build on the findings of this study and address its limitations. First, we will expand the study cohort through multi-center collaboration with national pediatric rare disease centers, which will increase statistical power to detect correlations between volume change and clinical symptom improvement and enable inter-observer reproducibility analysis. Second, we will extend the follow-up duration to at least 24–36 months to capture the long-term relationship between radiological and clinical outcomes, and to assess the correlation between intra-tumoral structural changes (e.g., cystic necrosis volume) and symptom improvement—an analysis that may reveal a stronger association than total volume alone. Third, we will collaborate with biomedical engineering teams to develop an automated segmentation plugin for 3D Slicer tailored to PNF, which will reduce the time required for post-processing and make the protocol feasible for routine clinical use. Fourth, we will develop a comprehensive PNF efficacy assessment system that integrates 3D volumetric measurement, intra-tumoral structural analysis, and validated NF1-specific clinical scales—addressing the scale sensitivity limitation and providing a more holistic evaluation of selumetinib's therapeutic effect. Finally, we will validate this 3D Slicer protocol in adult NF1-PNF patients, expanding its applicability to the entire NF1 population.

In conclusion, this study demonstrates that 3D Slicer is a technically feasible and highly reliable tool for the volumetric measurement of PNF in pediatric NF1 patients receiving selumetinib therapy, and it provides a standardized workflow for its clinical application. The absence of a statistically significant correlation between volume change rate and clinical symptom improvement in this study reflects the limitations of a small sample size, asynchronous radiological and clinical changes, and insufficient scale sensitivity—not a flaw in the 3D Slicer-based measurement method itself. As targeted therapy for NF1-PNF continues to evolve, accurate volumetric measurement will become an increasingly critical component of clinical management and research, and 3D Slicer—with its open-source accessibility and high reproducibility—will play a central role in this process. This study lays a solid foundation for future large-sample, long-term follow-up studies of PNF, and it aligns Chinese clinical practice with international guidelines for the quantitative assessment of this rare, debilitating tumor.

Conclusion

This study validates the technical feasibility, high reproducibility and unique clinical advantages of 3D Slicer-based three-dimensional volumetric measurement for the quantitative assessment of plexiform neurofibromas (PNF) in pediatric patients with neurofibromatosis type 1 (NF1) receiving selumetinib targeted therapy. We successfully established and standardized a complete operational workflow for PNF 3D reconstruction and volumetric measurement using this open-source software, with the coefficient of variation ranged from 0.1636% to 8.8114% confirming the method's excellent reliability—consistent with the range of international tumor volumetric measurement studies and meeting the rigorous requirements for clinical and research efficacy assessment.

In direct comparison with traditional 1D-RECIST and 2D-WHO criteria, the 3D Slicer-based protocol overcomes the inherent limitations of diameter/area-based measurements for PNF: it accurately delineates the diffuse, irregular "tree root-like" growth of PNF along nerve fascicles, captures subtle intra-tumoral structural changes (e.g., cystic necrosis) induced by selumetinib therapy, and provides a true reflection of actual tumor burden—addressing the critical clinical gap in accurate efficacy evaluation for NF1-PNF in the era of targeted therapy. This is the first systematic validation of this 3D volumetric measurement method for PNF in a Chinese clinical setting, filling the lack of standardized operational protocols for PNF volumetric assessment in domestic clinical practice and aligning our local evaluation standards with the international REiNS guidelines.

While no statistically significant correlation was observed between tumor volume change rate and the improvement of clinical symptoms (pain, quality of life, organ/limb function) in this study cohort, this finding reflects the inherent limitations of the exploratory research design—including a small sample size due to the rarity of NF1-PNF, the short clinical application time of selumetinib in China, asynchrony between radiological volume changes and clinical symptom improvement, and insufficient sensitivity of generic assessment scales for NF1-PNF—rather than a deficiency of the 3D Slicer-based measurement method itself. Descriptive analysis still indicated a qualitative positive trend between PNF volume reduction and clinical symptom improvement, a relationship that merits further verification with larger sample sizes and longer follow-up.

Notably, this study provides a free, accessible and reproducible quantitative tool for the clinical management and research of NF1-PNF, and lays a solid foundation for subsequent large-sample, multi-center and long-term follow-up studies of PNF targeted therapy. The standardized 3D Slicer workflow established here not only supports objective, dynamic monitoring of selumetinib efficacy for individual patients but also provides a unified data collection and analysis framework for future NF1-PNF clinical trials—an essential step for advancing the evidence-based management of this rare and debilitating pediatric genetic disorder.

In future research, we will expand the study cohort through multi-center collaboration, extend follow-up duration, and develop a comprehensive PNF efficacy assessment system that integrates 3D volumetric measurement, intra-tumoral structural feature analysis, and NF1-specific clinical assessment scales. We will also optimize the 3D Slicer protocol by developing automated segmentation plugins to reduce manual post-processing time, thereby enhancing its feasibility for routine clinical application. Ultimately, this work will contribute to a more scientific, accurate and personalized clinical diagnosis and treatment system for NF1 patients with PNF, and further advance the translational application of 3D medical image post-processing technology in the field of rare disease research.

Abbreviations

CR = Complete Response;

PD = Progressive Disease;

PR = Partial Response;

SD = Stable Disease;

WHO = World Health Organization;

RECIST = Response Evaluation Criteria in Solid Tumors;

REiNS = Response Evaluation in Neurofibromatosis and Schwannomatosis;

NF1 = Neurofibromatosis Type 1;

PNF = Plexiform Neurofibromas;

MRI = Magnetic Resonance Imaging;

CV = Coefficient of Variation;

SFU = Society of Fetal Urology;

QuickDASH = Quick Disabilities of the Arm, Shoulder and Hand;

AOFAS = American Orthopaedic Foot & Ankle Society;

NRS-11 = 11-point Numerical Rating Scale;

QoL = Quality of Life

Declarations

Consent for Publication

Written informed consent for the publication of this study’s data and results was obtained from the legal guardians of all enrolled patients.

AI Disclosure Statement

No generative artificial intelligence or AI-assisted technologies were used in the design, conduct, or writing of this manuscript.

Competing Interests

The authors declare no competing interests. No financial or non-financial benefits have been received or will be received from any party directly or indirectly related to the subject of this article.

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Rongkun Zhu and Yanan Zhang contributed equally to this work and share first authorship.**Conceptualization**: J. Guo, X. Hao; **Data Curation**: R. Zhu, Y. Zhang, X. Yang; **Formal Analysis**: R. Zhu, Y. Zhang; **Investigation**: R. Zhu, Y. Zhang, J. Guo, X. Hao; **Methodology**: R. Zhu, J. Guo; **Project Administration**: J. Guo, X. Hao; **Software**: R. Zhu, Y. Zhang; **Validation**: J. Guo, X. Hao; **Writing – Original Draft**: R. Zhu, Y. Zhang; **Writing – Review & Editing**: X. Yang, J. Guo, X. Hao.All authors have read and approved the final version of the manuscript and confirm the order of authorship as listed.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding authors on reasonable request.

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Figures

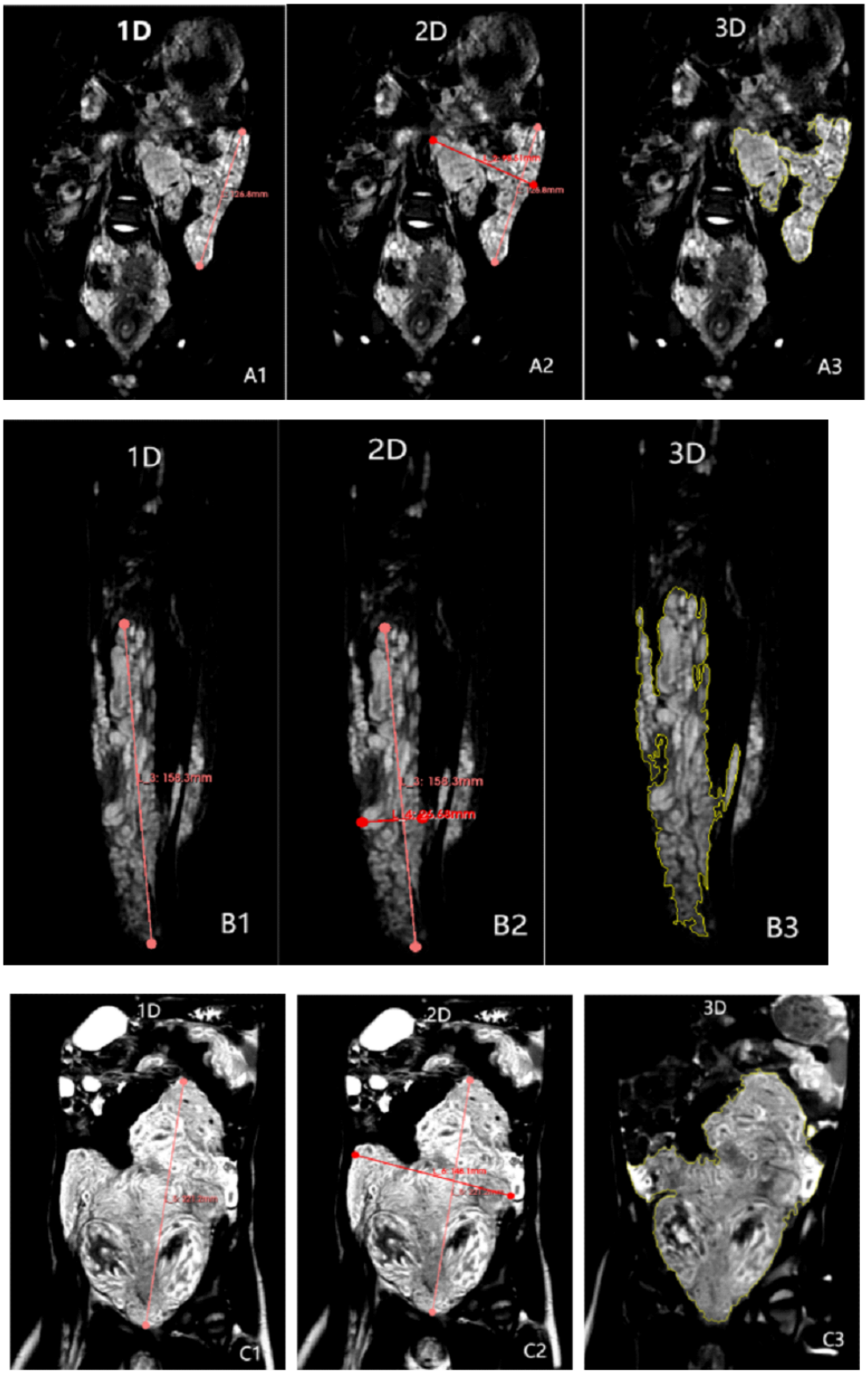


Figure 1

(A,B,C) MRI images and quantitative assessment of plexiform neurofibromas (PNF) in distinct anatomical sites

A: Retroperitoneal PNF; B: Lower leg PNF; C: Pelvic PNF. 1: 1D-RECIST longest diameter measurement; 2: 2D-WHO perpendicular diameter product measurement; 3: 3D Slicer-based volumetric measurement in this study. Direct comparison demonstrates the superior accuracy of 3D volumetric

measurement for capturing the true tumor burden of irregular, diffuse PNF lesions compared with conventional 1D/2D assessment methods.

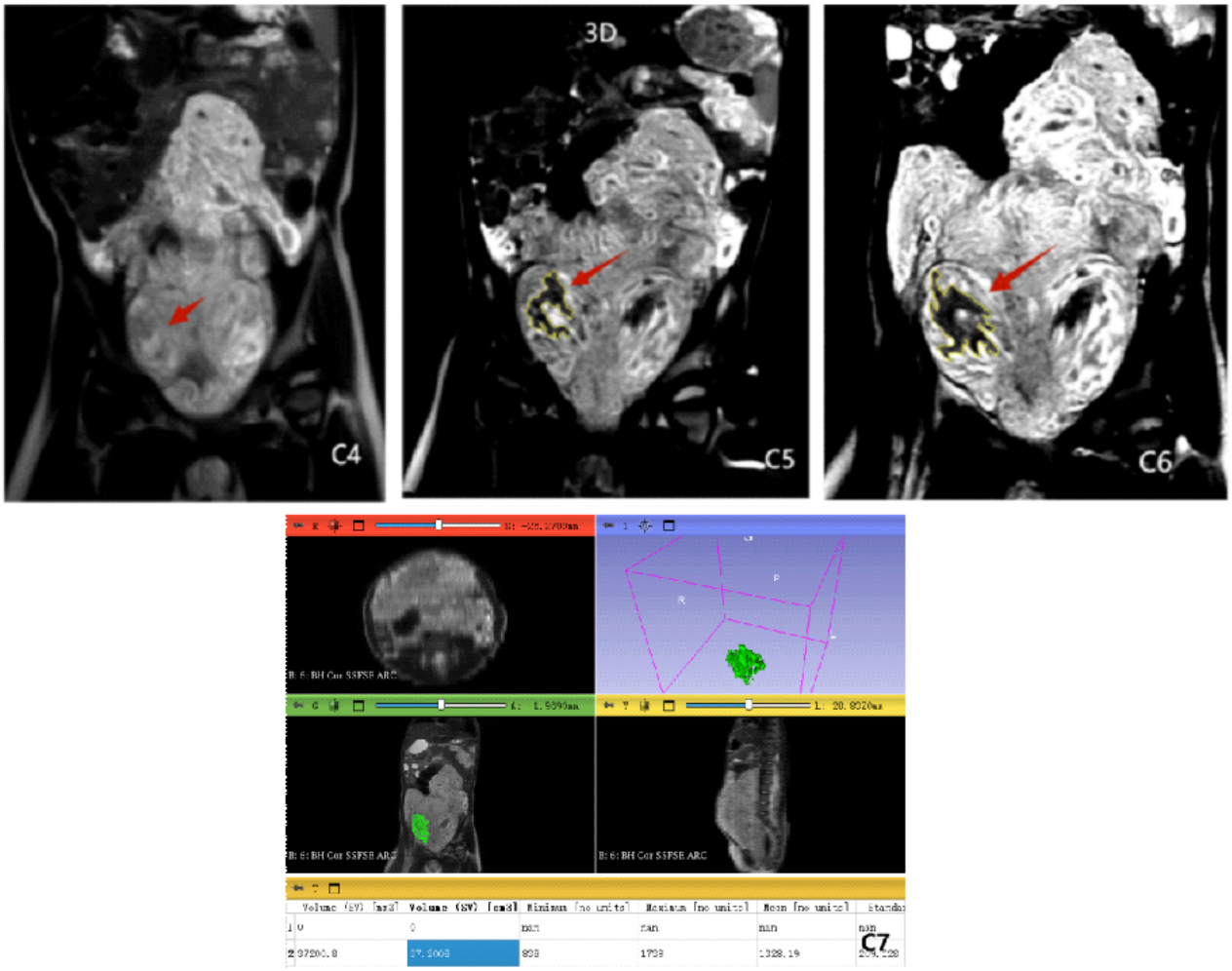


Figure 2

(C4-C7) Intra-tumoral cystic necrosis features and 3D volumetric analysis of pelvic PNF post selumetinib targeted therapy

C4: Pre-therapy baseline MRI characteristics of pelvic PNF; C5: Volumetric changes of pelvic PNF at 6 months post-therapy; C6: Internal structural alterations (cystic necrosis formation) of pelvic PNF at 18 months post-therapy; C7: 3D Slicer-based volumetric measurement of cystic necrotic areas in pelvic PNF. This targeted segmentation approach serves as an auxiliary efficacy evaluation method for large-volume PNF lesions where full volumetric measurement is time-consuming.

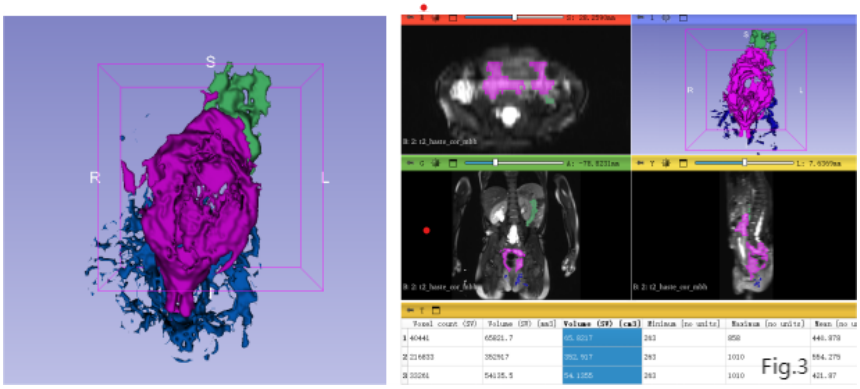


Figure 3

3D Slicer-based multi-lesion reconstruction and integrated volumetric analysis of a patient with clustered PNF across multiple anatomical sites

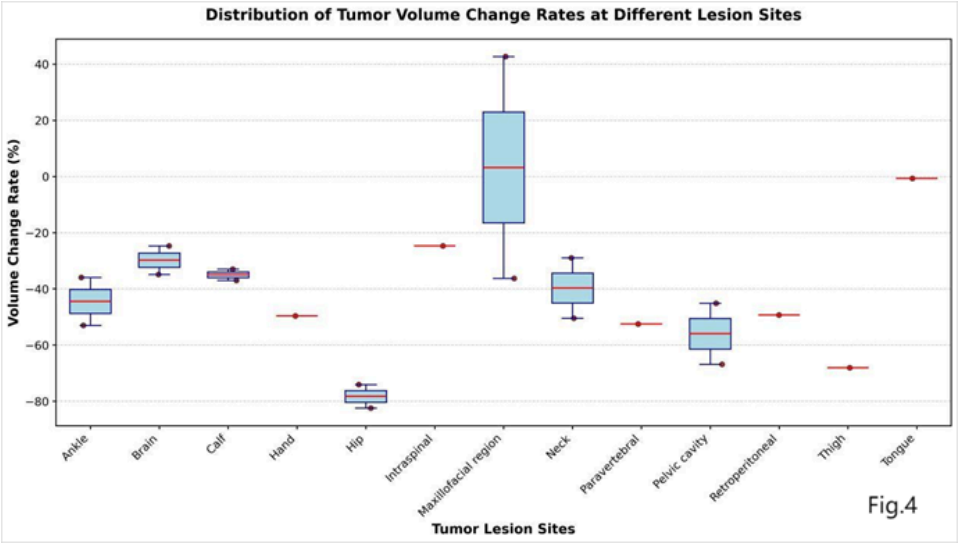


Figure 4

Quantitative distribution of tumor volume change rates in 20 PNF lesions (13 anatomical sites) post selumetinib therapy (3D Slicer measurement)