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Clinical Presentation, Surgical Management and Outcomes in Complex Neurofibromatosis: An Observational Study Done in a Tertiary Care Institute in Eastern India

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ABSTRACT

Background: Complex neurofibromatosis defines a subset of disorders characterized by varied clinical presentations and therapeutic challenges. The group includes individuals with Neurofibromatosis Type 1 (NF1), Neurofibromatosis Type 2 (NF2) and schwannomatosis who exhibit diverse clinical manifestations ranging from benign cutaneous tumors to severe neurological complications with systemic involvement.
Methods: The research was a prospective observational study done on 50 patients diagnosed with complex neurofibromatosis who underwent neurosurgical evaluation and treatment at a tertiary care institute in Eastern India over a study period of two years. The research aimed to characterize clinical presentations, surgical management and outcomes in complex neurofibromatosis.
Results: Benign pathology like neurofibromas and schwannomas was the most common diagnosis. Malignant peripheral nerve sheath tumors were detected in 4% of patients, indicating malignant transformation. Gross total resection was achieved in the majority of patients, followed by near total resection and subtotal resection. Motor functions and sensory functions were improved in 56% and 50% of the patients respectively, in the postoperative period which was statistically significant as tested by Wilcoxon signed-rank test ($W = 75.0$, $p < 0.001$ for motor functions and $W = 113.0$, $p = 0.007$ for sensory function). Statistical analysis with Spearman rank correlation test showed weak (non-significant; $p=0.218$) positive correlation between tumor size and preoperative pain score. The correlation between extent of tumor resection and size of tumor (Fisher–Freeman–Halton exact test; $p=0.0000788$) was found to be statistically significant.
Conclusion: This research concluded regarding consideration of tumor size in assessing extent of surgical resection in complex neurofibromatosis. It gave us a detailed understanding of the clinical manifestation, surgical indications and safety of the surgical management of complex neurofibromatosis in a tertiary care institute in Eastern India.

Keywords: Neurofibromatosis, schwannomatosis, neurofibroma, complex neurofibromatosis, schwannoma, malignant peripheral nerve sheath tumors

INTRODUCTION

Complex neurofibromatosis has a myriad of clinical features and very few present with symptoms that are amenable to surgical management(1,2). Although medical management of neurofibromatosis by targeted therapy has shown new avenues of research, surgical management still remains the principal mode of treatment. Surgical management of complex neurofibromatosis and its outcomes hold an impact on the quality of life of the patients(2,3). By analyzing treatment patterns and factors influencing success, the research seeks to provide insights to optimize care and guide future clinical practices. Despite advancements in understanding the genetic basis and clinical spectrum of complex neurofibromatosis supplemented by recent advancements in the field of monoclonal antibodies and targeted therapies(4,5), the optimal surgical strategies and outcomes in complex cases remain underexplored. Previous studies have highlighted the variability in treatment responses and the complexity of surgical decision-making, influenced by factors such as tumor location, size and associated comorbidities(6,7). The management of such patients often necessitates a multidisciplinary approach, with surgical intervention playing a crucial role in alleviating symptoms, preserving function and improving quality of life(8). This includes teams consisting of neurosurgeons, plastic surgeons, general surgeons, orthopedics, cardiothoracic surgeons, ophthalmologists, radiotherapy and neurologists. This institution-based observational study aimed to comprehensively examine the clinical presentations, surgical management strategies and outcomes among patients with complex neurofibromatosis. By analyzing a cohort of patients treated at our institute, we sought to delineate patterns of disease presentation, evaluate the efficacy of surgical interventions and identify factors influencing treatment success. Our findings aim to contribute valuable insights into optimizing the care of individuals affected by complex neurofibromatosis, thereby acting as guidance in propelling future clinical practices for management of this challenging disease.

The aims and objectives of our research were to characterize clinical presentations, surgical management and its outcome in complex neurofibromatosis; to describe the demographic and clinical profiles of patients diagnosed with complex neurofibromatosis, including subtype distribution. The research also documented the extent of surgical resection performed for managing complex neurofibromatosis-related tumors and deformities and evaluated the postoperative outcomes, including complications and patient-reported outcomes in terms of pain relief and functional status.

Our expected outcomes encompassed:

- A comprehensive description of the clinical presentations and tumor characteristics in patients with complex neurofibromatosis.
- An assessment of the extent of surgical intervention.
- An insight into factors that influenced surgical success and complications, aiding in personalized treatment planning.

MATERIALS & METHODS

The research was done to critically appraise clinical presentations, surgical management and postoperative outcomes of patients diagnosed with complex neurofibromatosis with neurosurgical involvement. The research was a prospective observational study conducted at the Department of Neurosurgery, Bangur Institute of Neurosciences, IPGME&R, Kolkata. This research work was done for a duration of two years. The research involved 50 patients diagnosed with complex neurofibromatosis who reported to the Neurosurgery Outpatient Department during the study period and required neurosurgical intervention. We had considered the incidence of NF1, NF2 and schwannomatosis observed in previous

studies with a power of 80% and 95% confidence level along with assuming a Type I error (α) of 0.05 and used the following formula for comparing two independent proportions and calculated the sample size (n):

$n=[(Z_{\alpha/2})^2 \times p(1-p)]/d^2$

where:

- $Z_{\alpha/2} = 1.96$ for 95% confidence interval
- p = expected proportion of complex neurofibromatosis based on previous literature/pilot data
- d = desired absolute precision (margin of error)

The research used a non-probability purposive sampling method as complex neurofibromatosis is a rare entity and specialized neurosurgical care is necessary to cover all the eligible cases who came to the institute during the specified research period. The patients who were diagnosed with Neurofibromatosis type 1 (NF1), Neurofibromatosis type 2 (NF2) or schwannomatosis and were undergoing surgical interventions for indications related to neurofibromatosis-related tumors were recruited into the research after obtaining an informed consent. The patients undergoing targeted therapies for complex neurofibromatosis were excluded from the research.

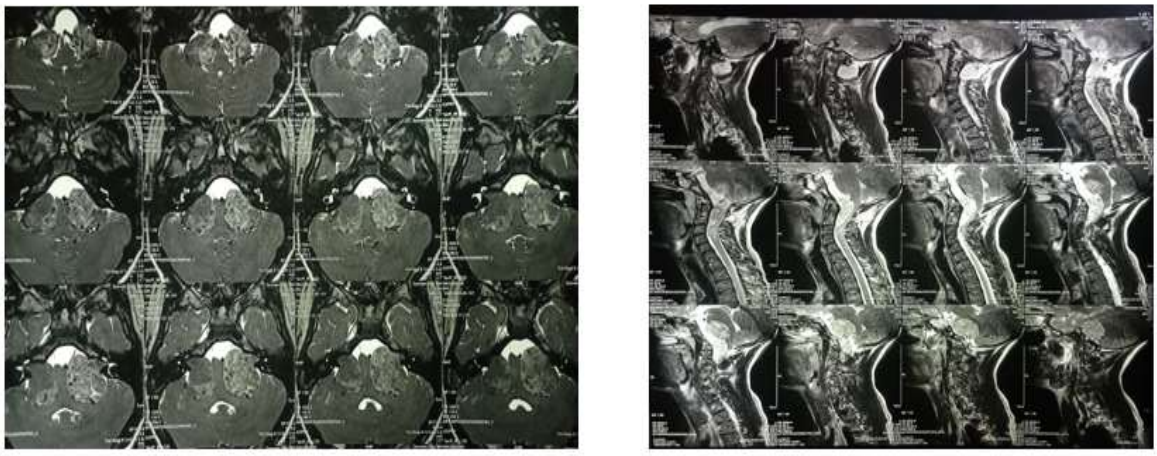


Image 1(a) showing MRITI-weighted contrast image showing bilateral vestibular schwannoma in a patient of NF2; (b) showing MRIT2- weighted image showing CV junction tumor in the same patient

Demographic information such as age, sex, address, occupation, and socioeconomic status was recorded for all patients. The clinical data were gathered in detail, including presenting symptoms, physical examination with neurological findings, tumor characteristics and treatment information with complications, which were recorded on a structured proforma that was pre-designed and pre-tested. Neurological impairments were recorded preoperatively and postoperatively. Motor activity of limb muscles was assessed by the Medical Research Council (MRC) grading system [from grade 0 (no movement or visible contraction) to grade 5 (normal power)]. A graded scale of Revised Nottingham Sensory Assessment ranging from 0 (absent sensation) to 2 (normal) for assessing light touch, temperature, pressure and tactile localization was used to measure sensory functionality. Pain severity was measured by the Numeric Pain Rating Scale, ranging from 0 (no pain),1-3 (mild pain),4-6 (moderate pain) to 7-10(severe pain) and recorded, both preoperatively and postoperatively to evaluate the impact of surgical intervention. Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) were done, wherever necessary to identify the location, size, extent, and invasion of the surrounding neural or

vascular structures of the tumor. Images 1 (a) and (b) show radiological images (MRI) of a single patient of NF2 presenting with characteristic bilateral vestibular schwannomas with cervico-vertebral (CV) junction tumor.

Diagnostic Criteria for Neurofibromatosis Type 1 (NF1):

Diagnosis of NF1 was established based on the presence of at least two of the following criteria**(9)**:

- Six or more café-au-lait macules larger than 0.5 cm in prepubertal individuals or larger than 1.5 cm in post-pubertal individuals
- Axillary or inguinal freckling
- Two or more cutaneous neurofibromas
- One plexiform neurofibroma
- Two or more iris Lisch nodules
- Optic glioma
- Characteristic osseous lesions such as sphenoid wing dysplasia, pseudarthrosis or severe kyphoscoliosis
- A heterozygous pathogenic NF1 variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells

Diagnostic Criteria for Neurofibromatosis Type 2 (NF2):

NF2 was diagnosed if any one of the following criteria was fulfilled(10):

- Bilateral vestibular schwannomas
- An identical NF2 pathogenic variant in at least 2 anatomically distinct NF2-related tumors (schwannoma, meningioma, and/or ependymoma).
- Either 2 major or 1 major and 2 minor criteria as described in the following:

Major criteria:

- Unilateral vestibular schwannoma
- First-degree relative other than sibling with NF2-related schwannomatosis
- 2 or more meningiomas
- NF2 pathogenic variant in an unaffected tissue such as blood

Minor criteria:

- Can count more than one of a type (like two distinct schwannomas would count as two minor criteria)
  - Ependymoma, meningioma (multiple meningiomas qualify as a major criteria), schwannoma (If the major criterion is unilateral vestibular schwannoma, at least one schwannoma must be dermal in location)
- Can count only once (like bilateral cortical cataracts count as a single minor criterion)
  - Juvenile subcapsular or cortical cataract, retinal hamartoma, epiretinal membrane in a person aged <40 years**,** meningioma

Diagnostic Criteria for Schwannomatosis: Schwannomatosis was diagnosed based on the following criteria(10):

- Diagnosis of SMARCB1- or LZTR1-related schwannomatosis can be made when an individual meets one of the following criteria:
  - At least one pathologically confirmed schwannoma or hybrid nerve sheath tumor and a SMARCB1 (or LZTR1) pathogenic variant in an unaffected tissue such as blood.
  - A shared SMARCB1 or LZTR1 pathogenic variant in two schwannomas or hybrid nerve sheath tumors.
- Diagnosis of 22q-related schwannomatosis can be made when an individual does not meet criteria for NF2, SMARCB1-related schwannomatosis, or LTZR1-related schwannomatosis, does not have a germline DGCR8 pathogenic variant, and has both of the following molecular features:
  - Loss of heterozygosity of the same chromosome 22q markers in two anatomically distinct schwannomas or hybrid nerve sheath tumors.
  - A different NF2 pathogenic variant in each tumor, which cannot be detected in unaffected tissue.

The primary outcomes of the research were recorded in terms of improvement in motor and sensory functions along with improvement in pain intensity following surgical intervention. Patients were evaluated during the immediate postoperative period and the follow-up visits at 3 months and 6 months following surgery regarding changes in pain intensity, motor power and sensory function. It also compared the tumor size at presentation with extent of surgical resection achieved during surgery. The secondary outcomes were assessment of postoperative motor improvement among subtypes of complex neurofibromatosis along with assessment of postoperative complications such as hemorrhage, infection and/or new or aggravated neurological impairments which were reported during immediate postoperative period or during follow-up at 3 months and 6 months. It also tried to assess any relationship between preoperative pain intensity and tumor size.

Statistical Analysis

Data was tabulated in Microsoft Excel sheets and then analyzed with the use of the GraphPad Prism software (version 5.0). Continuous variables were presented in terms of mean and standard deviation, whereas categorical variables were presented in terms of frequencies and percentages. Non-parametric data were analyzed using the Kruskal Wallis test. Spearman's rank correlation was applied to conduct correlation analysis of non-parametric data. Preoperative and postoperative neurological status (motor and sensory functions) was compared using Wilcoxon signed-rank test to assess statistical significance. The relationship between tumor size and completeness of surgical resection was evaluated using the Fisher–Freeman–Halton exact test. A p-value of less than 0.05 was regarded as statistically significant.

RESULT

The age distribution of the study population revealed that cases that required neurosurgical assessment were mostly prevalent in the young and middle-aged adults, with the median age and the greatest percentage of patients falling within the 31-40 years age group (24%). The mean age of the study was 38.4 years. The gender distribution showed a slight male predominance (58%) in the study population. The socioeconomic status distribution showed that most of the patients had lower-middle (34%) and lower socioeconomic (28%) classes and a smaller number were reported to be of upper socioeconomic class. Most of the patients belonged to Neurofibromatosis Type 1 (64%), followed by Neurofibromatosis Type 2 (24%) and lastly Schwannomatosis (12%). The most frequent presenting symptom was pain (72%) and almost 48% of the patients experienced motor deficits. Sensory deficits were also observed in 42% of patients, indicating the involvement of sensory pathways in a significant number of cases. 36% of the patients had a mass or swelling, indicating that presentation in many instances due to clinically detectable tumor raised the suspicion of diagnosis of complex neurofibromatosis. Incidence of cranial nerve involvement was seen in 20% of the patients, as per the occurrence of cranial nerve tumors, especially in the cases of Neurofibromatosis type 2. A smaller percentage of patients (12%) were observed to have bowel and bladder involvement (Table 1).

Table 1 showing distribution of clinical presentation of patients

Clinical Features	Number of Patients
Pain	36
Motor deficit	24
Sensory deficit	21
Mass/swelling	18
Cranial nerve involvement	10
Bowel/bladder involvement	6

Spinal involvement was the most common tumor location (44%), highlighting the significant burden of spinal pathology in neurofibromatosis patients. Cranial and peripheral nerve tumors were equally distributed (28% each), reflecting the multisystem nature of the disease with involvement across both central and peripheral nervous systems (Figure 1).

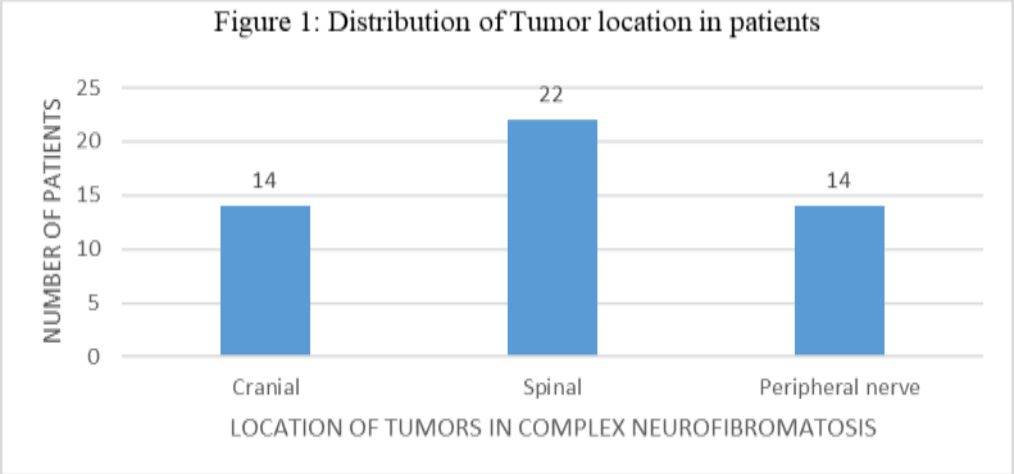


Figure 1: Distribution of Tumor location in patients

The majority of tumors were of medium size (3–5 cm), accounting for 42% of cases, followed by large tumors (>5 cm) at 34%, suggesting that a substantial proportion of patients present with larger size of tumors (Figure 2). Smaller tumors (<3 cm) were less frequent (24%).

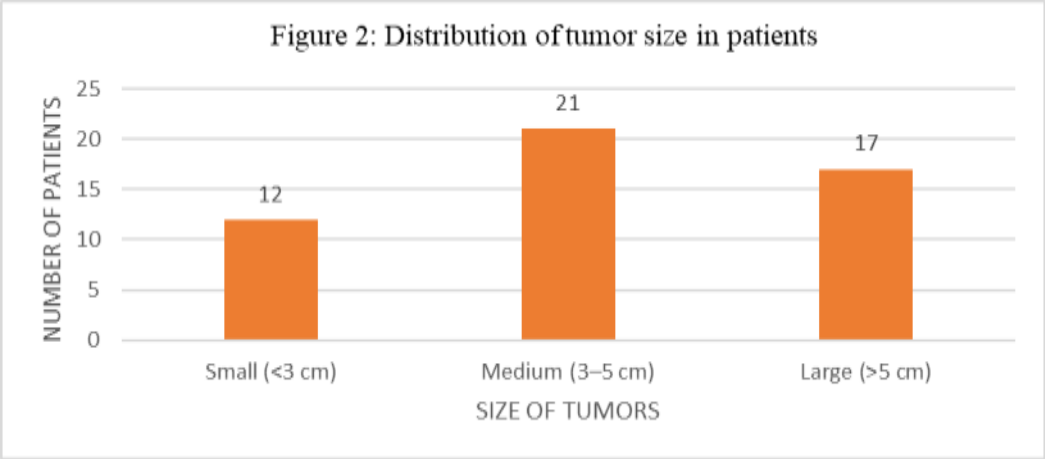


Figure 2: Distribution of tumor size in patients

The evaluation of motor functions revealed that 48% of the patients experienced moderate to severe motor weakness (MRC Grade 0 to Grade 3), which was an indication of substantial functional impairment preoperatively and 32% had mild weakness (Grade 4). Sensory assessment showed prevalent sensory impairment, with 48% of patients having scores 0 to 1. Most of the patients developed clinically relevant pain, with 68% of them reporting moderate to severe pain (scores 4 to 10) (Table 2).

Table 2 showing distribution of preoperative Neurological and Pain Assessment

		Number of Patients	Percentage (%)
MRC Grade	Grade 0–1	5	10.0%
	Grade 2	7	14.0%
	Grade 3	12	24.0%
	Grade 4	16	32.0%
	Grade 5	10	20.0%
Sensory Scale	Score 0	6	12.0%
	Score 1	18	36.0%
	Score 2	26	52.0%
Pain Score	0	6	12.0%
	1-3	10	20.0%
	4-6	18	36.0%
	7-10	16	32.0%

Neurofibroma constituted the largest proportion of tumors (36%), followed closely by schwannoma (30%) and meningioma (28%), indicating a relatively heterogeneous tumor distribution in the cohort. The low proportion of other tumors (6%) suggested that classical neurofibromatosis-associated lesions predominate in patients requiring neurosurgical intervention. The most frequent indicator suggestive of surgical intervention was pain, which was seen in 68% of patients; the second commonest indicator was progressive neurological deficit (52%), which enumerated the significance of surgical decompression in order to avoid further functional loss. The radiological progression of tumors was observed in a significant percentage of cases (40%) and noted as an important factor in operating decision-making.

The distribution of extent of surgical resection demonstrated that gross total resection was achieved in the largest proportion of patients (40%), followed by near total resection (24%) and subtotal resection (20%) (Figure 3). Decompression with biopsy constituted the smallest group (16%), reflecting cases where complete excision was not feasible due to tumor location, size, or involvement of critical neurovascular structures.

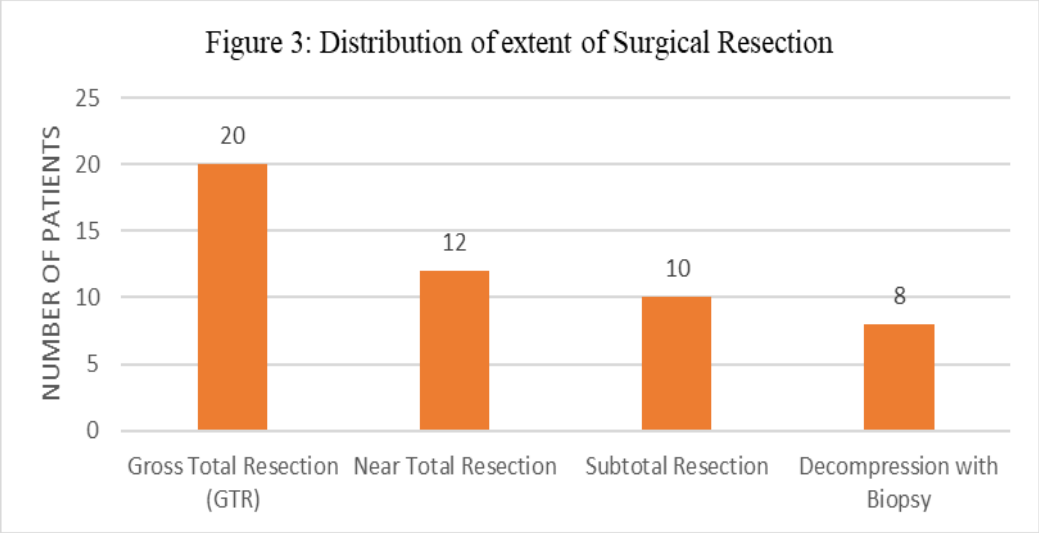


Figure 3: Distribution of extent of Surgical Resection

Most of the patients had no surgical complications (64%) with an uneventful postoperative course. Postoperative neurological deficit was the most frequent complication seen in 18%, followed by surgical site infection at 8% of the cases.

Cerebrospinal fluid (CSF) leak and hemorrhage were also not as common, with 6% and 4% of the patients respectively (Table 3).

Table 3 showing distribution of types of surgical complications

Type of Complication	Number of Patients	Percentage (%)
Postoperative neurological deficit	9	18.0%
Surgical site infection	4	8.0%
Hemorrhage	3	6.0%
CSF leak	2	4.0%
No complications	32	64.0%

The most prevalent type of tumor in the operated cases was neurofibromas and schwannomas (28% each), followed by meningiomas (24%). The plexiform neurofibromas constituted a significant percentage (16%), as they are complex in terms of development and are more likely to demand surgical treatment. A minor percentage of the cases (4%) were found to be malignant peripheral nerve sheath tumors. The assessment of neurological outcomes was classified as improvement, no change and worsening. The analysis of the neurological status before and after surgery revealed that the motor function improved in 28 patients (56%) and sensory function improved in 25 patients (50%). The percentage of patients who did not experience any difference in terms of their neurological status was relatively high, as 18 patients (36%) showed no change in their motor functions and 20 patients (40%) showed no change in their sensory function after operation. The loss in neurological status was observed in a smaller group of patients, with 4 patients (8.0%) demonstrating motor and 5 patients (10.0%) demonstrating sensory deterioration (both in cranial nerves or peripheral nerves). The improvement in motor and sensory function following surgery was found to be statistically significant (Table 4), however an absence of control group limits the causal association between neurological improvement and surgical intervention.

Table 4 showing statistical analysis of motor and sensory improvement after surgical intervention

Parameter	95% confidence interval (CI) for mean change/improvement	Wilcoxon signed-rank test value(W)	p-value
Motor improvement	0.32 to 0.76	75	0.000060
Sensory improvement	0.11 to 0.57	113	0.0069

The percentage of patients who achieved complete pain relief was 28%, which means that the pain was alleviated successfully in a considerable proportion of the cases (Figure 4). 44% of the patients complained of partial pain relief, which indicates that surgery helped to reduce the level of pain. Nevertheless, 20% of patients stated that the level of pain did not change after the surgery, which can be explained by such factors as chronic neuropathic pain, the presence of extensive tumor burden, the presence of residual disease or neural damage that is irreversible. A smaller proportion of patients (8%) reported an increase in pain after the operation, which might be a symptom of postoperative neural irritation, surgical manipulation of nerve structures or the development of the disease.

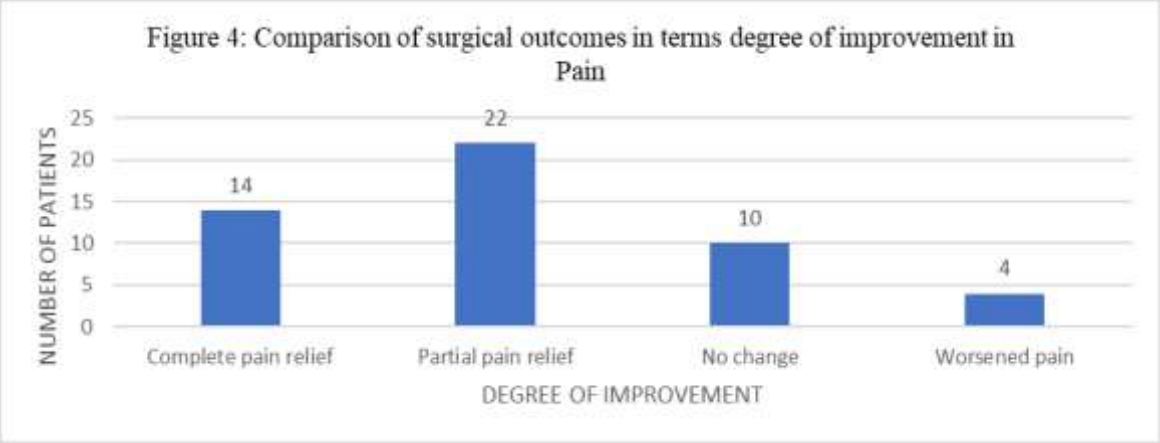


Figure 4: Comparison of surgical outcomes in terms of degree of improvement in Pain

Kruskal Wallis test showed that there was no statistically significant difference in postoperative motor improvement among patients with different subtypes of neurofibromatosis. The mean rank values indicated a slightly higher rank of the NF1 group (26.38) than the NF2(23.17) and the schwannomatosis (21.92) groups; however, the differences were low and they were not found to be statistically significant(p-value=0.532). Correlation analysis was done to determine the relationship between tumor size and preoperative level of pain in patients with complex neurofibromatosis. Since, both variables were ordinal and could not follow a normal distribution, therefore the application of Spearman's rank correlation coefficient was done to identify the strength and direction of the relationship between preoperative pain score and tumor size. The analysis of Spearman rank correlation revealed that the size of the tumor and preoperative pain score were weakly correlated. The conclusion of this finding was that patients with bigger tumors were more likely to report higher pain scores before the operation; but the association was weak. This correlation was not statistically significant ($p = 0.218$) and it indicated that tumor size was not a robust predictor of pain severity. Smaller tumors (<3 cm) were more frequently managed with gross total resection, whereas larger tumors (>5 cm) were more commonly associated with subtotal resection or decompression and biopsy procedures. The association between tumor size and completeness of surgical resection was found to be statistically significant, indicating that increasing tumor size adversely affects the likelihood of complete tumor excision (Table 5).

Table 5: Association between tumor size and extent of surgical resection with statistical test results

Tumor size	Gross total resection n (%)	Near-total resection n (%)	Subtotal resection n (%)	Decompression + biopsy n (%)	Total
<3 cm	10 (83.3)	2 (16.7)	0 (0.0)	0 (0.0)	12
3–5 cm	9 (42.9)	7 (33.3)	4 (19.0)	1 (4.8)	21
>5 cm	1 (5.9)	3 (17.6)	6 (35.3)	7 (41.2)	17
Total	**20 (40.0)**	**12 (24.0)**	**10 (20.0)**	**8 (16.0)**	**50**

Fisher–Freeman–Halton exact test ($P < 0.001$)

Data are presented as n (%). Owing to sparse expected cell frequencies, the assumptions for the Pearson χ^2 test were violated; therefore, the Fisher–Freeman–Halton exact test was used to assess the association between tumor size and extent of surgical resection.

DISCUSSION

This research puts emphasis on demographic characteristics, clinical presentation, tumor profiles, surgical outcomes, surgical complications and the role of chosen statistical tests in the interpretation of postoperative outcomes.

The age distribution of the present research demonstrated that the majority of patients belonged to the third to fifth decades of life, with the highest proportion in the 31–40 years age group, suggesting that although complex neurofibromatosis is a genetic disorder present from early life, clinically significant manifestations requiring neurosurgical intervention tend to appear in early to middle adulthood. These findings are consistent with the observations of *Stafstrom et al. (2017)*, who reported that neurological manifestations of neurocutaneous disorders often become clinically evident over time rather than at birth**(11)**.

A slight male predominance was observed in the present research, which was comparable to the findings reported by *Karaconji et al. (2019)*, where a marginal male preponderance was noted in clinical presentations of neurofibromatosis, although the disease itself does not demonstrate a strong gender bias genetically**(12)**. The relatively small difference in gender distribution in the present research further supports the notion that gender is not a significant determinant of disease severity or need for surgical intervention. The majority of patients in the present research belonged to the lower-middle socioeconomic class, indicating a higher utilization of tertiary care services by these groups. While direct comparative quantitative data from previous studies are limited in this aspect, similar trends of increased tertiary care access among urban and socioeconomically disadvantaged populations have been described in institution-based studies. This distribution likely reflects referral patterns and accessibility of specialized neurosurgical care rather than true disease prevalence. The current research demonstrated that Neurofibromatosis Type 1 (NF1) was the most common subtype, which is consistent with the established epidemiological pattern of neurofibromatosis. Similar findings have been reported by *Nix et al. (2020)*, who highlighted that NF1 constitutes the majority of neurofibromatosis cases, particularly those presenting with central nervous system and peripheral nerve involvement**(13)**. The predominance of NF1 in the present research further supports its higher likelihood of requiring neurosurgical intervention due to its association with symptomatic spinal and peripheral nerve tumors.

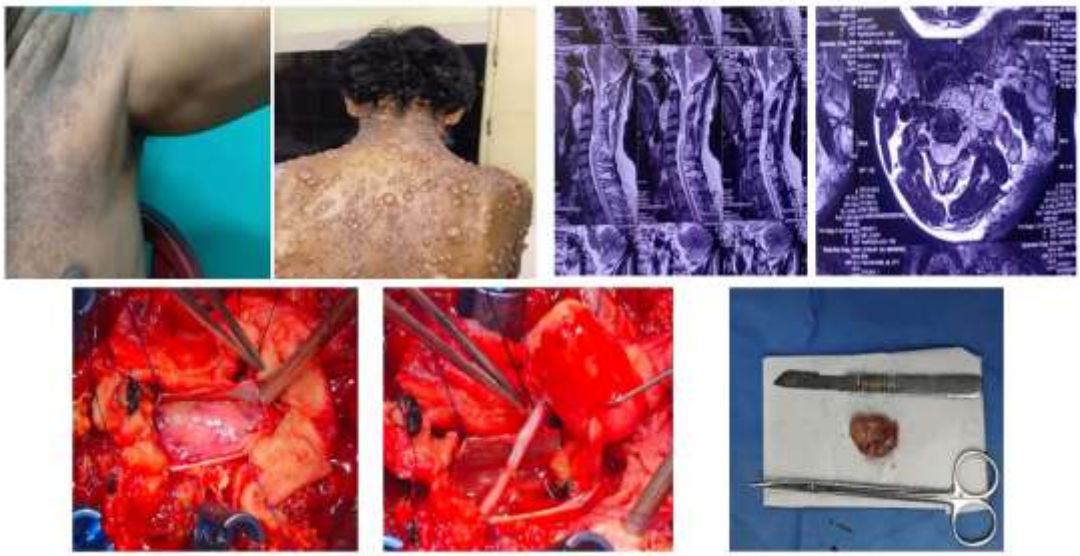
The results stipulated pain as the most common presenting symptom, followed by motor deficits and sensory deficits in this study. This pattern is consistent with the findings of *Dombi et al. (2016),* who reported pain as a major clinical concern in patients with neurofibromatosis, often contributing significantly to disease burden and the need for therapeutic intervention **(5)**. The high prevalence of neurological deficits in the research further reflects the impact of tumor-related compression on neural structures, particularly in spinal and peripheral nerve involvement. Cranial nerve involvement observed in this research, predominantly among those with Neurofibromatosis Type 2, was in agreement with observations by *Goutagny et al. (2012)*, who highlighted the presence of neurological and neurobehavioral manifestations in neurofibromatosis patients, reflecting the multisystem involvement of the disease**(14)**.

A distribution of location of tumors in this research was comparable with the findings reported by *Bergqvist et al. (2020)*, where spinal involvement was identified as a major contributor to morbidity in neurofibromatosis patients due to its association with neurological deficits and functional impairment**(15)**. With respect to tumor size, the majority of tumors in the research were of medium (3–5 cm) and large size (>5 cm), indicating that a significant proportion of patients presented with advanced disease. This pattern suggests delayed clinical presentation or slow tumor progression prior to surgical referral, which may contribute to the higher incidence of neurological impairment observed in these patients. Similar observations have been

described in previous literatures, such as *Cai et al. (2018)* and *Plotkin et al. (2022)*, where larger and more complex tumors were associated with increased surgical difficulty and worse functional outcomes**(10,16)**. The evaluation of the motor and sensory functions revealed that the majority of the patients experienced moderate to severe motor weakness along with sensory affection, indicating affection of motor and sensory pathways. The current findings on motor and sensory profiles are in accordance with previous studies like *Kolesnik et al. (2017)***(17)**. Pain assessment showed that most of the patients developed clinically relevant pain (scores 4 to 10), which was a primary presenting complaint that led to neurosurgical care. The current findings are in accordance with studies like *Wolters et al. (2025)* and *Benkli et al. (2015)***(18,19)**, thereby indicating that patients with complex neurofibromatosis often displayed pronounced neurological and pain-related issues before getting surgical care. The most frequent indications for surgery were pain and progressive neurological deficit, highlighting that symptom severity and functional impairment were the primary drivers of surgical decision-making rather than radiological findings alone. This observation is consistent with the research by *Blakeley et al. (2016)*, which emphasized that clinical symptom burden and functional limitations play a central role in determining intervention strategies in neurofibromatosis-related conditions**(20)**. The suspicion of malignant transformation, although observed in a smaller proportion of patients, remained a critical indication for surgery due to the aggressive nature and poor prognosis associated with malignant peripheral nerve sheath tumors. This finding was comparable to the recommendations by *Avery et al. (2017)*, who highlighted that early surgical intervention is essential in cases with suspected malignant change, particularly in plexiform neurofibromas, to improve outcomes and reduce disease-related morbidity**(21)**.

Gross total resection was achieved in the largest proportion of patients, while decompression with biopsy constituted the smallest group, reflecting cases where complete excision was not feasible due to tumor location, size or involvement of critical neurovascular structures. The findings were similar to studies based on surgical management of complex neurofibromatosis like *Taleb et al. (2011), Zhao et al. (2018), Kotch et al. (2023)* showing that complete tumor excision was achievable in a significant proportion of cases while a considerable number of patients required partial resection or decompression, highlighting the surgical complexity associated with complex neurofibromatosis-related tumors**(3,6,7)**. The overall complication rate was relatively low, indicating that neurosurgical management of complex neurofibromatosis-related tumors is generally safe in a tertiary care setting. The complication rates are comparable to those reported in previous studies like *Tamura et al. (2021)* and *Kresak & Walsh et al. (2017)*, where postoperative neurological deficits and wound-related complications have been described as the most frequent adverse outcomes in neurofibromatosis-related surgeries**(1,2)**. Postoperative neurological deficits in the present research also reflect the inherent surgical risk associated with tumors involving peripheral nerves, spinal cord and cranial nerves, particularly in cases with infiltrative growth patterns. *Shin et al. (2025)* also highlighted that complex neurofibromatosis-associated tumors often encase nerve fascicles, increasing the risk of neurological injury during surgical intervention**(22)**. Similarly, the observed surgical site infection rate aligns with reported rates in neurosurgical literatures like *Zhao et al. (2018), Taleb et al. (2011)* and *Wagener et al. (2023)*, where factors such as prolonged operative duration and extensive surgical exposure contribute to infection risk**(6,7,23)**. Overall, the complication profile observed in the present research is consistent with existing literature

demonstrating acceptable morbidity rates in specialized neurosurgical centers. The relatively low incidence of severe complications in the research supported the safety and feasibility of surgical intervention, provided that careful patient selection, meticulous surgical technique and adequate postoperative monitoring are maintained. The histopathological examination in the research revealed that the majority of lesions were benign. This distribution reflects the known predominance of benign peripheral nerve sheath tumors in complex neurofibromatosis and highlights the heterogeneous pathological spectrum observed in patients undergoing neurosurgical intervention. The predominance of neurofibromas and schwannomas in the present research is consistent with the molecular and pathological mechanisms described by *Li et al. (2022)*, who emphasized the role of NF1 gene dysfunction in promoting tumorigenesis across multiple neural tissue types, thereby contributing to diverse tumor histology. This supported the observation that neurofibromatosis is characterized by variable tumor presentations rather than a single uniform pathology**(24)**. Images 2 (a) and (b) show the diverse presentation of patient with NF1. The same patient showing multiple cervical tumors along with cutaneous neurofibromas [Images 2(c) and (d)]. Intraoperatively, a well-defined encapsulated tumor was excised [Images (e) and (f)].



Images 2 (a) showing café-au-lait spots; (b) showing multiple cutaneous neurofibromas in a patient of NF1; (c) & (d) showing MRIT2-weighted sagittal and axial images of same patient showing multiple tumors in cervical spine; (e) & (f) showing intraoperative images and (g) showing specimen after resection

Malignant peripheral nerve sheath tumors (MPNSTs) were identified in the present research, indicating a relatively low but clinically significant rate of malignant transformation. This finding is comparable with existing literature, such as *Miettinen et al. (2017)*, where malignant transformation in neurofibromatosis has been reported in a minority of patients**(25)**. *Khosravi et al. (2023)* highlighted the role of genetic and epigenetic mechanisms, including miRNAs and lnc RNAs, in driving malignant progression in NF1-associated tumors, supporting the biological basis of such transformation**(26)**. The presence of malignant tumors in the present research reinforces the importance of histopathological examination in establishing definitive diagnosis and guiding management strategies, including the need

for close follow-up and consideration of adjuvant therapy in selected cases.

This research highlighted motor improvement in 56% of patients (approximate standard effect size r ≈ 0.70) and sensory improvement in 50% of patients (approximate standard effect size r ≈ 0.49) following surgical intervention, while stabilization of neurological status was seen in 36% (motor) and 40% (sensory) of cases (Figure 5). Postoperative deterioration was relatively low, occurring in 8% of motor and 10% of sensory functions, indicating an acceptable surgical risk in a complex patient population. These findings suggest that surgical decompression and tumor excision were effective in improving or stabilizing neurological function in the majority of patients. These results are comparable to those reported by *Murphy et al. (2020)*, who demonstrated that timely surgical intervention in complex neurofibromatosis-related neurological conditions resulted in significant clinical improvement or stabilization in a majority of patients**(27)**.

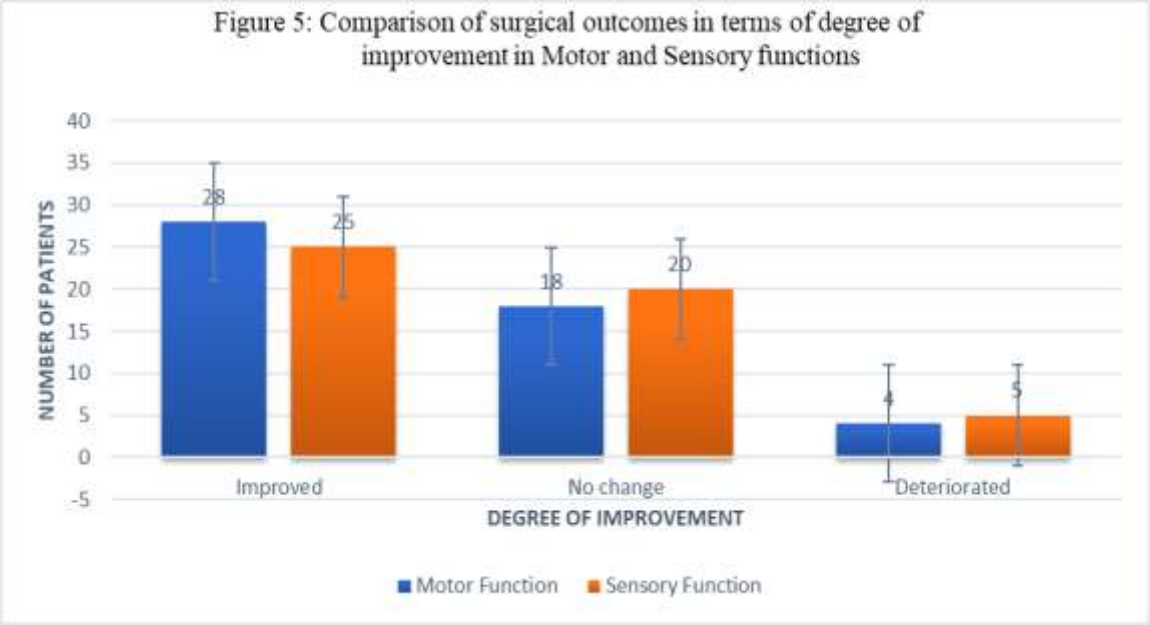


Figure 5: Comparison of surgical outcomes in term of degree of improvement in motor and sensory functions

The low rate of postoperative neurological deterioration in this research is also consistent with previously reported complication rates of approximately 10–15% in neurosurgical series, according to studies like *Ardern-Holmes et al. (2017), Fisher et al. (2022) and Hsu et al. (2022),* supporting the safety and efficacy of surgical management**(8,28,29)**. The present research showed no statistically significant difference in postoperative motor improvement across complex neurofibromatosis subtypes, indicating that neurological recovery is not significantly influenced by disease subtype. This observation aligns with findings of previous studies, which emphasize that clinical manifestations and outcomes in neurofibromatosis are more dependent on tumor characteristics and anatomical factors rather than genetic subtype alone**(6,7)**. The present research showed 72% of patients experienced complete or partial pain relief following surgical intervention (complete relief: 28%, partial relief: 44%), indicating a significant symptomatic benefit of surgery. This finding reinforced the established role of surgical decompression and tumor excision in alleviating pain caused by nerve compression, distortion or ischemia. Despite the overall positive outcomes, 28% of patients in the present research reported

either no improvement or worsening of pain following surgery. This was consistent with the findings of *Kongriangkai et al. (2019)*, who emphasized that pain in neurofibromatosis is multifactorial and may persist despite adequate tumor removal due to underlying neuropathic mechanisms**(30)**. Postoperative pain may also arise due to surgical manipulation of neural tissues, resulting in inflammation, neural sensitization, or scar formation, thereby limiting the extent of pain relief achievable through surgery alone. The variability in pain outcomes observed in the present research highlights the complex and heterogeneous nature of pain in complex neurofibromatosis. These findings underscore the importance of realistic preoperative counselling and appropriate patient selection. While surgical intervention remains an effective modality for pain reduction in a majority of patients, a subset may require adjunctive multimodal pain management strategies, including pharmacological therapy and long-term follow-up. Overall, the results support an individualized approach to pain management in complex neurofibromatosis, integrating both surgical and non-surgical modalities based on patient-specific factors.

The Kruskal Wallis test comparing postoperative motor improvement across complex neurofibromatosis subtypes did not show a statistically significant difference. This indicates that the subtype of complex neurofibromatosis did not significantly influence postoperative motor recovery in the present research. The genetic heterogeneity of neurofibromatosis and its variable clinical expression supported the observation that clinical outcomes may not be strictly determined by subtype classification alone. Similarly, correlation analysis between tumor size and preoperative pain severity demonstrated a weak positive correlation which was not statistically significant. This suggests that tumor size was not a strong predictor of increased pain severity in the research population. This finding is consistent with observations by *Wolters et al. (2015)*, who reported that pain in neurofibromatosis is multifactorial and often related to nerve compression, tumor infiltration, and surrounding tissue involvement rather than tumor size alone**(18)**. The lack of statistically significant associations in both analyses reflects the complex interplay of multiple clinical factors such as tumor location, extent of neural involvement, chronicity of symptoms and individual pain perception. These variables are not adequately captured by single-parameter statistical testing, which explains the absence of strong statistical correlations. The absence of a significant difference in motor outcomes across neurofibromatosis subtypes further suggests that surgical outcomes are more likely influenced by tumor characteristics, anatomical considerations, and surgical factors rather than the genetic subtype. This aligns with current clinical understanding that neurosurgical decision-making in complex neurofibromatosis is primarily guided by symptom severity, functional impairment and radiological findings rather than subtype classification. The association between tumor size and extent of surgical resection was found to be statistically significant (Fisher–Freeman–Halton exact test p-value=0.0000788) indicating that increasing tumor size adversely affects the likelihood of complete tumor excision (Figure 6). Gross total resection was achieved in 83.3% of tumors measuring <3 cm, compared with 42.9% of tumors measuring 3–5 cm and 5.9% of tumors measuring >5 cm. Also, decompression with biopsy was more frequent among tumors measuring >5 cm (41.2%) than among tumors measuring 3–5 cm (4.8%) or those measuring <3 cm (0%). These findings suggest a strong association between increasing tumor size and reduced extent of resection. The findings emphasize the need for a comprehensive and individualized approach to patient management rather than reliance on isolated quantitative parameters.

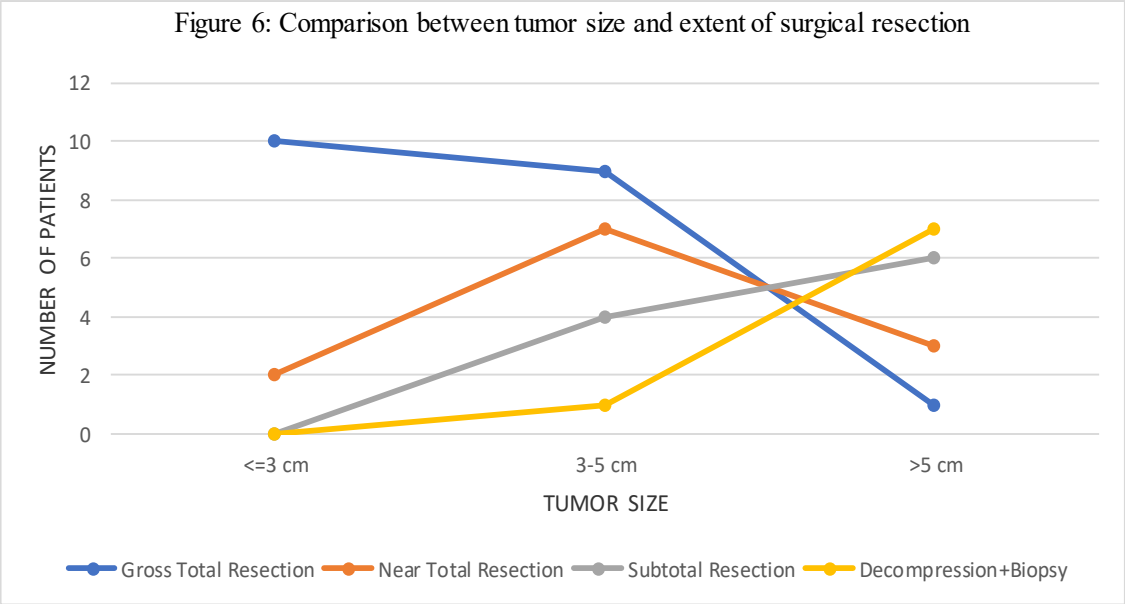


Figure 6: Comparison between tumor size and extent of surgical resection

The different types of complex neurofibromatosis in the research provided clinical and pathological heterogeneity that could have affected the comparison of outcomes and obscured subtype trends. The post-intervention follow-up was not very long in the case of a chronic and lifelong illness like complex neurofibromatosis, which limits the evaluation of long-term outcomes, prognosis, recurrence rates and delayed complications. The absence of diligent follow-up for recurrence in tumor growth also limits the scope of the study. The relatively short duration of follow-up and limited sample size in the present research may restrict the ability to assess long-term recurrence patterns. Previous studies, such as *Iasella et al. (2025)*, have emphasized the need for prolonged surveillance in neurofibromatosis due to its chronic and progressive nature. It also reported that tumor progression and new lesion development may occur over extended periods, reinforcing the importance of long-term follow-up**(31)**.

Continuous follow-up with regular clinical and radiological evaluation is essential for early detection and timely management of recurrent or newly developed lesions. There was no analysis of associations since the research was descriptive and had a small sample, which could weaken the causal interpretation of the associations. Lack of a control or comparison group hampered the possibility of directly comparing the outcome of surgery with non-surgical management.

CONCLUSION

The research found clinical heterogeneity in presentation of complex neurofibromatosis, with typical symptoms being pain and impairment of the nervous system treated by neurosurgery. The results revealed that the symptomatic burden and functional compromise were the main factors to base the surgical management. Surgical treatment led to a recovery or stabilization in neurological parameters in the majority of patients with significant reduction in pain. A histopathological analysis established that a large number of peripheral nerve sheath tumors were benign, whereas few turned out to be malignant tumors, showing the significance of close follow-up. The outcomes indicated tumor size being the key determinant in individualized surgical decision-making for effective management of the condition. The statistically significant correlation between tumor size and extent of resection emphasized the consideration of tumor size in planning appropriate surgical

goals in complex neurofibromatosis which may indirectly affect the disease prognosis. Future studies may include complex neurofibromatosis investigations on a multicentric and larger scale with extended follow-ups to gain a thorough comprehension of the outcomes of surgical treatment in the long-term prognosis, the recurrence rates and the variables affecting the neurological outcomes. The integration of sophisticated imaging, genetic profiling, and molecular markers could be used to assist in risk classification, early diagnosis of malignant transformation, and personalized treatment planning. The future researches in the comparison of surgical and non-surgical methods of management and the role of adjuvant treatments could offer better evidence to support clinical decision-making. Recent advances in the field of medical management of complex neurofibromatosis have opened avenues for treatment of complex neurofibromatosis at the genetic level. Hence, surgical management along with molecular therapy is the standard of care for complex neurofibromatosis in the future. On the whole, the research was aimed at achieving its goals as it gave a detailed understanding of the clinical manifestation, surgical indications and safety of the neurosurgical treatment of complex neurofibromatosis in a tertiary care institute in Eastern India.

Declaration by Authors

Ethical Approval: Approved

Ethical Committee Name: Institutional Ethics Committee, IPGME&R Research Oversight Committee, Institute of Postgraduate Medical Education and Research, Kolkata

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REFERENCES

1. Tamura R. Current Understanding of Neurofibromatosis Type 1, 2, and Schwannomatosis. Int J Mol Sci. 2021; 22(11):5850. doi:10.3390/ijms22115850
2. Kresak J, Walsh M. Neurofibromatosis: A Review of NF1, NF2, and Schwannomatosis. J Pediatr Genet. 2016 Mar;5(2):98–104. doi:10.1055/s-0036-1579766
3. Kotch C, Brosius SN, De Raedt T, Fisher MJ. Updates in the Management of Central and Peripheral Nervous System Tumors among Patients with Neurofibromatosis Type 1 and Neurofibromatosis Type 2. Pediatr Neurosurg. 2023;58(5):267–280. doi:10.1159/000529507
4. Fisher MJ, Shih CS, Rhodes SD, Armstrong AE, Wolters PL, Dombi E, et al. Cabozantinib for neurofibromatosis type 1–related plexiform neurofibromas: a phase 2 trial. Nat Med. 2021;27(1):165–73. doi:10.1038/s41591-020-01193-6
5. Dombi E, Baldwin A, Marcus LJ, Fisher MJ, Weiss B, Kim A, et al. Activity of Selumetinib in Neurofibromatosis Type 1–Related Plexiform Neurofibromas. N Engl J Med. 2016;375(26):2550–2560. doi:10.1056/NEJMoa1605943
6. Taleb FS, Guha A, Arnold PM, Fehlings MG, Massicotte EM. Surgical management of cervical spine manifestations of neurofibromatosis Type 1: long-term clinical and radiological follow-up in 22 cases: Clinical article. J Neurosurg Spine. 2011;14(3):356–66. doi:10.3171/2010.9.SPINE09242
7. Zhao F, Wang B, Yang Z, Zhou Q, Li P, Wang X, et al. Surgical treatment of large vestibular schwannomas in patients with neurofibromatosis type 2: outcomes on facial nerve function and hearing preservation. J Neurooncol. 2018;138(2): 417–424. doi:10.1007/s11060-018-2812-x
8. Hsu CK, Denadai R, Chang CS, Yao CF, Chen YA, Chou PY, et al. The Number of Surgical Interventions and Specialists Involved in the Management of Patients with Neurofibromatosis Type I: A 25-Year Analysis. J Pers Med. 2022;12(4):558. doi:10.3390/jpm12040558
9. Legius E, Messiaen L, Wolkenstein P, Pancza P, Avery RA, Berman Y, et al. Revised diagnostic criteria for neurofibromatosis type 1 and Legius

syndrome: an international consensus recommendation. Genet Med. 2021;23(8):1506–1513. doi:10.1038/s41436-021-01170-5

10. Plotkin SR, Messiaen L, Legius E, Pancza P, Avery RA, Blakeley JO, et al. Updated diagnostic criteria and nomenclature for neurofibromatosis type 2 and schwannomatosis: An international consensus recommendation. Genet Med. 2022 Sep;24(9):1967–1977. doi: 10.1016/j.gim.2022.05.007
11. Stafstrom CE, Staedtke V, Comi AM. Epilepsy Mechanisms in Neurocutaneous Disorders: Tuberous Sclerosis Complex, Neurofibromatosis Type 1, and Sturge–Weber Syndrome. Front Neurol. 2017;8;87. doi:10.3389/fneur.2017.00087
12. Tanya Karaconji, Eline Whist, Robyn V Jamieson, Maree P Flaherty, John R B Grigg. Neurofibromatosis Type 1: Review and Update on Emerging Therapies. Asia-Pac J Ophthalmol. 2019;8(1):62-72. doi:10.22608/APO.2018182
13. Nix JS, Blakeley J, Rodriguez FJ. An update on the central nervous system manifestations of neurofibromatosis type 1. Acta Neuropathol (Berl). 2020;139(4):625–641. doi:10.1007/s00401-019-02002-2
14. Goutagny S, Bah AB, Henin D, Parfait B, Grayeli AB, Sterkers O, et al. Long-term follow-up of 287 meningiomas in neurofibromatosis type 2 patients: clinical, radiological, and molecular features. Neuro-Oncol. 2012;14(8):1090–6. doi:10.1093/neuonc/nos129
15. Bergqvist C, Servy A, Valeyrie-Allanore L, Ferkal S, Combemale P, Pierre Wolkenstein, et al. Neurofibromatosis 1 French national guidelines based on an extensive literature review since 1966. Orphanet J Rare Dis. 2020;15(1):37. doi:10.1186/s13023-020-1310-3
16. Cai W, Steinberg SM, Bredella MA, Basinsky G, Somarouthu B, Plotkin SR, et al. Volumetric MRI Analysis of Plexiform Neurofibromas in Neurofibromatosis Type 1. Acad Radiol. 2018;25(2):144–152. doi: 10.1016/j.acra.2017.09.004
17. Kolesnik AM, Jones EJH, Garg S, Green J, Charman T, Mark Henry Johnson, et al. Early development of infants with neurofibromatosis type 1: a case series. Mol Autism. 2017;8(1):62. doi:10.1186/s13229-017-0178-0
18. Wolters PL, Burns KM, Martin S, Baldwin A, Dombi E, Toledo-Tamula MA, et al. Pain interference in youth with neurofibromatosis type 1 and plexiform neurofibromas and relation to disease severity, social-emotional functioning, and quality of life. Am J Med Genet A. 2015; 167A (9):2103–2113. doi:10.1002/ajmg.a.37123
19. Benkli B, Vu PD, Abd-Elsayed A, Slopis JM, Geng Y, Chung M. Chronic Pain in Neurofibromatosis 1, Neurofibromatosis 2, and Schwannomatosis: A Review on Epidemiology, Pathophysiology, Symptomatology and Treatment. Pain Physician. 2025;28(2):105–15.
20. Blakeley JO, Plotkin SR. Therapeutic advances for the tumors associated with neurofibromatosis type 1, type 2, and schwannomatosis. Neuro-Oncol. 2016; 18(5):624–38. doi:10.1093/neuonc/nov200
21. Avery RA, Katowitz JA, Fisher MJ, Heidary G, Dombi E, Packer RJ, et al. Orbital/Periorbital Plexiform Neurofibromas in Children with Neurofibromatosis Type 1. Ophthalmology. 2017;124(1):123–132. doi: 10.1016/j.ophtha.2016.09.020
22. Shin MR, Brown M, Siegel B, Turnacioglu S. Neurofibromatosis review with focus on rehabilitation intervention. Curr Probl Pediatr Adolesc Health Care. 2025; 55(11):101886. doi: 10.1016/j.cppeds.2025.101886
23. Wagener K, Beckhaus J, Boekhoff S, Friedrich C, Müller HL. Sporadic and neurofibromatosis type 2-associated meningioma in children and adolescents. J Neurooncol. 2023;163(3):555–563. doi:10.1007/s11060-023-04344-0
24. Li M, Wang Y, Fan J, Zhuang H, Liu Y, Ji D, et al. Mechanistic Insights into the Long-range Allosteric Regulation of KRAS Via Neurofibromatosis Type 1 (NF1) Scaffold Upon SPRED1 Loading. J Mol Biol. 2022;434(17):167730. doi: 10.1016/j.jmb.2022.167730
25. Miettinen MM, Antonescu CR, Fletcher CDM, Kim A, Lazar AJ, Quezado MM, et al. Histopathologic evaluation of atypical neurofibromatous tumors and their transformation into malignant peripheral nerve sheath tumor in patients with neurofibromatosis 1—a consensus overview. Hum Pathol. 2017; 67:1–10. doi: 10.1016/j.humpath.2017.05.010

26. Khosravi T, Oladnabi M. The role of miRNAs and lncRNAs in neurofibromatosis type 1. J Cell Biochem. 2023;124(1):17–30. doi:10.1002/jcb.30349
27. Murphy C, Vassallo G, Burkitt-Wright E, Hupton E, Eelloo J, Lewis L, et al. A retrospective regional study of aqueduct stenosis and fourth ventricle outflow obstruction in the paediatric complex neurofibromatosis type 1 population; Aetiology, clinical presentation and management. Clin Neurol Neurosurg. 2020; 193:105791. doi: 10.1016/j.clineuro.2020.105791
28. Ardern-Holmes S, Fisher G, North K. Neurofibromatosis Type 2: Presentation, Major Complications, and Management, With a Focus on the Pediatric Age Group. J Child Neurol. 2017;32(1):9–22. doi:10.1177/0883073816666736
29. Fisher MJ, Blakeley JO, Weiss BD, Dombi E, Ahlawat S, Akshintala S, et al. Management of neurofibromatosis type 1-associated plexiform neurofibromas. Neuro-Oncol. 2022;24(11):1827–1844. doi:10.1093/neuonc/noac146
30. Kongkriangkai AM, King C, Martin LJ, Wakefield E, Prada CE, Kelly-Mancuso G, et al. Substantial pain burden in frequency, intensity, interference and chronicity among children and adults with neurofibromatosis Type 1. Am J Med Genet A. 2019;179(4): 602–607. doi:10.1002/ajmg.a.61069
31. Iasella MP, Ruttens D, Hompes D, Vandecaveye V, Sciot R, Deroose C, et al. Close Follow-Up of Patients with Neurofibromatosis Type 1 Reduces the Incidence of Malignant Peripheral Nerve Sheath Tumour. Cancers. 2025;17(8):1306. doi:10.3390/cancers17081306

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