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Management of neurofibromatosis type 1-associated plexiform neurofibromas

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Abstract

Plexiform Neurofibromas (PN) are a common manifestation of the genetic disorder neurofibromatosis type 1 (NF1). These benign nerve sheath tumors often cause significant morbidity, with treatment options limited historically to surgery. There have been tremendous advances over the past two decades in our understanding of PN, and the recent regulatory approvals of the MEK inhibitor selumetinib are reshaping the landscape for PN management. At present, there is no agreed upon PN definition, diagnostic evaluation, surveillance strategy, or clear indications for when to initiate treatment and selection of treatment modality. In this review, we address these questions via consensus recommendations from a panel of multidisciplinary NF1 experts.

Keywords

MEK inhibitor | neurofibroma | neurofibromatosis 1 | plexiform | review

Plexiform neurofibromas (PN) are histologically benign nerve sheath tumors that occur commonly in individuals with the tumor predisposition syndrome neurofibromatosis type 1 (NF1). They are a significant cause of morbidity and, until recently, no effective medical therapies were available. PN arise within nerves and consist of multiple cell types, including Schwann cells, fibroblasts, perineural cells, mast cells, and macrophages.[1] While PN development requires biallelic loss of *NF1* in Schwann cells,[2,3] the *NF1*$^{+/-}$ microenvironment also contributes to PN tumorigenesis.[1,4] The recent regulatory approvals (including United States, Europe, Brazil) of the MEK inhibitor (MEKi) selumetinib for children with NF1 and symptomatic, inoperable PN, as well as promising results from other clinical trials, have changed the clinical landscape with the potential to create a paradigm shift in the management of PNs. This manuscript represents consensus generated across the multidisciplinary authorship team reached after review and discussion of available peer-reviewed literature for the management of NF1-associated PN (see Supplementary Material).

PN Definitions: Clinical, Pathologic, and Imaging

There is no agreed upon PN definition; however, several PN classification systems have been proposed previously using histopathologic, clinical, and imaging findings (Table 1). In the past two decades, with the advent of clinical trials for PN, clinicians have taken a broad view on defining PN based on clinical and imaging findings. Here we propose a clinically relevant, MRI-based classification system of PN that incorporates aspects of these previous systems (Figure 1). We classify PN based on: 1) morphology or internal structure, 2) depth, and 3) relationship to adjacent tissues (Figure 2, Supplementary Figure S1). This classification system may not be fully applicable to some tumors, such as paraspinal PN (which can extend from the spinal nerve root causing diffuse nerve thickening) and discrete neurofibromas (Supplementary Figure S1).

The term "distinct nodular lesion" (DNL) has been used in more recent literature to describe peripheral nerve sheath tumors with a characteristic MRI appearance (Figure 3). These lesions are well-demarcated, appear encapsulated, are ≥3 cm, lack the central target sign characteristic of classic PN, and can be present within or outside of a PN.

Epidemiology, Clinical Presentation, Work-up and Screening, and Genotype–Phenotype Correlations

Epidemiology

Clinically-detectable PN are seen in approximately 30% of individuals with NF1.[5] Case series utilizing whole-body MRI (WB-MRI) estimate the PN prevalence is 50–60% in individuals with NF1 (median PN number of 1.4–3).[6–9] Many PN are diagnosed before 5 years of age suggesting that they may be congenital or develop early in childhood.[10] PN can arise throughout the entire body, but are more common in the craniofacial area, neck, pelvis, and lower extremities.[6,9,11–14]

Clinical Presentation

Asymptomatic and symptomatic PN often coexist within the same individual. Tumor location, size, nerve involvement, and age may all impact symptoms and potential for complications (see "Morbidity" section). In children, >60% of symptomatic PNs are located in the head and neck; in contrast, PN in the thorax and abdomen usually remain asymptomatic.[9,14] Among adults, PN involving the abdominopelvic region, brachial plexus, and lumbosacral plexus carry a high risk of morbidity.[12,15] Dermatologic features can offer clues to PN presence, including thickening of the dermis or the presence of coarse hair or hyperpigmentation (Supplementary Figure S2). Rarely hemorrhage can occur in PN and can be life-threatening.[16,17]

PN may transform to atypical neurofibromas (AN)/atypical neurofibromatous neoplasm of uncertain biological potential (ANNUBP), characterized by at least two of the following features: cytological atypia, hypercellularity, loss of neurofibroma architecture, and an increased mitotic index.[18,19] These tumors are potentially premalignant lesions with unique biology (frequently characterized by heterozygous or homozygous loss of *CDKN2A/B*)[20] and growth characteristics.[11,21] AN/ANNUBP may be asymptomatic, or present with pain and functional deficit. Individuals with AN/ANNUBP are at higher risk for the development of malignant peripheral nerve sheath tumors (MPNST), with a 33% incidence in one study versus the cumulative MPNST risk of 15.8% in the general NF1 population.[18,21,22]

Work-up and Screening

All individuals with NF1 should be assessed for the presence of PN by careful examination and monitored for PN growth. Standard evaluation includes history, physical, and neurological exam. Regional or WB-MRI is the imaging modality of choice for identification and characterization of PN. This is generally indicated in individuals with symptoms suggesting PN or with visible PN to assess size and impingement on critical structures. These findings inform appropriate management (observation and surveillance intervals, additional diagnostic evaluations, or possible treatment).[23] Some practitioners advocate for baseline WB-MRI, particularly in late adolescence or early adulthood when transitioning from pediatric to adult care. This practice is based on reports that total body PN burden is correlated with lifetime risk of MPNST[8,24] and data suggesting that if PN are not present by early adulthood they are unlikely to develop.[25,26] In the future, screening of children with WB-MRI to detect asymptomatic PN may become warranted, if prospective studies identify factors predictive of progression and demonstrate an improved outcome with earlier

Table 1. Published Definitions of Plexiform Neurofibromas (PN) Based on Histopathologic, Clinical, and Imaging Characteristics

Terminology		Description	Reference
Histopathologic		*Neurofibroma:* Benign Schwann cell neoplasm with thin, often wavy nuclei, wispy cell processes, and a myxoid to collagenous ("shredded carrots") matrix. *PN:* Diffusely enlarging and replacing a nerve, often involving multiple nerve fascicles.	18
Histopathologic		*Neurofibromas:* Neurofibromas are characterized by cytologically bland spindle cells with thin, wavy nuclei representing the neoplastic Schwann cell, immersed in a variably loose myxoid stroma. Stromal collagen is characteristic, colorfully likened in classic pathology descriptions to shredded carrots. A variety of other cells are also identifiable in neurofibroma, including perineurial and perineurial-like cells, fibroblasts, and mast cells. *PN:* Plexiform neurofibroma is defined by its involvement of multiple nerve fascicles, each surrounded by perineurium. It most often involves a large nerve or plexus, imparting a bag-of-worms or ropy gross appearance.	19
Clinical description		A proliferation of cells in the nerve sheath extending across the length of a nerve and involving multiple nerve fascicles The term …'plexiform' does not imply involvement of a nerve plexus…rather a network-like growth of neurofibroma involving multiple fascicles of a nerve, leading to a diffuse mass of thickened nerve.	101
Imaging	Nodular	Confined to the nerve	102
	Diffuse	Impinging on surrounding soft tissue	
Imaging	Circumscribed	Locally circumscribed	6
	Plexiform	Invasive or involved multiple nerves	
Imaging	Superficial/deep	Above/below the muscle fascia	103
	Fascicular-nodular	Collection of smaller components that were tubular or spherical or both	
	Diffuse	Lack of any definable geometry	
Imaging	Fascicular	Tubular or rope-like configuration	12
	Nodular	Small, round lesions of different diameter	
	Diffuse	No definable geometry	
	Superficial	Located cutaneously or subcutaneously respecting epifascial membrane and not penetrating into muscle with no clear demarcating borders	
	Displacing	Multinodular smoothly defined borders compressing adjacent structures, primarily along main nerves	
	Invasive	Conglomerating tumors which could not be divided from each other and which penetrate into muscle, fascia, joints, and surrounding tissue	

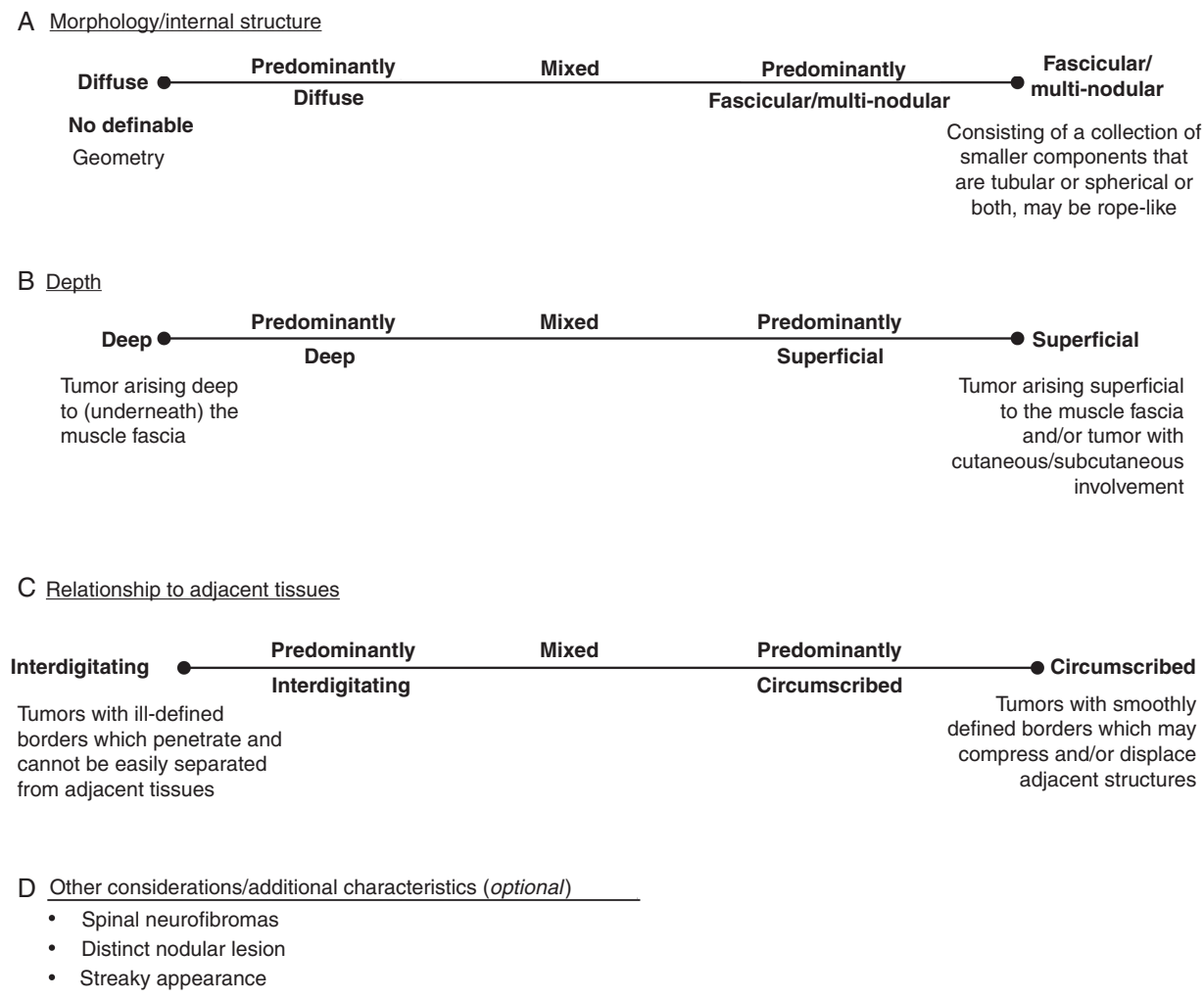

Fig. 1 Proposed plexiform neurofibroma classification schema. For each tumor, determine classification in each category (A–C, D optional).

identification. A biopsy to ascertain the histologic diagnosis of a PN is not needed unless concerning clinical or imaging findings suggest atypical behavior or malignant transformation.

Genotype–Phenotype Correlations

Attempts to correlate *NF1* germline gene variants with specific clinical features have been largely unsuccessful. However, there are some clinically relevant genotype–phenotype correlations predictive of mild[27–33] or more aggressive[29,33,34] phenotypes (Supplementary Table S1)

Natural History

The growth of PN varies between tumors both within and across individuals; however, growth rates remain relatively constant within a PN for prolonged periods of time.[11,25,35] Younger age correlates with more rapid tumor growth (Figure 4A).[11,25,35,36] In children, PN growth rate exceeds increase in body weight over time, suggesting that PN growth is not related solely to normal growth during childhood.[11,35,36] PN growth rate ≥20% per year by volume is unusual after adolescence,[11] and preliminary data in adults (median age 42 years) suggest <5% of PN grow at that rate.[26] Most PNs in older adolescents and adults grow slowly or not at all.[11,25,26]

Spontaneous PN shrinkage over time has been reported in some individuals,[11,25,26] but mainly in adults. In one study, 59% of tumors in 26 adults demonstrated a spontaneous decrease in volume on MRI of ≥20% over nine years.[26] By contrast, in a study of individuals ≤35 years old, a volume decrease of ≥ 10% was seen in only 8.8% of tumors with a median decrease of 3.6% per year.[11] Importantly, spontaneous PN volume decreases ≥20% per year have not been reported.[11,25,26]

No significant differences in estimated PN growth rates have been noted in relation to tumor location, patient sex, race, concurrent pregnancy, or hormonal changes associated with puberty.[11,37,38] In addition, there

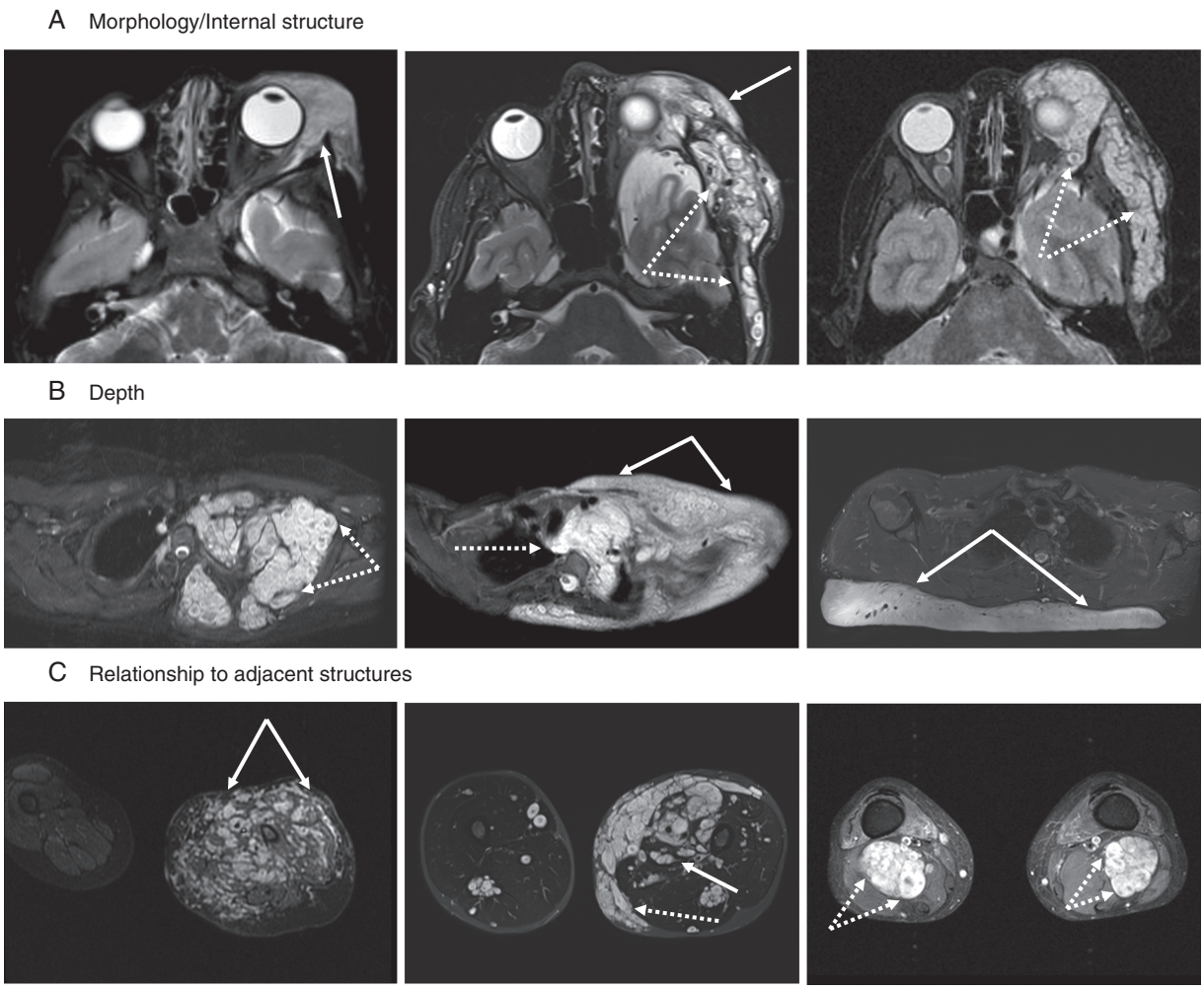

Fig. 2 MRI examples of plexiform neurofibromas (PN) demonstrating tumor characteristics used in the proposed classification schema. All images are fat suppressed with STIR (short tau inversion recovery) technique. (A) The internal structure can be homogeneous without notable architectural elements (left panel, solid arrow), appear as conglomerate of small nodules (right panel, dotted arrows), or show a combination of both features (middle panel). (B) Any portion of peripheral nerves may be affected by PN. Proximal nerve segments give rise to deep internal PN (left panel, dotted arrows), superficial PN (right panel, solid arrows) are associated with terminal nerve branches, but many lesions have components of both (middle panel). (C) The interface between PN and surrounding tissues can range from interdigitating and intricately connected (left panel, solid arrows) to sharply defined and well separated (right panel, dotted arrows), with most lesions falling in between those two extremes (middle panel).

are no prospective data on the impact of hormone medications such as oral contraceptive medications on PN growth rate.

DNL show key differences in growth patterns compared to classic PN, suggesting biological differences. Some DNL have faster growth rates (≥20% per year may be seen even in adulthood) and develop at later ages compared to PN (Figure 4B).[11] In addition, AN/ANNUBP frequently show a distinct nodular appearance on MRI.[21] Additional studies are required to determine if DNL are an imaging correlate for AN/ANNUBP and if they warrant closer surveillance than PN. Growth of single nodular lesions within a PN or rapid tumor growth of ≥20% per year in patients ≥15 years of age should raise concern for tumor transformation to AN/ANNUBP or MPNST.[11]

Tumor Imaging and Measurement

Imaging plays a vital role in the management of people with PN (Supplementary Table S2) as a screening tool at baseline (see "Work-up and Screening" above), for surveillance (in individuals with known PN), to evaluate treatment response, and for preoperative assessment for surgical planning.

Conventional MRI sequences with short tau inversion recovery (STIR) and T2-weighted sequences with fat saturation visualize PN optimally, can be performed without the administration of intravenous contrast material, and are preferred over computed tomography (CT).[39,40] Regional MRI and WB-MRI have different advantages. Regional MRI

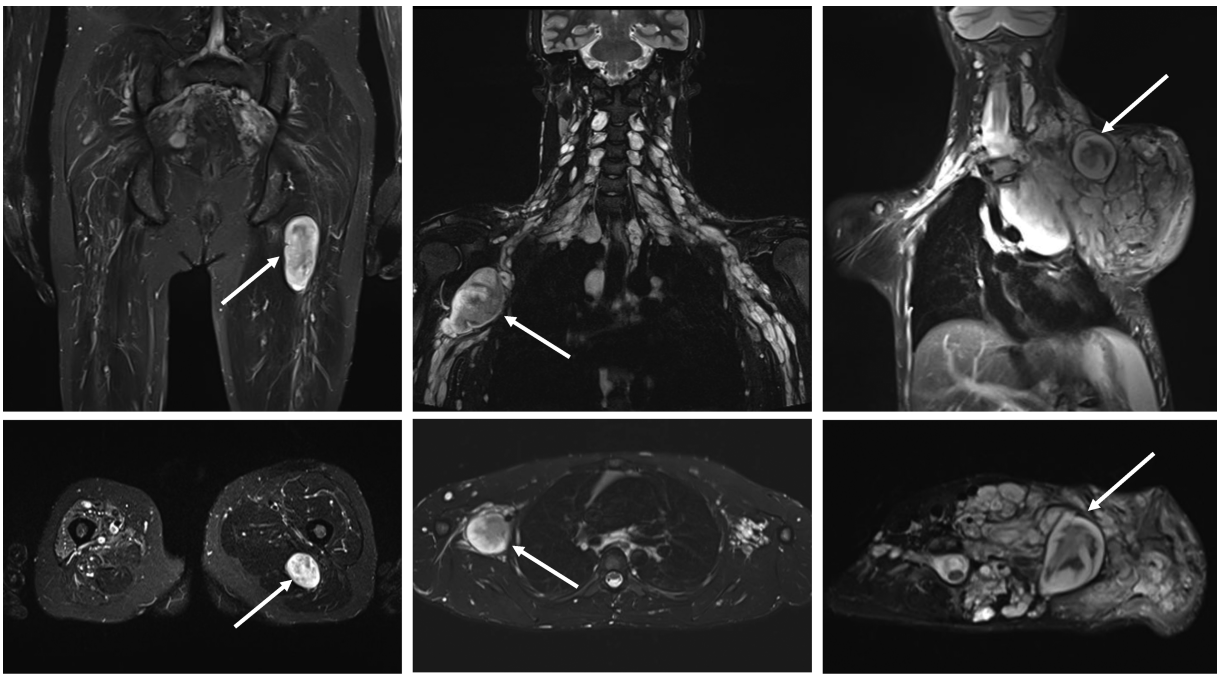

Fig. 3 Coronal (top row) and axial (bottom row) STIR MRI examples of distinct nodular lesions (DNL) in patients with NF1. The left panels show a DNL (arrow) arising from the left sciatic nerve. In the middle panels, plexiform neurofibroma (PN) can be seen along the brachial plexus on both sides, with a prominent nodule present on the right (arrow). On the right, the DNL (arrow) stands out from the background of a large neck, shoulder, and chest PN.

allows evaluating a specific PN in greater detail by optimizing the field of view (FOV) and is recommended for clinical trials. WB-MRI is advantageous in patients with multiple tumors or very large PN that cross traditional anatomic planes. Supplementary Table S2 summarizes MRI protocols and indications.

Imaging for Surveillance

For surveillance of known PN, regional MRI is utilized more often than WB-MRI.[23] Currently, there is no data to support nor consensus on appropriate intervals for monitoring known PN, with intervals ranging from 3 to 24 months in a survey of 30 NF1 practitioners[23]; and clinical practices may vary beyond this. Factors to consider when selecting scanning intervals include: age of patient, tumor location, presence of PN-associated morbidity, imaging appearance, and whether growth of the PN is known from prior imaging. Imaging intervals may be extended for those with clinically or radiographically stable PN over time, or shortened if there is a change in imaging appearance or new symptoms.

For PN concerning for malignant transformation (Supplementary Figure S3 and Supplementary Table S2), metabolic imaging using ^{18}F-fluorodeoxyglucose (FDG) PET with CT (FDG-PET/CT) has high diagnostic accuracy for detection of MPNST arising in the background of PN (sensitivity: 89–100%; specificity: 72–94%) using semi-quantitative markers such as standard uptake values (SUV) and tumor to liver ratio.[41] However, AN/ANNUBP frequently also have avid uptake of FDG on PET imaging.[21] Further, there is a wide range of SUVmax that can be associated with MPNST or AN/ANNUBP and benign PN. Hence, awareness of the risk of a false positive result of FDG-PET in people with NF1 is important, and targeted biopsy is often needed to confirm the histology. Of note, differences in software and methodology may impact quantitative SUV analysis and limit generalization across institutions. There is emerging interest in WB FDG-PET/MRI for NF1 to reduce ionizing radiation from CT.[42] More recently, diffusion weighted MR imaging and dynamic contrast enhanced sequences have been evaluated and shown to detect MPNST with high diagnostic accuracy (sensitivity: 92–100%; specificity: 94–98%).[43,44] To date, these advanced MRI techniques have been piloted by only a few institutions. Prospective studies are underway to compare advanced MRI with FDG-PET for this purpose. Last, WB FDG-PET/CT, WB FDG-PET/MR, and diffusion weighted imaging can be used to target the site of biopsy for a suspicious PN component, and to detect local and/or distant metastases in patients with MPNST.[45,46]

Imaging for Treatment Response

For clinical care, regional or WB-MRI is performed prior to initiating a new therapy. For assessing treatment response, standard one-dimensional (1D) or 2D measurements may be sufficient, although given the complex shape and potential extensive size of PN, linear measurements may be

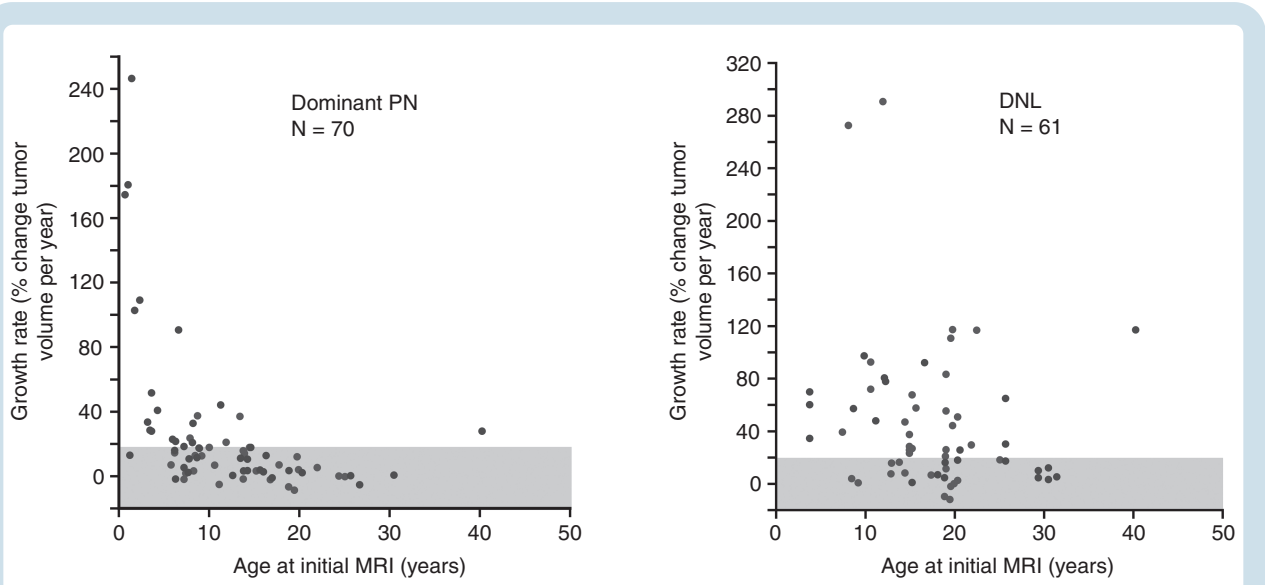

Fig. 4 Tumor growth rate plotted against patient's age at initial MRI for plexiform neurofibromas (PN) (A) and distinct nodular lesions (DNL) (B). A moderate negative correlation was observed for PN, whereas only a weak association was noted for DNL. Adapted from Akshintala S, et al. *Neuro Oncol.* 2020.[6] *Reprinted with permission.*

difficult to reliably measure and track. In the setting of a clinical concern such as suspected treatment failure or treatment-related toxicity, 3D volumetric analysis may have value in the risk-benefit assessment of continuing treatment[47]; however, access to 3D imaging tools is currently limited.

For clinical trials, 3D volumetric tumor analysis is recommended, as it reproducibly detects minor size changes.[47,48] Accurate longitudinal assessment of PN requires consistent image acquisition and 3D measurement tools (eg 3DQI-NF, MINT, BRAIN Lab, MEDex) (Figure 5). Imaging on clinical trials and when treating PN is performed at baseline and serially (typically every four months for the first year with increased intervals subsequently).[47]

Preoperative Imaging Strategy

For PN undergoing resection, localized MRI with FOV encompassing the entire tumor is recommended. CT can assess osseous or pulmonary involvement and, in some cases, can be used to place a preoperative marker to localize a suspicious component that is surrounded by PN. Both CT and MR angiography can assess the intratumoral course of important blood vessels and the need for preoperative embolization.

Morbidity

Impact on Function and Appearance

Depending on their location, PN can cause a wide variety of symptoms including visual or hearing impairments, airway obstruction, speech and swallowing difficulties, motor dysfunction, bowel or bladder dysfunction, disfigurement, and other symptoms. PN-related morbidities are primarily caused by direct impact of the tumor on surrounding structures, and may be life-threatening when they compress vital organs. In one retrospective review of children with PN, the most common PN-related symptoms were pain and motor dysfunction.[49] In another series, the most common symptoms that lead to PN-directed surgical interventions were neurologic deficits, disfigurement, orthopedic symptoms, and airway difficulties.[13]

Notably, children with NF1 and symptomatic PN have a higher mortality rate (3.2%) compared with children without PN or with asymptomatic PN (0.5%).[13] Tumor size impacts the severity of PN-related symptoms, with symptomatic PN and those causing motor impairment tending to be larger.[10,49] These functional impairments have a negative impact on overall quality of life (QOL) for individuals with NF1,[50] emphasizing the need to monitor for improvement in these areas to detect the clinical impact of treatment.

There are few validated functional outcome measures for NF1-related complications; however, progress is being made. For evaluation of motor function, there is good inter- and intra-rater reliability for the Functional Reach, Timed Up and Go, and 10-Meter Walk tests in adults with NF1.[51] In addition, the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) international collaboration has published evidence-based, consensus recommendations for assessment of various functional measures for PN-related morbidities, such as airway[52] and vision.[53] The phase 2 study of selumetinib for children with symptomatic, inoperable PN used prospective functional outcome measures and demonstrated objective improvement in strength, range of motion, and pulmonary function.[54] These results were crucial to the recent regulatory approvals of selumetinib for PN, supporting the inclusion of functional evaluations in future clinical trials for PN.

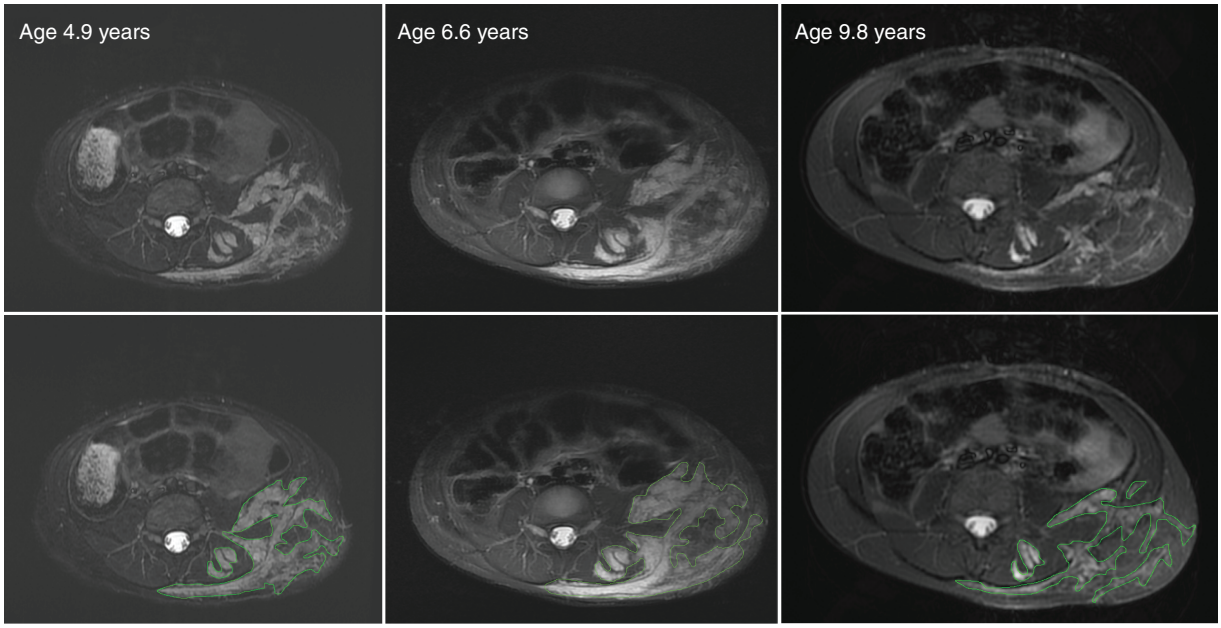

Fig. 5 Longitudinal assessment of plexiform neurofibroma (PN) size using volumetric MRI analysis. While the longest diameter of the left flank lesion remained almost the same over time, the bulk of the PN increased visibly between 4.9 years and 6.6 years of age, at which point the patient started selumetinib therapy resulting in PN shrinkage. Volumetric analysis is performed by identifying tumor contours as shown by the outlines in the bottom panels. This technique allows to detect small changes sensitively and reproducibly.

Impact on Pain

Pain in individuals with NF1-PN can be episodic, chronic, or both; localized to the site of a PN or diffuse; and can range widely in functional impact.[55] The prevalence of pain in individuals with NF1-PN is not well established. Based on natural history studies, only a minority of patients (11–30%) experience significant PN-related pain.[10,36,56] The rate is higher (31–37%) for those enrolled in clinical trials.[54,57] In contrast to PN, pain is often the predominant and/or presenting symptom in most individuals with AN and MPNST[21,58,59]; thus, progressive, severe pain in a PN should raise clinical suspicion for malignant transformation.[59,60]

The mechanisms by which PN cause pain are not well understood and may be neuropathic, visceral, bony, and inflammatory. Pain may be independent of direct tumor effect and may be potentiated by mechanisms leading to hyperalgesia.[61] For example, dysfunction of RAS can result in alteration of pain pathways.[62]

Pharmacologic and nonpharmacologic interventions can reduce PN-related pain (Supplementary Table S3). Recent PN clinical trials reported a reduction of pain, as measured by pain intensity and pain interference, in individuals with tumor response.[54,63,64] There are no NF1- or PN-specific trials using traditional pharmacological agents to treat neuropathic pain, such as GABAergic medications, antidepressants, opioid analgesics, anti-inflammatory drugs, and cannabinoids.

Acceptance and Commitment Therapy (ACT), a cognitive behavioral therapy (CBT) with effectiveness in individuals with chronic pain,[65] significantly decreased pain interference in a recent randomized controlled trial of adolescents and adults with NF1 and PN-related pain.[66] Traditional CBT and mindfulness-based therapies have potential for treating PN pain, but more rigorous research is needed in the NF1 population.[67,68] Additional, potential nonpharmacological interventions for PN pain include heart rate variability biofeedback,[69] acupuncture,[70] and transcutaneous electrical nerve stimulation (TENS).[71]

Impact on Psychosocial Functioning and Quality of Life

Natural history studies indicate that 1/3 of children and adolescents with NF1-PN experience parent-reported social-emotional difficulties such as anxiety, depression, and social withdrawal, with greater disease severity associated with worse internalizing problems[72] and worse QOL.[73] PRO measures completed by pediatric[54] and adult patients[74] enrolling on PN clinical trials documented reduced QOL, with greater PN volume correlated with worse QOL in the adults. Patients of all ages share concerns regarding the impact of PN on social and emotional health, which manifests differently across age groups, reinforcing the importance of assessing psychosocial functioning across the lifespan.[55,75] Medical treatments for PN have resulted in both parent- and child-reported improvements in emotional and/or social aspects of QOL.[54,76] Additionally, e-health interventions that address coping with NF1 symptoms and stress resulted in improvements in QOL[77] and may be relevant for individuals with PN.

Management

Indications for PN-directed Medical or Surgical Treatment

Careful selection of treatment versus observation for PN is important to maximize benefit and minimize risk. Several factors should be considered, including the age of the patient, and whether the PN is causing or at risk for causing morbidity, or demonstrates progressive growth. In most cases, the goal of treatment is improvement or prevention of PN-associated morbidity. The presence of morbidity, especially when refractory to symptomatic treatment, is of paramount importance. In addition, individuals with PN adjacent to or compressing structures such as the spinal cord or airway may not be symptomatic, but are at risk for future morbidity should the tumor grow.

Understanding if the PN is growing is helpful, as the larger the tumor gets, the more likely it may cause morbidity.[49] However, PN growth must be assessed in the context of its growth rate and present/impending morbidity. For example, a PN with rapid growth (>20% increase in volume in the prior year) with impending morbidity is likely a candidate for intervention, while a tumor that is slowly increasing in size (eg 5% per year) with no actual or impending morbidity may warrant observation. Age of the patient is important, especially in cases where PN growth rate is unknown because prior imaging is unavailable. In such cases, age may influence decision-making, as young children are more likely to have growing PN.[11,35] In sum, PN that are causing morbidity, or are growing and associated with impending morbidity, should be considered for treatment. In contrast, in most cases, stable tumors not causing morbidity should be observed, as they may never progress or cause symptoms.

If treatment is indicated, selection of surgical versus medical management should be evaluated with input from a multidisciplinary team including surgeons (general surgery, neurosurgery, orthopedic surgery, plastic surgery, etc.) and NF experts in medicine/pediatrics (oncology/neuro-oncology, neurology, etc.). In general, surgery is the optimal choice if the PN can be resected without significant morbidity. Unfortunately, as PN are invested with the nerve, this is challenging in most cases. Although there are no robust prospective studies on outcomes, the largest retrospective series suggest that complete tumor excision can be achieved in only 15% of cases,[78] with PN re-growth occurring in 43% of those who underwent partial or subtotal resection,[13,78] and permanent sequelae (mostly neurologic) in 5–18% of patients.[13,78] Other considerations include whether resection can be achieved in a single versus multiple surgeries, what recovery may entail, and the urgency of need for tumor reduction. For example, at present, none of the medical therapies approved or tested shrink PN rapidly; thus, for a PN with spinal cord compression causing new and progressive neurological dysfunction, surgery (even subtotal resection) may be indicated to decompress the spinal cord and prevent permanent neurologic disability. When considering medical treatment (such as a MEKi or enrollment on a clinical trial), specific contraindications or preexisting conditions (eg certain cardiac and ophthalmologic conditions) or concerns about using a particular therapy (ie logistics, medication formulation, compliance, long-term safety, etc.) should be assessed.

Assessing for AN and/or MPNST

Prior to starting therapy for a PN, clinicians must be confident that there has not been malignant transformation of the PN. Change in tumor growth rate along with new onset or recent change of PN-related pain should prompt a careful consideration for possible malignancy prior to the initiation of therapy for PN, as the treatment of MPNST is substantively different. Work-up may include additional imaging (see "Imaging for Surveillance" above) and/or tumor biopsy. As many PN are heterogeneous, biopsy should target the area of most concern based on imaging (eg the region with the highest SUV or restricted diffusion); multiple core samples are encouraged in consultation with surgery as applicable. As AN often appear as DNL on MRI either within or separate from a typical PN,[21] biopsy of rapidly growing DNL should be considered. In addition, patients receiving medical treatment for PN remain at risk for MPNST.

Treatment

Surgery

Decisions regarding indications for and scope of surgery need to be tailored to the tumor's extent, location, growth rate, radiologic features, and within the context of the individual patient's overall health. Indications for surgical intervention include actual or impending neurologic compromise or impingement on vital structures. Relative indications for surgical intervention may include pain, disfigurement, and aim to improve activities of daily living. In addition, as MPNST generally arise within preexisting PN and are not always easily distinguished from benign lesions, biopsy plays an important role in distinguishing these diagnoses. The risk of tumor re-growth following surgery is influenced by age and PN location. Retrospective studies[13,78] suggest that tumor control is most difficult in young children and in those whose tumors involve the head, neck, and trunk.

PN in two specific locations, orbital–periorbital plexiform neurofibroma (OPPN) and paraspinal PN, deserve special attention. Although 10–22% of patients with OPPNs suffer vision loss from strabismic amblyopia, no studies exist to support early surgical treatment of strabismus or of the OPPN itself. Given the complex anatomy of OPPNs, which often extend into the orbital muscles, nasolacrimal duct, and the face, a consensus panel recommended nonoperative therapy in the absence of significant tumor growth.[79] Debulking surgery can be considered for progressive tumors that might compromise critical structures or lead to functional decline or disfigurement.

Paraspinal PN with extension into the epidural space can lead to spinal cord compression and progressive radiculomyelopathy. Two small series suggest that the intraspinal component of paraspinal PNs generally involves multiple levels and is amenable to surgical intervention with good functional outcomes and only a small likelihood of recurrence. In one study of 13 patients with cervical cord compression (11 with multi-level cord compression), weakness resolved in 45% of those who underwent subtotal resection of the intraspinal component of the PN, and 18% had no further progression of neurologic abnormalities.[80] A separate study reported 10 patients with PN-related progressive myelopathy (8 with multi-level involvement) or cauda equina dysfunction; gross total resection of the intraspinal PN component was achieved for nine patients. Nine patients had complete recovery of neurological function and the other had significant improvement.[81] Of note, PN that compress the spinal cord without associated symptoms or neurological findings do not necessarily require treatment.

For patients with PN many unanswered questions remain regarding the role of tissue sampling, prophylactic surgery (ie, to prevent malignant transformation), or more aggressive resections to address disfigurement (including face transplantation). For the recently described AN, marginal resection by an experienced surgeon should be considered if feasible without significant morbidity.[82]

Medical Treatment

The emerging understanding of PN pathogenesis, along with the development of preclinical models that mimic patients' tumors in terms of histology and location, has contributed to new precision oncology approaches targeting the tumorigenic Schwann cell and/or the tumor microenvironment.[83] Since the late 1990s, more than 20 clinical trials of targeted therapies for NF1-PN were launched (Table 2). Efficacy trials mostly used progression free survival (PFS) or partial response (PR) as primary objectives, adapting each study's endpoint to the study population enrolled and goals of the study. Several advances have both improved and accelerated the development of clinical trials for PN. The establishment of 3D volumetric MRI analysis of PN provided a more sensitive and reproducible measurement of PN growth and response than 1D or 2D analysis, and has been incorporated into many efficacy trials using volume change as a primary endpoint.[47] Recent trials include patient reported and functional outcome assessments as key secondary endpoints, as the importance of demonstrating clinical benefit is increasingly recognized. Finally, the REiNS international collaboration has helped define standard outcome measures for clinical trials. Additionally, in 2007, the NF Clinical Trials Consortium (NFCTC), sponsored by the Department of Defense NF Research Program, was formed with the goal of advancing clinical trial research for patients with NF. The NFCTC includes 25 clinical centers in the U.S. and Australia (https://www.uab.edu/nfconsortium) and has launched four PN studies (Table 2).

The majority of completed trials have not resulted in a clinically meaningful improvement in PFS or in PR (PN volume decrease ≥20%). Exceptions were a phase II trial of imatinib, which demonstrated PR in a subset of very small PN (<25 mL), and a phase 2 study of peginterferon-α-2b (INF- α), which demonstrated rare PR and substantially prolonged median PFS (29.4 months) compared to the placebo arm (10.6 months) of the previously conducted double-blind, randomized trial with tipifarnib.[84,85]

The recent success of MEKi, targeting a downstream effector of RAS, has changed the landscape for PN management. Phase 1/2 clinical trials of the MEKi selumetinib for children with inoperable symptomatic PN resulted in PR in 71% and 74% of patients, respectively.[54,86] Importantly, patients also experienced less pain and improved function and quality of life while on treatment.[54] Based on these findings, selumetinib became the first medical treatment approved by the FDA for the management of PN in children. Similar responses have been seen in an ongoing phase 2 trial of selumetinib for adults with symptomatic, inoperable PN (NCT02407405).[87] Other MEKi's show promise as well. Interim results from an ongoing phase 2 study of binimetinib for progressive or symptomatic PN (NCT03231306) reveal PR in 70% (14/20) of pediatric and 65% (13/20) of adult participants.[88,89] Mirdametinib had a response rate of 42% (8/19) in adolescents (≥16 years of age) and adults with progressive or symptomatic PN,[63] and a larger study (NCT03962543) in both children and adults is ongoing. Preliminary results of a phase 1/2a trial of trametinib in children with PN (NCT02124772) revealed PR's in 46% (12/26)[90]; other studies using trametinib are in progress (NCT03363217, NCT03741101) (Table 2).

A recent phase 2 trial of cabozantinib, a small molecule tyrosine kinase inhibitor of c-Kit, VEGFR2, MET, RET, FLT3, and the TAM family receptors, for adolescents and adults with progressive or symptomatic, inoperable PN demonstrated a 42% (8/19) PR rate,[64] and has completed enrollment of a stratum of children (3–15 years of age) (NCT02101736). Caution is advised in comparing response rates between studies, given the differences in age at enrollment, PN inclusion criteria, and study design.

A major challenge going forward will be the identification of individualized treatment schedules and/or therapeutic combinations that can provide the best outcomes for all patients who require treatment for PN. These new agents have known and potentially unknown toxicities. Practitioners considering prescribing should be familiar with the various adverse events, potential interventions for side effects, and need for close monitoring. Thus, these agents are best prescribed by providers who have an appropriate infrastructure to rapidly address issues that arise on treatment. Intermittent dosing of effective agents may be a means to reduce toxicity and improve tolerability in patients on long-term therapy.[91,92] This is being evaluated in a clinical trial of selumetinib for patients with NF1-associated tumors (NCT03326388). At present, the ideal length of treatment, durability of response, and long-term adverse events of continuous targeted inhibition are unknown. In addition, some PN do not respond or maintain a durable response to monotherapy. Combination therapies may be needed to improve overall response rate, durability of response, and depth of response. Last, although most studies have focused on treatment of PN already associated with morbidity, preventative therapy (ie treating the PN before it causes morbidity) may be a way to improve overall outcomes for patients with PN. Studies are planned

Table 2. Clinical Trials for NF1 Plexiform Neurofibromas

Phase 1										
Enrollment Dates	Agent (Route)	Mechanism of Action	Trial Design	Median Age (Range) (Years)	*N*	Median Baseline PN Volume (Range) (ml)	MTD	DLT	Response Data	Reference
1997–1999	Thalidomide (po)	Inhibit angiogenesis, anti-inflammatory (TFN-alpha)	4 cohorts of 5 patients; dose-escalation	17.5 (6–41)[a]	20	NA	4 mg/kg/d (max 200 mg/d) continuous	None	4 with minor response (2D)	104
1998–2000	Tipifarnib (po)	Farnesyl transferase inhibitor	3 + 3	6 (4–16)	42 (17 w/ NF1)	NA	200 mg/m^2/dose BID for 21 of 28 day cycle	Myelosuppression, rash, GI toxicity	NA (2D)	105
2001–2006	Peginterferon alpha-2b (sc)	Inhibit proliferation and angiogenesis	3 + 3	9.3 (1.9–34.7)	30	NA	1 μg/kg/wk	Fatigue, behavior changes, neutropenia, myoclonus, ↑ AST/ALT	1/17 pts (3D)	106
2003	Pirfenidone (po)	Antibiotic- modulates cytokine action Anti fibrotic	Pharmacokinetically-guided dose-escalation	10.5 (3–19)	16	NA	500 mg/ m^2/dose TID continuous	Diarrhea, nausea and vomiting	No PR (3D)	107
2008	Photodynamic Therapy (iv, implantable light source)	LS11 photosensitizer + light leads to vascular occlusion, thrombosis	3 + 3	NA	NA	NA	NA (study halted early due to equipment unavailability)	NA	NA	NCT 00716469
2008–2011	Sorafenib (po)	Inhibitor of CRAF, BRAF, RTK (VEGFR-2,3, PDGFR-β, c-kit, Flt3)	3 + 3	8 (6–12)	9	443 (5–10,162)	Unable to determine; intolerable	Tumor pain, rash, mood alteration	No PR (3D)	108
2011–2014	Selumetinib (po)	MEK inhibitor	3 + 3	10.9 (3–18.5)	24	1205 (29–8,744)	25 mg/ m^2/dose BID continuous dosing	Elevated CPK, cellulitis, urticaria, decreased LVEF, mucositis, rash	PR 17/24 (3D)	86
2015–2017	Pexidartinib (PLX3397) (po)	Microenvironment	Rolling six, 3 dose levels	16 (4–21)	16 (3 w/ NF1)	NA	No MTD, highest dose level tolerated: 800 mg/m^2/dose continuous dosing	None	No PR for NF1 patients	109

Table 2. Continued

Phase 2										
Dates	**Agent (Route)**	**Target (Tumor Cell, Microenvironment, Both)**	**Trial Design**	**Median Age (Range) (Years)**	***N***	**Median Baseline PN Volume (Range) (ml)**	**Median TTP (mo)/N with PR (PN Volume ≥ 20%↓)**	**Max PN Volume Decrease**	**Activity (Yes/No)**	Reference
2001–2007	Placebo	Placebo	Randomized, placebo controlled, double blinded, cross-over (TTP)	8.5 (3–21.5)	29	316 (39.6–4896)	TTP = 10.6 mo/0 PR	7%	NA	76
	Tipifarnib	Tumor			31	572 (20.5–5573)	TTP = 19.2 mo/0 PR	11%	No	
2000–2004	Pirfenidone-Adults (po)	Microenvironment	Open label, single arm,	30 (±13.5)[a]	24	NA	NA	>30%	7/24 PR (≥15% PN decrease 3D)	110
2004–2010	Pirfenidone-Children and young adults (po)	Microenvironment	Open label, single arm	8.9 (3–18.8)	36	349 (15–5629)	TTP = 13.2 mo/0 PR	12%	No	84
2006–2009	Imatinib (po)	Both	Open label, single arm	13 (3–52)	36	NA	6 PR	38%	Yes	111
2006–2014	Peginterferon alpha-2b (sc)	Both	Stratum 1: Asymptomatic PN	12.4 (2.8–20.5)	27	440 (9.4–6370)	1 PR (not confirmed)	NA	No	85
			Stratum 2: Orbital PN, PN with pain, or PN with decrease in performance status	9.4 (1.7–21.1)	26	Orbital PN 178 (34–283) Pain PN 503 (95–13,327) Performance status PN 615 (9.7–1,018)	1 PR	NA	No	
			Stratum 3: Progressive PN	7.1 (1.6–17.6)	29	288 (14–3102)	TTP = 29.4 mo	NA	Yes	
2008–2014	Sirolimus (po)	Tumor	Stratum 1: Progressive PN	7.9 (3–45.4)	49	186 (13–4808)	TTP = 15.4 mo 0 PR	17%	Yes	112
			Stratum 2: Nonprogressive PN	16 (3–35)	12	784 (23–2476)	0 PR	7.4%	No	113
2011–2014	Everolimus (RAD001) (po)	Tumor	Open label, single arm	31.6 (19.5–46.4)[a]	23	54.5 (9–453.8)	0 PR	NA	No	114
2014–2017	Mirdametinib (PD-0325901) (po)	Tumor	Open label, single arm	24 (16–39)	19	797.8 (NA)	8 PR	28%	NA	63

Table 2. Continued

Phase 2										
Dates	**Agent (Route)**	**Target (Tumor Cell, Microenvironment, Both)**	**Trial Design**	**Median Age (Range) (Years)**	***N***	**Median Baseline PN Volume (Range) (ml)**	**Median TTP (mo)/N with PR (PN Volume ≥ 20%↓)**	**Max PN Volume Decrease**	**Activity (Yes/No)**	Reference
2014-present	Cabozantinib (XL184) (po)	Both	Stratum 1: Adults	22 (16–34)	23	557 (57–2954)	8 PR (of 19 evaluable)	38%	Yes	64
			Stratum 2: Pediatric	NA	NA	NA	NA	NA	NA	NCT 02101736
2015–present	Selumetinib (po)	Tumor	Stratum 1: PN morbidity	10.2 (3.5–17.4)	50	487 (5–3820)	37 PR	55.1%	Yes	54
			Stratum 2: No PN morbidity	12.3 (4.5–18.1)	25	381(12–3159)	18 PR	46.3%	Yes	115 NCT 01362803
2015–present	Trametinib (po)	Tumor	Phase 1/2 dose escalation, disease expansion	5.5 (1–16)	26	NA	12 PR	NA	Yes	90 NCT 02124772
2016–present	Selumetinib (po)	Tumor	Open label, single arm (adults)	33 (18–60)	23	NA	16 PR	41%	Yes	87 NCT 02407405
2017–present	Binimetinib (MEK162) (po)	Tumor	Stratum 1: Adults	23 (18–55)	25	410 (7–3129)	13 PR (of 20 evaluable)	35.2%	Yes	88,89 NCT 03231306
			Stratum 2: Pediatric	12 (2–16)	20	326 (8–6661)	14 PR	54%	Yes	
2019–present	Mirdametinib (PD-0325901) (po)	Tumor	Stratum 1: Adults	NA	NA	NA	NA	NA	NA	NCT 03962543
			Stratum 2: Pediatric							

Abbreviations: CPK, creatine phosphokinase; D, day; DLT, dose limiting toxicity; ED, erectile dysfunction; GI, gastrointestinal; iv, intravenous; LVEF, left ventricular ejection fraction; mo, months; MTD, maximum tolerated dose; *N*, number; NA, not available; PN, plexiform neurofibroma; po, oral; PR, partial response; sc, subcutaneous; TNF, tumor necrosis factor; TTP, time to progression; 2D, area; 3D, volumetric.
[a]Mean age reported.

to evaluate if prophylactic MEKi treatment of asymptomatic PN in high-risk locations can prevent tumor progression and morbidity.

Radiation Therapy

Evidence for using radiation therapy (RT) for treatment of PN is limited to retrospective studies. Biologic rationale for RT use is extrapolated from treatment of similar benign tumors including schwannoma and meningioma. Series using stereotactic radiosurgery (SRS) for benign spinal tumors (meningioma, schwannoma, and neurofibroma) include mostly adults, only a few with NF1, and do not specify if patients with PN were included.[93–95] Stereotactic approaches are highly conformal techniques used to deliver high doses of RT to focal, well-defined tumors. As PN often have indistinct borders, delineation of RT target volumes for highly conformal techniques can be difficult. The few case reports using RT specifically for PN include various techniques (both conventional fractionation and stereotactic approaches), have limited follow up, and are not sufficient to inform management recommendations.

Primary concerns with use of RT in NF1-PN are compounding of the baseline risk of RT-induced neoplasms in NF1, as well as the malignant degeneration of PN into MPNST.[22,96–98] There is also theoretical concern that RT could exacerbate underlying vasculopathy in patients with NF1, who are high risk for vasculopathy. RT should be avoided for the treatment of PN, particularly in children given this known risk and unknown benefit. This recommendation does not supplant clinical judgement in individual circumstances if RT is considered for local control and symptom management when resection or systemic therapy are not options. Multidisciplinary input regarding all treatment options, including resection, systemic therapies, and clinical trials, and careful weighing of the risk-benefit ratio, should be considered prior to recommending the use of RT for PN.

Alternative Therapies

Little is known about the use of complementary and alternative medicine (CAM) in the prevention and treatment of PN. In a survey of 1489 individuals in the Children's Tumor Foundation NF registry,[99] approximately 25% of respondents with NF1 regularly take dietary supplements or nutraceuticals specifically to treat symptoms associated with their NF. PN were the second most common complication targeted by nutraceutical use. Vitamin D and Fish oil were the most commonly used nutraceuticals overall, and turmeric/curcumin and bee propolis were the most common supplements used to try to prevent or treat PN. Cannabis derivatives were the most commonly used nutraceutical to treat NF-related pain. Of the 64 separate nutraceuticals indicated in the survey results, there are few reports of preclinical or prospective clinical data to support their use. In one small series, 2 patients receiving a combination of the Mediterranean diet and Curcumin had improvement in cutaneous neurofibroma tumor burden and one patient had a reduction in PN size, although these results have not been validated in a larger population.[100] Overall, although CAM and nutraceuticals are frequently used and discussed in the NF1 population, there is little data to support efficacy in treating NF1-PN at this time.

Conclusion

Many recent advances have been made in the management of NF1-PN. In addition to surveillance, symptomatic management, and surgery, effective targeted medical therapies such as MEKi have become available. The regulatory approvals of the MEKi selumetinib for children with symptomatic inoperable PN is an important advance. PN which are causing morbidity, or growing and at risk for impending morbidity, should be considered for treatment with the modality deemed most appropriate based on location, symptoms, and patient goals. Validated preclinical models and meaningful clinical trial designs and outcome measures are available to guide clinical development of novel therapies. The clinical implementation of therapies for NF1 requires careful consideration of multiple factors and should be done with the input of a multidisciplinary team experienced in NF1.

Supplementary Material

Supplementary material is available at *Neuro-Oncology* online.

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