Treatment of malignant peripheral nerve sheath tumors in pediatric NF1 disease

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Abstract
Background Malignant peripheral nerve sheath tumors (MPNSTs) are rare yet highly aggressive soft tissue sarcomas. Children with neurofibromatosis type 1 (NF1) have a 10% lifetime risk for development of MPNST. Prognosis remains poor and survival seems worse for NF1 patients.

Methods This narrative review highlights current practices and pitfalls in the management of MPNST in pediatric NF1 patients.

Results Preoperative diagnostics can be challenging, but PET scans have shown to be useful tools. More recently, functional MRI holds promise as well. Surgery remains the mainstay treatment for these patients, but careful planning is needed to minimize postoperative morbidity. Functional reconstructions can play a role in improving functional status. Radiotherapy can be administered to enhance local control in selected cases, but care should be taken to minimize radiation effects as well as reduce the risk of secondary malignancies. The exact role of chemotherapy has yet to be determined. Reports on the efficacy of chemotherapy vary as some report lower effects in NF1 populations. Promisingly, survival seems to ameliorate in the last few decades and response rates of chemotherapy may increase in NF1 populations when administering it as part of standard of care. However, in metastasized disease, response rates remain poor. New systemic therapies are therefore desperately warranted and multiple trials are currently investigating the role of drugs. Targeted drugs are nevertheless not yet included in first line treatment.

Conclusion Both research and clinical efforts benefit from multidisciplinary approaches with international collaborations in this rare malignancy.

Keywords Emerging therapies · MPNST · NF1 · Radiotherapy · Surgical treatment · Systemic treatment

Introduction
Children with neurofibromatosis type I (NF1) are at an increased risk of developing multiple tumors including neurofibromas as a result of neurofibromin inhibition involved in the Ras pathway [1]. NF1 disease is a frequent genetic disease, affecting 1 in 3000 to 5000 people. The cumulative life time risk of developing malignant peripheral nerve sheath tumors (MPNST) is 8–13% [2–5]. MPNSTs are rare in the general population encompassing only 2–4% of all soft tissue sarcomas [6]. Less than 10% of those patients are children [7, 8], but MPNST is the third most common non-rhabdomyosarcoma STS (NRSTS) in children [9]. Of all MPNSTs, almost 40–50% of patients are NF1 patients; the remaining 50–60% develop sporadically or are radiation-induced [10–15].

Genetically, NF1 is characterized by the loss of heterozygosity of the NF1 tumor suppressor gene, although not in all patients [16]. Loss of NF1 function leads to activation of the Ras pathway and upregulation of mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) leading to cell proliferation [17]. NF1 patients develop neurofibromas, plexiform neurofibromas, in a nerve plexus lateral of the vertebrae and sacrum. For malignant transformation, loss of neurofibromin alone is not enough to develop an MPNST [18]. Although the landscape of tumor drivers in MPNST is not clear yet, MPNST are characterized by extensive genetic
instability with several frequently observed genetic alterations considered as tumor driver events. The most frequent events are amplification of receptor tyrosine kinases and mutations of the genes CDKN2A/p16, SUZ12, TP53, and PTEN. One or more are considered necessary in the development of an MPNST [19–24].

The cornerstone of treatment in MPNST remains surgical excision, which is strongly associated with improved survival. However, MPNSTs have been reported initially unresectable in 17–53% of children, which is higher than any other pediatric NRSTS [25–29]. Radiotherapy and chemotherapy are incorporated in the treatment of unresectable or large, localized pediatric MPNST [29]. Despite curative intents of treatment, survival remains relatively poor with 5-year survival rates of 51–66% [8, 25, 29]. Promisingly, survival has improved over the past decade in pediatric MPNST [8]. And children have a superior survival in comparison with adult patients [7, 8]. Although the influence of NF1 on survival is strongly debated in adults [30], in pediatric series, it has repeatedly been shown an independent predictor of survival [8, 25, 29, 31]. Importantly, NF1 children tend to present with larger tumors than non-NF1 patients, and the outcome is still poor and unsatisfactory. There is a need for novel treatment strategies and compounds.

This review will discuss the surgical approach to these tumors, current treatment recommendations, and emerging therapeutic options in pediatric NF1–associated MPNST.

**Genomic landscape**

NF1 disease is based on a germline mutation in the NF1 gene on chromosome 17q11.2. The NF1 gene is large, spanning 350 kb of genomic DNA and encoding 11–13 kb mRNA containing 59 exons, and results in a 320-kDa neurofibromin protein. Neurofibromin downregulates the Ras protein, and frequent germ line or somatic mutations are present in several human cancers. Therefore, NF1 is considered a tumor suppressor gene. More than 500 mutations in the NF1 gene have been identified. Mostly, they result in truncation of the neurofibromin protein and loss of function [32]. The development of neurofibromas result as a loss of a second allele, although this cannot be established in all neurofibromas, possibly due to the complex and large NF1 gene or to the existence of other, so far unknown genes involved in a second hit [16]. The understanding of the genomic landscape of MPNST in NF-related and non-NF1-related disease is complex and incomplete. A number of recurrent pathological events are recognized, lacking a consistent pattern among individuals and tumors. It includes recurrent loss of “classical” tumor suppressor genes NF1, TP53, CDKN2A/p16 and more recently also mutations in PRC2 complex genes [20, 33]. The PRC2 complex consists of chromatin-modifying proteins involved in epigenetic suppression of gene expression. In MPNST, loss of function mutations have been observed in SUZ12 and EED in a mutually exclusive manner, and also in regulators of the PRC2 complex, such as EPC1, CHD4, AEBP2, and ATRX [24]. In addition, it should be noted that there is considerable intra-tumor heterogeneity, complicating our understanding of tumor driver events in MPNST [34].

**Diagnostics of MPNST**

Whenever a malignant tumor arises from a peripheral nerve or within a pre-existent neurofibroma, diagnostic criteria are fulfilled for an MPNST. However there is still lack of standardized pathology diagnostic criteria outside these settings. Cells involved may resemble Schwann cells, perineurial cells, and fibroblasts; tumors can therefore morphologically be heterogeneous. Classically, MPNSTs consist of monomorphic spindle cells arranged in long fascicles. Due to alternating cellularity, a marble-like aspect is commonly given. Perivascular cuffs are a typical feature. Nuclei are often wavy or buckled, and mitotic figures may be numerous. The cytoplasm is inconspicuous. When arising in a neurofibroma, high cellularity with fasicular arrangement and mitotic figures make the diagnosis of an MPNST. However, there is a broad morphological spectrum ranging from spindle cell (most common) to epithelioid and pleomorphic histology [35, 36]. Immunohistochemistry shows variable features with incomplete staining of S100 and SOX10 in up to 85% of the cases, in contrast to melanoma and schwannoma that are commonly strongly positive for these markers. However, very importantly, when these markers are absent, an MPNST cannot be ruled out. CD34 and EMA may be positive but they are unspecific and therefore not very helpful. MDM2 is expressed in a subset of tumors often NF1 related, but there is no amplification of the corresponding gene as seen in dedifferentiated liposarcoma [35–37]. Loss of H3K27me3 due to mutational inactivation of the PRC2 complex has been observed in a subset of MPNST showing often high-grade morphology and an association with previous radiation therapy or sporadic occurrence. In NF1-related tumors, this protein is aberrant to a lesser extent. Neurofibromas with or without atypia are reported to have a retained protein, which can aid in the distinction from MPNST [38]. Methylation profiling seems to be a reliable molecular technique to differentiate biologically relevant groups of peripheral nerve sheath tumors as well [39].

**Imaging of MPNST**

In NF1 patients, the distinction between (plexiform) neurofibroma and MPNST is complex. They may both present with similar symptoms, making it commonly impossible to differentiate between benign and malignant lesions based just on clinical presentation [40, 41]. Imaging plays an important role in diagnostic work-up, as biopsies are cumbersome in NF1 patients especially since they may be painful and result in
persisting nerve damage [42]. Additionally, in NF1 patients, sampling errors are common [43, 44]. Magnetic resonance imaging (MRI) is widely used but may be inadequate to detect and especially distinguish benign and malignant lesions [45, 46]. Although the presence of a target sign, a hypointense region on T2-weighted images, represents a benign lesion with great likelihood, its absence is unspecific [47]. The use of 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET-CT) has gained popularity in NF1 patients to detect MPNSTs. Several studies suggest a high sensitivity of up to 95% to detect MPNSTs using the maximum standardized uptake values (SUVmax) [45, 48, 49]. However, while the most commonly used threshold is ≥ 3.5, an ideal threshold is lacking as some studies suggest high false positive rates using this threshold [50, 51]. Numerous studies have tried to find parameters with higher accuracy and reproducibility to detect MPNSTs. This includes the use of the SUVmax to liver SUVmean or SUVmax (T/L ratio) which generally results in equal accuracy as SUVmax [52–54]. Thresholds vary between 1.5 and 3.0, and an ideal threshold has yet to be established. The use of T/L ratio does however diminish measurement variations between scanners. Delayed scanning at 4 h has been proposed as well and may increase specificity, but requires more resources and exposes patients to additional radiation [55]. More recently, functional MRI sequences including diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) have shown promising results [50, 56]. Because MPNSTs show increased cellularity, minimal ADC values of < 1 × 10−3 may be useful. Reported sensitivity ranged between 89 and 98% and specificity 93 and 94%. Further research is however necessary to establish their role in the diagnostic work-up of MPNST. The use of PET-MRI scans in NF1 populations is attractive as it combines the accuracy of both modalities and diminishes radiation exposure [46, 51].

**Liquid biopsies**

Liquid biopsies have established an important role in detection and treatment of numerous cancers over the past decades. These include breast cancer [57], prostate cancer [58], and lung cancer [59], but they have not yet been widely used in NF1 and sarcomas. To date, three studies have been published on liquid biopsies, reporting the utility of four circulating biomarkers. One study found elevated levels of adrenomedullin (ADM) as a potential biomarker of malignant transformation among NF1 patients with and without MPNST [60]. Concentrations of ADM were higher among patients with MPNST compared with those with only plexiform neurofibromas (0.24 vs 0.18 ng/mL, p = 0.03). Another study reported soluble AXL (sAXL) to be higher among NF1 patients with plexiform neurofibromas and MPNSTs compared with NF1 patients with dermal neurofibromas only [61]. But sAXL could not differentiate MPNST patients from those with plexiform neurofibromas only. The third study found insulin growth factor-binding protein 1 (IGFBP1) elevated in MPNST patients compared with NF1 control patients [62]. IGFBP1 levels were able to detect MPNST with 90% sensitivity and 50% specificity. The same study also found elevated levels of regulated upon activated T-cell expressed and secreted (RANTES) to detect MPNST with 90% sensitivity and 26% specificity.

**Staging of MPNST**

MPNSTs are present in 5–11% of cases with synchronous metastases [13, 15, 63]. Metastatic sites of MPNST are similar to other STS and usually involve the lungs. They may also metastasize to the bone and liver, and in rare occasions to the regional lymph nodes and even the brain [63, 64]. Staging of MPNSTs therefore requires at least preoperative lung CT scanning which may be accompanied with an 18F-FDG-PET scan. Other staging modalities may be used in selected cases but generally do not play a role in MPNST work-up. Avidity of other lesions than the MPNST on 18F-FDG-PET scan may however require further investigation. A sentinel node procedure should not routinely be employed, because of the low probability of lymph node involvement.

**Surgical management**

**Surgical margins**

Ideally, MPNSTs should be removed with clear margins in order to minimize local recurrence rates and optimize survival, making it the routine treatment of choice [11, 13, 65, 66]. Postoperative morbidity is however high when resecting MPNSTs, especially when they originate from major nerves or in the brachial or sacral plexus. Contrarily, conventional and even atypical neurofibromas can be excised using nervesaving surgery resulting in minimal morbidity yet with low recurrence rates [67]. It is therefore important to have a reliable diagnosis before surgically excising a nerve sheath tumor in NF1 patients, as unnecessary function loss may be avoided in a patient cohort that is already prone to disabilities. Nonetheless, even when obtaining microscopic-free margins (R0), MPNSTs can recur [10–12, 68, 69]. Some argue that this may be due to its perineural origin, and microscopic skip lesions may be present along the nerve [70]. In a recent survey, several surgeons would advocate possibly resecting more of the nerve of origin, but this has not been studied in a clinical setting [71]. Fresh frozen coupes may be indicated intraoperatively to ascertain complete resection in nerve endings [10, 12, 70]. However, several large MPNST cohorts in adults have shown that microscopic-positive margins do not impair survival [11, 13, 15]. It has also been shown that close margin
surgery, including epineural dissection of adjacent nerves, in combination with radiotherapy does not significantly increase recurrence rates in STS [72, 73]. This indicates that MPNSTs arising from a plexus could initially be treated with en bloc resection of its originating nerve, yet nerves that are not completely encompassed by tumor may be spared. Such a surgical approach may obviate the need for a forequarter amputation in some children, which is important to bear in mind when children may survive well beyond 5–10 years [8, 29].

**Reconstructions**

Resection of functional nerves is sometimes inevitable and postoperative functional deficits are reported in 30–40% of MPNST patients [74]. Especially when survival is slowly increasing for pediatric patients, preventive or counter-acting measures should be taken into consideration. To date, functional reconstructions, reconstructions aimed at restoring lost function, are only rarely performed in any STS [75, 76]. Reasons for this include the hesitance of surgeons to perform such operations, not knowing the possibilities for reconstruction, and the lack of literature on indications and outcome as the focus of research has been on improving oncological outcomes [76]. Nonetheless, research has shown that good functional outcomes can generally be expected despite the use of radiotherapy and chemotherapy, even in nerve reconstructions [76–78]. A recent unpublished survey among several surgical subspecialties involved in MPNST treatment showed that there is interest in performing functional reconstructions in MPNST patients, but surgical oncologists were least likely to consider such reconstructions even though they operated most patients. Regardless of subspecialty, respondents reported a minimal prognosis of 3 years or more before functional reconstructions should be considered. With an increasing knowledge of the use of (acute) nerve transfers in trauma and brachial plexus birth palsy, these techniques could be incorporated in the treatment of MPNSTs as well. Especially, since children are known to experience better results after nerve reconstruction than adults [79]. Moreover, distal nerve transfers may facilitate reconstruction outside of an irradiated field and diminish time to restoration of function. Other options to restore function also include tendon transfers or grafting as well as innervated (free) muscle transfers or cutaneous flaps. Exact choice for reconstruction relies on multiple factors such as tumor location, defect size, and need for coverage of soft tissue defects. Combining the knowledge of reconstructive possibilities by nerve and reconstructive surgeons as an extension to oncological resections may therefore improve the delicate balance between oncological and functional outcomes. Discussions regarding function preservation must be held before initial surgery and be weighed in when considering prognosis and the use of radiotherapy. The use of free flaps may for instance diminish postoperative complications when radiotherapy is administered [80, 81]. Future research should be encouraged to explore the field of functional status after MPNSTs in children, and define indications and guidelines to incorporate functional reconstructions as part of the surgical treatment plan.

**Radiotherapy**

The exact use of radiotherapy in MPNST is controversial, even more so in pediatric patients, as improvement of oncological outcomes needs to be considered in light of potential side effects. Radiotherapy is administered to increase local control of MPNST, but has not shown to affect overall survival (OS) [11, 15, 82]. The dosage of radiotherapy usually followed adult STS guidelines that recommended 60–66 Gy in a postoperative setting or 50 Gy preoperatively for tumors ≥ 5 cm and positive margins [82–84]. In adults, it has shown that preoperative administration reduces long-term fibrosis and therefore enhances limb function, albeit a higher rate of postoperative complications [85, 86]. In children, several studies try to limit the dose of irradiation for STS. Radiation treatment is known to stunt growth of involved tissues and a reduced dose may be beneficial in decreasing side effects. However, this reduced dose is not based on randomized trials and it may limit the effectiveness of irradiation. In the European paediatric Soft Tissue Sarcoma Study Group (EpSSG), irradiation doses for NRSTS ranged from 50.4–54 Gy for tumors of high grade (G2 or 3), size > 5 cm, or irresectable tumors [29]. In a recent nationwide series of pediatric MPNST in the Netherlands including 70 patients, radiotherapy was administered in 37.5%, with no difference between NF1 and sporadic patients [8]. Preoperative radiotherapy was applied in 20% of children receiving radiotherapy. Although both pediatric studies could not confirm the additive role of radiotherapy in pediatric MPNST, based on the adult results with a higher treatment dose, it is advised to apply radiation in pediatric MPNST also [13].

**Chemotherapy**

The role of chemotherapy in MPNST is limited, especially in NF1-associated MPNST and has not been fully established [9, 27, 87–90]. In advanced MPNST disease where it is estimated that negative margins cannot be achieved by surgery alone, (neo) adjuvant chemotherapy and radiotherapy are applied. In adult studies, the most established chemotherapeutic drugs in MPNST and STS patients are ifosfamide and doxorubicin, alone or in combination [91]. In pediatric NRSTS, various chemotherapy combinations are used, including vincristine, cyclophosphamide, ifosfamide, doxorubicin, and dactinomycin [27, 89]. The most recent pediatric MPNST
study used the combination ifosfamide and doxorubicin, in analogy to the most used combination in adults [29]. In a recent adult analysis, the chemotherapy response varied between 17.9 (NF1 related) and 44.4% (non-NF1 related) [92]. Two pediatric studies studied chemotherapy response in (non) NF1 disease. In a German-Italian study including 167 pediatric MPNST patients, the response to chemotherapy was significantly lower in NF1 in comparison with non-NF1 patients, i.e., 17.6% and 55.3%, respectively [25]. In the EpSSG study including 26 evaluable chemotherapy patients, the chemotherapy response was 46.2% with no difference between NF1 (40%) and non-NF1 patients (50%) [29]. The role of chemotherapy in pediatric MPNST is mostly for children with unresectable disease providing moderate chemotherapy response, and most data indicate a lesser chemotherapy responsiveness in children with NF1 disease.

### Survival

In the large meta-analysis of American and European pediatric NRSTS, NF1-associated MPNST was the most unfavorable STS in children. The OS for all STS was 60.0% and 51.5% at 5 and 10 years, respectively. For MPNST-NF1 the 5-year OS was 11.1% (3.8–32.3%), while the 5-year OS in the MPNST non-NF1 group was 44.7% (32.1–62.3%) [9]. Earlier studies reported an outcome of 5-year OS of 55.1% for non-NF1 pediatric MPNST and 32.1% for NF1 MPNST in a cohort of 167 pediatric patients [25]. Two more recent cohorts of patients showed ameliorated survival outcomes. In a cohort of 51 patients, the 5-year OS for localized non-NF1 MPNST was 80% and 42.6% for NF1-related MPNST [29]. Another study reported 5-year OS of 52.4% for NF1-related MPNST and 75.8% for non-NF1-related MPNST [8]. These results are relatively favorable compared with outcome in adult patients with MPNST. In most mentioned pediatric studies, chemotherapy was included in the standard for care for large or advanced MPNST and seems to indicate a role in the systemic therapy in the treatment of pediatric MPNST. For metastatic and recurrent disease in both adult and pediatric patients, the results of treatment are extremely poor and there is a need for other treatment strategies in MPNST.

### Emerging therapeutic options

Considering the biology of MPNST tumors, obvious and potential targets can be recognized. Growth and activation receptors, such as vascular endothelial growth factor receptors (VEGFR), epidermal GFR (EGFR), and platelet-derived GFR (PDGFR), activate two pivotal intracellular activation pathways, i.e., the MAPK signal transduction pathway and the P13K-AKT-mammalian target of rapamycin (mTOR).

Potential targets for therapy are found on all three levels of normal signal transduction, i.e., receptor kinases, MAPK pathway, and the P13K-AKT-mTOR pathway. Currently, the most considered in NF1 disease is inhibition of the MAPK pathway via MEK inhibitors (MEKi). MEKi potentially neutralize the loss of NF1 in controlling Ras activation. Selumetinib is a MEK1/2 inhibitor therefore can convey an anti-tumor signal by inhibiting Ras signals. In pediatric NF1 patients, selumetinib was very effective in controlling the growth of inoperable plexiform neurofibromas. Partial response was observed in 17/24 patients (71%) [93]. Selumetinib was consequently approved in 2019 by the US FDA for treatment of pediatric patients (≥3 years) with symptomatic or inoperable plexiform neurofibroma. In the treatment of MPNST, selumetinib has not yet been approved, but several trials including (plexiform) neurofibromas and some including MPNST are being conducted (i.e., NCT03433183, NCT02124772). Targeting of upstream tyrosine kinase receptors, alone or in combination with chemotherapy, can also de-activate the MAPK or mTOR pathways. A phase 2 randomized study of doxorubicin plus olaratumab (anti-PDGFRα antibody) compared with doxorubicin monotherapy showed a better OS and trend towards improved median progression-free survival for the combination treatment arm [94]. The study included MPNST patients but did not report separate analyses of this subgroup. Imatinib inhibits specifically the tyrosine kinase domain in ABL (effective in BCR-ABL translocated leukemia), c-KIT, and PDGFR. Imatinib has proven activity in other (pediatric) STS, including dermatofibrosarcoma protuberans (DFSP), gastrointestinal stromal tumor (GIST), and desmoid fibromatosis. However, in MPNST, imatinib has not been found effective [95, 96]. Other RTK inhibitors, such as erlotinib, sunitinib, sorafenib, cediranib, and dasatinib, are all potential inhibitors of NF1-related tumors but have not been found effective in few phase 1 studies with limited information on effectiveness, and they all reported on considerable side effects [97–102]. Inhibition of the mTOR pathway has been effective in several tumor models [103]. One trial in 25 adult MPNST patients administered everolimus and bevacizumab combination therapy, but found only stable disease in 3 patients [104]. Currently, several combination therapies with mTOR inhibition are being undertaken including at least in some part of MPNST patients (NCT02584647, NCT01661283, NCT03433183, NCT02008877, NCT02601209). Anti-GD2-based immunotherapy could potentially be useful in MPNST. Gangliosides are abundantly expressed in neuro-ectodermal-derived tissues (Schwann cells) and tumors. In neurofibromas, the expression of gangliosides has been established [105]. For MPNST, this has not yet been studied. The CH(O)14,18 chimeric mouse-human anti-GD2 antibody has proven to be safe and effective in pediatric high risk neuroblastoma tumors resulting in significantly increased OS [106]. Dinutuximab has been FDA-approved and dinutuximab-beta has been EMA-approved for...
standard use in high risk neuroblastoma. So far, no studies applying anti-GD2 antibodies in MPNST or other neuro-ectodermal tumors (melanoma, non-small cell lung cancer) have been conducted. Another type of immunotherapy using anti-CTLA4 and/or anti-PD(L)-1 inhibitors has proven effectiveness in several tumors (melanoma, non-small cell lung cancer, mesothelioma and others). A recent phase 2 trial combining nivolumab with ipilimumab in advanced sarcomas yielded promising effects, although the study did not specify the included types of sarcomas [107]. One trial is currently ongoing in MPNSTs specifically investigating the effect of pembrolizumab (NCT02691026). Oncolytic viruses have proven effective in vivo, and one trial is currently investigating the effect of oncolytic measles virus in MPNST patients (NCT02700230) [103].

Conclusion

Pediatric NF1 patients have a 10% lifetime risk–developing MPNST. MPNSTs are genetically unstable tumors with multiple genetic alterations superimposed on the germ line NF1 genetic defect. MPNSTs are relatively chemo-insensitive tumors for which the mainstay of treatment is still resection with tumor-free margins. We eluded novel possibilities to use reconstructive techniques such as nerve reconstructions to increase postoperative function without compromising survival. Adjuvant radiotherapy is important in establishing local control in R1 resections. However, the NF1 deficiency carries a risk for increased secondary tumors later in life. Many novel and potential compounds aimed at the molecular pathways involved in growth and development of MPNST and neurofibromas have been recognized. Considering the rarity of MPNST, for future trials, it is important to combine MPNST patients with patients with plexiform neurofibroma or in combination with other sarcomas (basket trials). Advancing the future of NF-affected individuals is important and challenging.

Code availability Not applicable

Authors’ contributions All authors contributed equally.

Data availability Not applicable

Compliance with ethical standards

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Ethics approval Not applicable

Consent to participate Not applicable

Consent for publication Not applicable

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