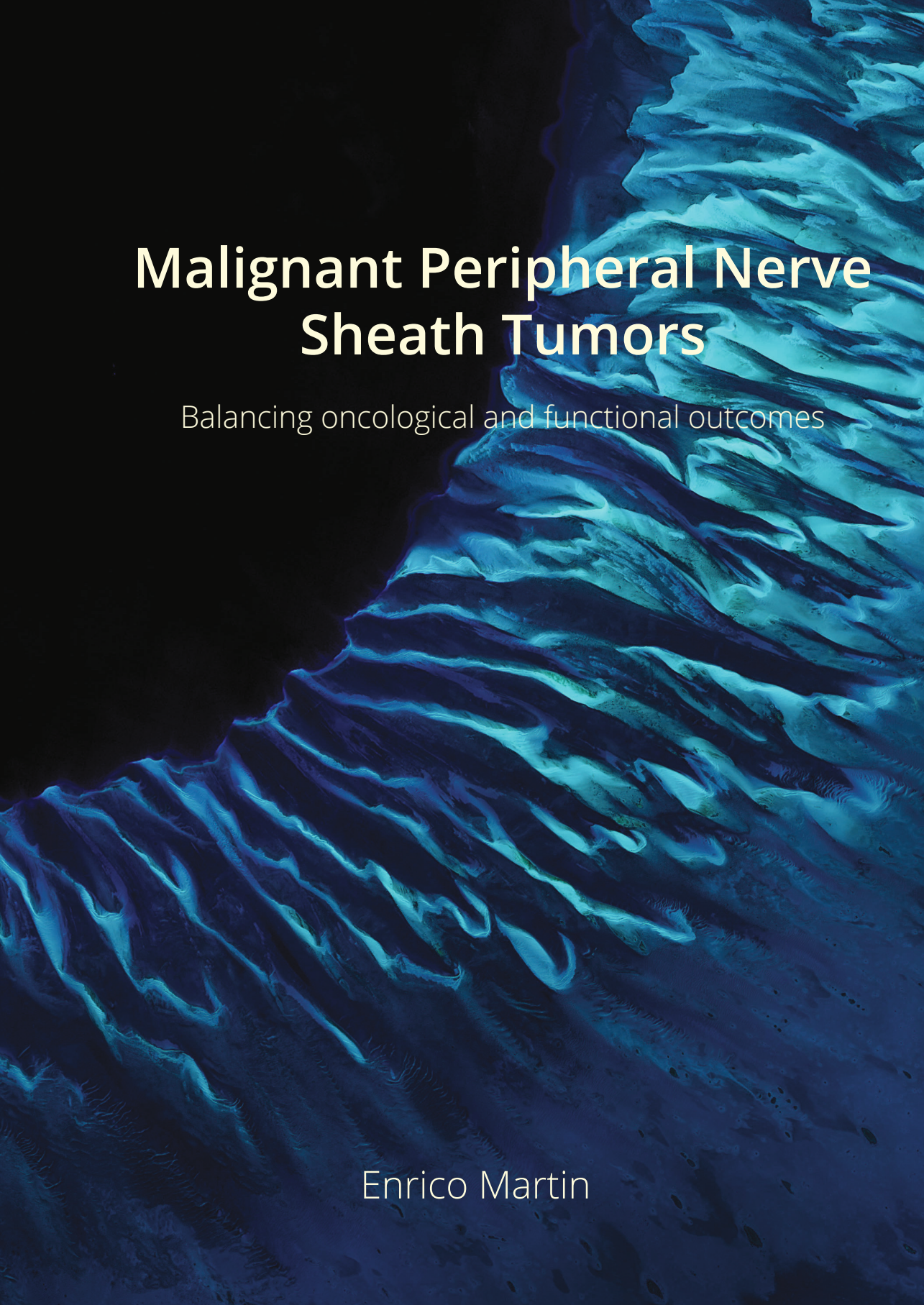

Malignant Peripheral Nerve Sheath Tumors

Balancing oncological and functional outcomes

Enrico Martin

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Malignant Peripheral Nerve Sheath Tumors: Balancing oncological and functional outcomes

PhD thesis, Utrecht University, the Netherlands

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Malignant Peripheral Nerve Sheath Tumors

Balancing oncological and functional outcomes

Maligne Perifere Zenuwschedetumoren

Een balans tussen oncologische en functionele uitkomsten

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

donderdag 10 december 2020 des middags te 2.30 uur

door

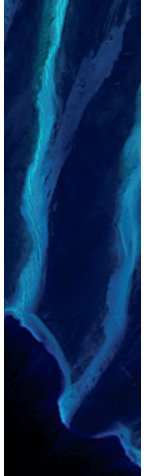
Enrico Martin

geboren op 8 januari 1995
te Leiderdorp

Promotoren:	Prof. dr. J.H. Coert Prof. dr. C. Verhoef Prof. dr. M.A.J. van de Sande
Copromotor:	Dr. W.J. van Houdt

For my family and friends

CONTENTS



1

General Introduction and Thesis Outline

Epidemiology of MPNST

Malignant peripheral nerve sheath tumors (MPNSTs) are a rare subtype of soft tissue sarcoma (STS). STS comprise approximately 80 different subtypes of which at least half are aggressive and carry the potential of metastasizing. MPNSTs are aggressive sarcomas originating from peripheral nerve supporting tissues and can therefore occur in any part of the body making up 2-3% of all STS.[1,2] Based on data from the Dutch cancer registry (IKNL) the incidence of MPNST is approximately 1.7 per million inhabitants (**Figure 1**). This means that 25-30 new patients present annually in the Netherlands. Although most patients present with sporadic disease, 25-50% of MPNSTs are associated with neurofibromatosis type 1 (NF1).[3–6] NF1 is an autosomal dominant condition with an incidence of 1:3000.[7] NF1 patients carry a loss-of-function germline mutation in the *NF1* gene which encodes the Ras inhibiting protein neurofibromin.[8] Activated Ras signaling consequently results in cell survival and proliferation. Due to their germline mutation, NF1 patients commonly have multiple benign dermal neurofibromas or plexiform neurofibromas, but are also at an increased risk of developing malignant tumors over the course of their life. MPNSTs are the main cause of death in the NF1 population and patients carry an estimated 8-16% lifetime risk of developing an MPNST.[7,9] Besides sporadic and NF1-associated MPNSTs, a smaller subset (5-10%) of MPNSTs are radiation-induced.[3,4,6] MPNSTs have a dismal prognosis with 5-year survival rates varying between 40-60% for localized disease.[3–6,10–12] Additionally, 10-20% of patients will present with metastatic or unresectable disease and up to 50% will develop metastases over time.[3–6,13–15]

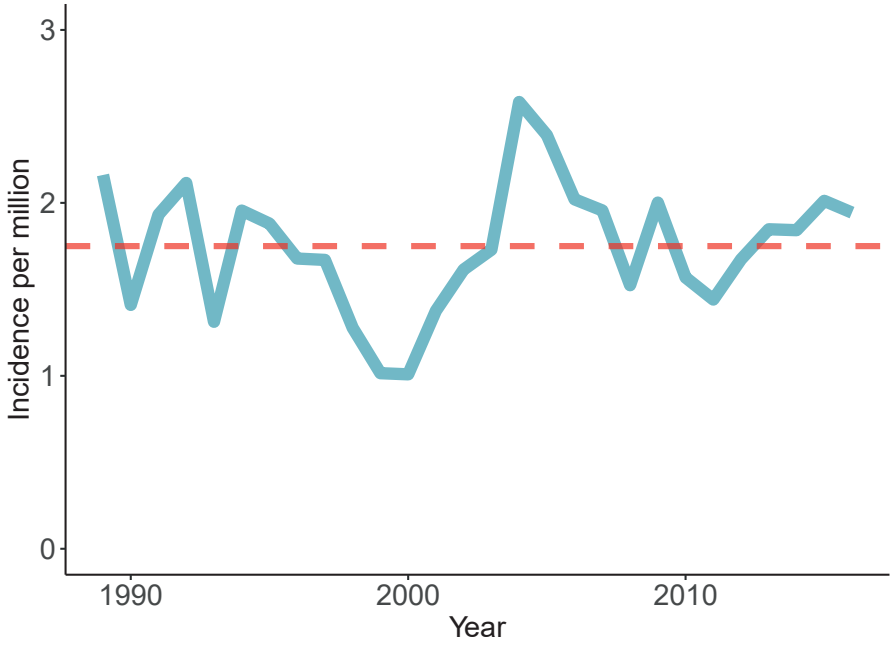


Figure 1 Incidence of MPNST in the Netherlands

General treatment

Treatment of MPNST typically follows high-grade STS guidelines.[16] Correct diagnosis before treatment is advised and generally requires the use of MRI and biopsy. However, in both sporadic and NF1 patient populations, MPNSTs originating in or near major nerves may present with similar symptoms as benign nerve sheath tumors (BPNST).[17,18] The diagnostic accuracy of MRI is furthermore doubted as BPNSTs and MPNSTs can show similar characteristics on MRI.[19,20] This is especially troublesome in the NF1 population as many patients have numerous deep-seated (plexiform) neurofibromas and repeated biopsies are cumbersome, painful, and possibly damaging.[21] The use of positron emission tomography-computed tomography (PET-CT) has gained popularity in NF1 patients as it has shown increased accuracy compared to MRI for the detection of MPNST.[22] However, the exact use and ideal thresholds for semiquantitative parameters remain unknown. Subsequent treatment of an MPNST requires complete surgical resection, as it has been the only proven therapy to increase survival in localized disease.[4,15] Radiotherapy can be administered, similar to other STS, to improve local control in case of positive margins or large tumors.[4,23,24] Neoadjuvant administration of radiotherapy is gaining popularity in STS as it decreases radiation field and dosage.[25,26] The use of radiotherapy can be questioned as it has not been shown to affect survival and can cause growth problems in a pediatric population and possibly secondary malignancies in NF1 patients. Despite the use of wide resections and radiotherapy, MPNSTs recur and metastasize commonly. The use of chemotherapy is controversial, although some studies suggest a benefit in high-grade, large, and deep MPNST.[27,28] Chemotherapy is more commonly administered in pediatric MPNST and its use is already implemented in the European Pediatric Soft Tissue Sarcoma Study Group and Children's Oncology Group guidelines. In any metastasized MPNST cytotoxic chemotherapy regimens have unsatisfactory responses. New therapies are therefore warranted and several studies have tried to elucidate altered cellular pathways in MPNSTs that are eligible for targeted therapy.[29,30] Ideal pathways are nevertheless not yet known. Overall, there remains a lack of solid evidence for ideal treatment of MPNSTs. This is further complicated by its rareness and presentation to several surgical subspecialties possibly resulting in divergent treatment strategies.

Grading and staging of MPNST

The use of current grading and staging systems in MPNST is debated. Such systems could aid prognostication and impact treatment allocation. STS are commonly staged by the American Joint Committee of Cancer (AJCC) staging system for STS (**Table 1**). The AJCC staging system is however of minor prognostic value in MPNST.[3,5,6] Histological grading for STS including MPNSTs are done according to the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system (**Table 2**). The FNCLCC is widely used, but has only been shown to differentiate prognosis in MPNSTs between grade 1 and 3 in one study.[15] Hence, current staging and grading systems do not seem to be of great prognostic value in MPNST. Low-grade MPNSTs according to either AJCC or FNCLCC make up less than 10% of patients with yet an unclear group of intermediate grade MPNSTs. NF1-related tumors complicate the matter further, as (plexiform) neurofibromas may transition into MPNSTs (**Table 3**). So-called atypical neurofibromas/ atypical neurofibromatous neoplasms of uncertain biological potential (ANNUBP) may show mitoses as well and can be seen as a transitional state before becoming truly malignant.[29] When more than 3 mitoses per 10 high-power fields are seen one should consider it a low-grade MPNST according to a recent consensus overview.

Table 1 American Joint Committee on Cancer soft tissue sarcoma staging system 8th edition.

Grade	Definition
Grade 1	Any well-differentiated tumor
Grade 2	Moderate to poorly differentiated tumor ≤5cm
Grade 3	Moderate to poorly differentiated tumor >5cm
Grade 4	Any metastatic tumor

cm: centimeter

Risk factors

Staging MPNSTs is thus difficult as most MPNSTs are high-grade and can present and behave differently. Additional risk factors should therefore possibly be taken into account. Until now risk factors in MPNST have varyingly been reported in literature, including the effect of tumor site, tumor depth, age, NF1 status, and treatment-related factors.[3–6,10–12] NF1 status is notably the most debated risk factor as many authors proposed a negative influence of NF1 disease on survival, yet a meta-analysis in 2012 contradicted this phenomenon for studies published after 2000.[30] Ever since, there has been one large study in adult patients still suggesting a negative influence of NF1 disease nevertheless.[6] In children specifically, risk factors have been studied even less commonly. Yet most reported presence of NF1 disease to have a worse prognosis independent of other factors.[10,31,32] Many studies on MPNST have been limited by

Table 2 Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) gradng system.

Scoring system		Definition
Tumor differentiation		
	1 point	Tumor closely resembling adult mesenchymal tissue
	2 points	Tumor for which histological typing is certain
	3 points	Embryonal and undifferentiated sarcomas
Mitotic count		
	1 point	0-9 mitoses per 10 HPF
	2 points	10-19 mitoses per 10 HPF
	3 points	≥20 mitoses per 10 HPF
Tumor necrosis		
	0 points	No tumor necrosis
	1 point	≤50% necrosis
	2 points	>50% necrosis
Histological grade		
	Grade 1	Total score of 2-3
	Grade 2	Total score of 4-5
	Grade 3	Total score of 6-8

HPF: high-power field

their population size as few have been able to report on more than 100 patients. Then again, most were single center and single surgical subspecialty cohorts of patients.

Functional status

In STS literature, focus has remained on improving oncological outcome and diminishing postoperative complications. However, as STS are usually large tumors requiring major resections of soft tissues, postoperative morbidity can be significant, yet these outcomes have had little attention in literature. Although nowadays a limb-sparing approach is standard-of-care for extremity STS, amputations are still performed. Indications for amputations differ, but major neurovascular involvement is still often a reason for amputation, because of anticipated functional deficit.[33–35] It has additionally been shown in several studies that the resection of any nerve in extremity STS results in diminished function.[35–40] MPNSTs arise from nervous tissue and occur most commonly in the extremities, brachial plexus, or lumbosacral plexus.[11] Nevertheless, postoperative morbidity has rarely been studied in MPNST specifically even though they are at high risk of function loss by definition. In extremity STS generally, the resection of nerves may be prevented by epineural dissection whenever the tumor encases the nerve by less than 50-75%.[41,42] It is a technique in which the surgeon performs a planned positive margin thus requiring the administration of radiotherapy. This combination does not

impair oncological outcome in STS. Even so, its application and safety in MPNST is not entirely clear as guidelines simply recommend performing complete and wide resections to achieve R0 margins. The resection of nerves is likely to be inevitable in many cases, but functional reconstructions may still be possible. Such reconstructions include the reconstructions of tendon, muscle, and nerve function and are increasingly being employed in trauma cases, yet are not standard of care in any STS.[43,44] Nerve reconstructions provide the opportunity to not only regain motor function, but also restore lost sensation. Moberg already proposed in the '50s that an insensate hand as good is as a non-functional hand.[45]

Table 3 Pathological definitions of transitional states between neurofibroma, low-grade MPNST and high-grade MPNST.

Diagnosis	Pathological definition[a]
Neurofibroma	Benign Schwann cell tumor with thin, wavy nuclei, wispy cell processes, and myxoid to collagenous matrix. Immunohistochemistry includes extensive but not diffuse positivity of S100 and SOX10 and a lattice-like CD34 positive fibroblastic network.
Plexiform neurofibroma	A neurofibroma which is diffusely enlarging and replacing a nerve, commonly including multiple nerve fascicles. It is delineated by EMA positive perineurial cells.
Neurofibroma with atypia	Neurofibroma with only atypia, generally manifesting as scattered bizarre nuclei
Cellular neurofibroma	Neurofibroma with hypercellularity, but retained neurofibroma architecture and <1 mitosis per 50 HPF
ANNUBP	Schwann cell tumor with at least 2 of 4 features: cytologic atypia, loss of neurofibroma architecture, hypercellularity, >1 mitosis per 50 HPF and <3 mitoses per 10 HPF
Low-grade MPNST	ANNUBP feature, but with 3-9 mitoses per 10 HPF and no necrosis
High-grade MPNST	MPNST with at least 10 mitoses per 10 HPF or 3-9 mitoses per 10 HPF combined with necrosis.

[a]: classification adapted from Mietinnen et al. 2017[29], ANNUBP: atypical neurofibromatous neoplasm of uncertain biologic potential, HPF: high-power field, MPNST: malignant peripheral nerve sheath tumor

Aim and outline of this thesis

Because of the rare nature and heterogeneous presentation of MPNST many questions remain unanswered. This thesis set out to investigate various knowledge gaps regarding oncological treatment and outcome of MPNST (**Part I**) as well as to explore the field of functional outcomes and reconstructions in these patients (**Part II**).

In **Part I** this thesis will study several questions regarding treatment variation in MPNSTs, risk factors associated with survival, diagnostic accuracy of current imaging techniques, and future possibilities for non-cytotoxic treatment. In **Chapter 2** we will investigate the treatment variation and association with survival per tumor site, including rare tumor sites as intracranial and spinal tumors. To obtain enough cases we will use the Surveillance, Epidemiology, and End Result database. As no study has yet been able to investigate a truly nationwide cohort of patients, thus minimizing selection and referral bias, in **Chapter 3 and 4** we will investigate overall treatment of MPNST in the Netherlands. We will use the Dutch cancer registry and national pathology database to identify all patients from 1989 onwards. As children and adult patients are generally treated differently, **Chapter 3** will focus on adult patients and **Chapter 4** on pediatric patients. In **Chapter 3** we will further explore differences in treatment and survival between retroperitoneal and non-retroperitoneal MPNST. In **Chapter 4** we will investigate differences in treatment and survival between NF1 and non-NF1 associated MPNSTs in children. Also, in **Chapter 2-4** we will investigate the association of clinicopathologic and treatment-related factors with survival. As treatment of MPNSTs may vary and different surgical subspecialties treat these patients, we will explore what drives differences in oncological treatment considerations in **Chapter 5** by means of an international survey. In **Chapter 6** we will investigate diagnostic accuracy of currently available non-invasive tests to detect MPNSTs. Current literature will systematically be reviewed and using Bayesian bivariate meta-analyses the accuracy of several MRI and PET characteristics will be studied. Additionally, the use of liquid biopsies will be assessed. As MPNSTs respond poorly to current cytotoxic systemic treatment regimens, in **Chapter 7** we will investigate current literature on possibilities for targeted- and immunotherapies. Literature will systematically be reviewed to assess all *in vivo* evidence as well as published and ongoing human trials investigating such therapies.

In **Part II** this thesis will investigate functional outcomes and morbidity after the resection of MPNST as well as exploring the option for the use of functional reconstructions to possibly diminish morbidity. In **Chapter 8 and 9** we will systematically review literature to investigate the use and outcomes of functional reconstructions in extremity STS. The effect of radiotherapy and chemotherapy on success rates of reconstructions will be assessed as well. In **Chapter 8** all case series describing the reconstruction of tendons, muscles, and nerves will be reviewed. In **Chapter 9** all cases, including case reports, of nerve reconstructions specifically will be reviewed in depth. As morbidity is

likely high in MPNSTs, but functional reconstructions seem uncommonly used, we will investigate current attitudes of surgeons towards incorporating function preservation in MPNSTs in **Chapter 10**. Differences in attitude between surgical subspecialties will therefore be assessed in specific. Finally, an international collaboration among several surgical subspecialties was set up for this thesis including 10 Dutch cancer centers and the Mayo Clinic in Rochester to retrospectively collect data on both oncological and functional outcomes in MPNSTs (the **MONACO** study). In **Chapter 11** we will use data acquired in the **MONACO** study to investigate the prevalence of postoperative motor and critical sensory loss, patients at high risk for postoperative morbidity, and the use and outcomes of functional reconstructions in MPNST.

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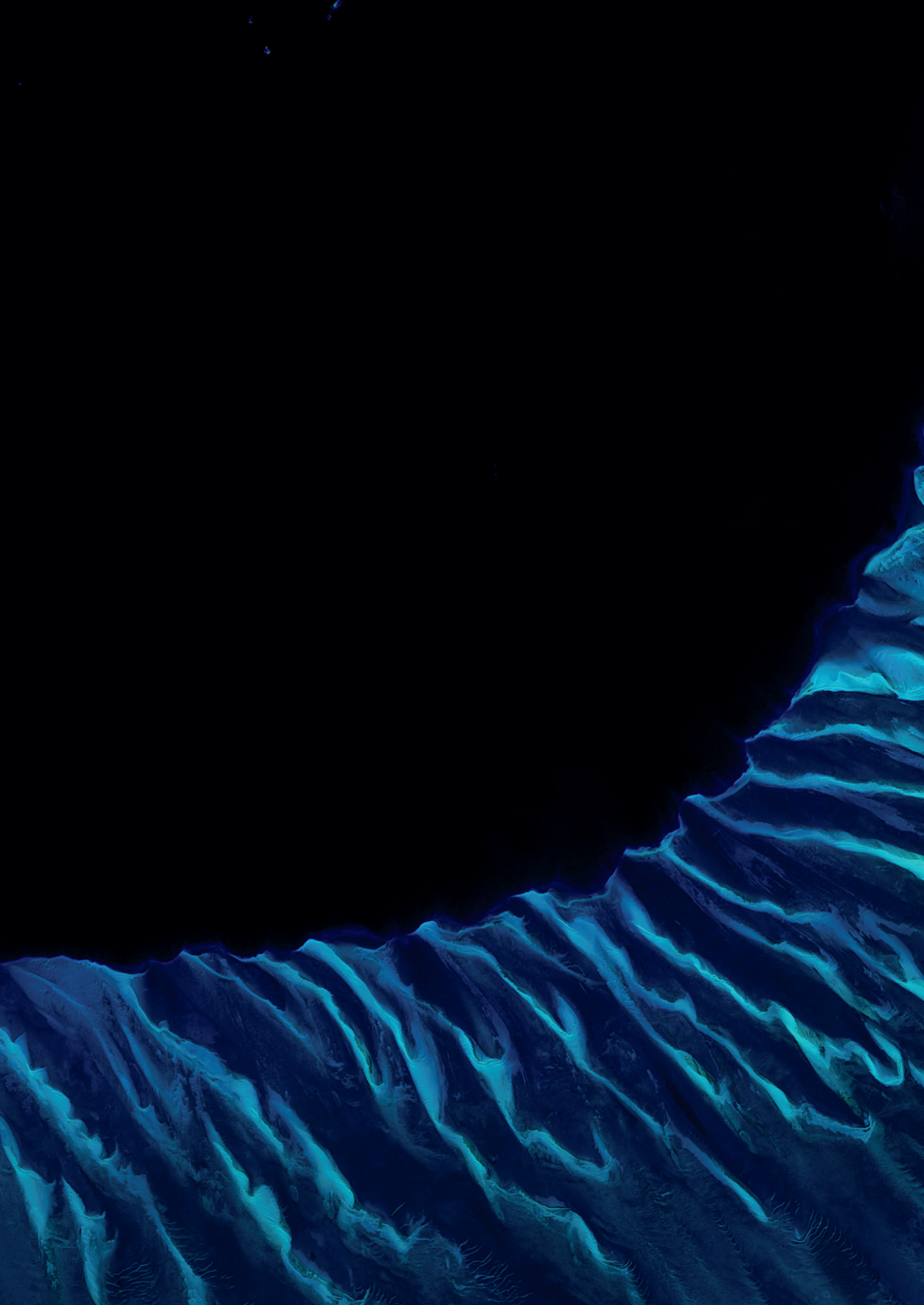

PART I

Oncological Outcomes and Treatment of MPNST

2

Treatment and Survival Differences Across Tumor Sites in Malignant Peripheral Nerve Sheath Tumors: a SEER Database Analysis and Review of the Literature

Martin E
Muskens IS
Coert JH
Smith TR
Broekman MLD

Neuro-Oncology Practice. 2019 Apr, 6(2): 134-43.

Abstract

Background Currently, literature is scarce on differences across all possible tumor sites in malignant peripheral nerve sheath tumors (MPNSTs). To determine differences in treatment and survival across tumor sites and assess possible predictors for survival, we used the Surveillance, Epidemiology, and End Results (SEER) database.

Methods MPNST cases were obtained from the SEER database. Tumor sites were recoded into: intracranial, spinal, head and neck (H&N), limbs, core (thorax/abdomen/pelvis), and unknown site of origin. Patient and tumor characteristics, treatment modalities, and survival were extracted. Overall survival (OS) was assessed using univariable and multivariable Cox-regression hazard models. Kaplan-Meier survival curves were constructed per tumor site for OS and disease-specific survival (DSS).

Results 3267 MPNST patients were registered from 1973-2013; 167 intracranial (5.1%), 119 spinal (3.6%), 449 H&N (13.7%), 1022 limb (31.3%), 1307 core (40.0%), and 203 unknown (6.2%). The largest tumors were found in core sites (80.0mm, IQR: 60.0-115.0mm) and the smallest were intracranial (37.4mm, IQR: 17.3-43.5mm). Intracranial tumors were least frequently resected (58.1%), whereas spinal tumors were most often resected (83.0%). Radiation was administered in 35.5-41.8%. Independent factors associated with decreased survival were: older age, male sex, black race, no surgery, partial resection, large tumor size, high tumor grade, H&N site, and core site (all $p<0.05$). Intracranial and pediatric tumors show superior survival (both $p<0.05$). Intracranial tumors show superior OS and DSS curves, whereas core tumors have the worst ($p<0.001$).

Conclusion Superior survival is seen in intracranial and pediatric MPNSTs. Core and H&N tumors have a worse prognosis.

Introduction

Malignant peripheral nerve sheath tumors (MPNST) are rare sarcomas, encompassing only 2%-4% of all soft tissue sarcomas.[1,2] The incidence of these tumors is 1:100.000 in the general population.[3] However, in patients with neurofibromatosis type 1 (NF1) the incidence may be as high as 3-13% [4–6] and 23 to 51% of all MPNSTs are related to NF1.[4,7–12] A slight predominance in males has been reported.[7,9,10,13] The peak incidence of these tumors differs between NF1-related tumors and sporadic tumors. NF1 patients have an incidence peak in the third and fourth decades, sporadic tumors are usually diagnosed in the sixth decade.[12] Although some suggest a worse prognosis for NF1 patients, its influence on survival has recently been subject of debate.[9–12,14,15]

Currently, no standardized treatment for MPNSTs exists.[3,10,16] Gross total removal of the tumor with wide margins is still considered the best prognostic factor for overall survival, which is reflected in the European Society for Medical Oncology Guidelines.[17] The ability for complete resection largely depends on the location of the tumor and its adjacent structures.[4,18–22] The efficacy and indications of radiotherapy remain to be a subject of debate.[23] Additionally, the role of chemotherapy in the treatment of MPNSTs is currently still under investigation,[24] with recent evidence indicating an added value of neoadjuvant epirubicin and ifosfamide in high grade, large, and deep MPNSTs.[25]

Differences in survival per tumor site have repeatedly been reported.[10,11,14,26] However, variation in outcomes has not been assessed across all anatomical sites, mainly due to the rare nature of MPNSTs. The Surveillance, Epidemiology, and End Results (SEER) program is a cancer registry that collects data from 18 geographic areas across the United States, encompassing approximately 28% of its population. As such, the SEER database provides a means of assessing possible predictive factors of survival and treatment strategies for rare tumors as MPNSTs at different anatomical sites. This study appraises the differences in patient characteristics, treatment, and survival for MPNSTs arising from different sites in the SEER database.

Methods

Data Source

Data were obtained from the SEER database from 1973-2013. The International Classification of Disease for Oncology (ICD-O-3) histology codes were used to identify cases. Malignant peripheral nerve sheath tumors (ICD-O-3: 9540/3, 9560/3, 9561/3) from any site were selected. Our Institutional Review Board has exempted the SEER program from review.

Covariates

Covariates extracted for analysis were: sex, age (≤18, 19-59, and ≥60 years), race (White, Black, Asian & other), tumor site, SEER tumor grade (I-IV), tumor size, extent of resection, administration of radiotherapy, timing of radiotherapy to surgery (prior to, after, during, prior to and after surgery), and survival. Tumor sites were recoded using ICD-O-3 site codes into: intracranial, spinal, head and neck, limbs, core (including chest, abdomen, and pelvis), and NOS (not otherwise specified or unknown, **Supplemental Table 1**). In the SEER database, tumor size is determined from pathological reports, or from radiologic reports in case of preoperative treatment, unclear pathological reports, or in case no surgery was performed. Surgical procedures were coded differently in the SEER before and after 1998 and extent of resection can be interpreted from them. A single variable was constructed using codes prior to 1998 and after 1998 to evaluate extent of surgical resection from all time periods. These were recoded into the following subgroups: no surgery, biopsy, partial resection, gross total resection, surgery not otherwise specified, and unknown status of surgery (**Supplemental Table 2**).

Statistical analysis

Data were stratified per tumor site and descriptive statistics were performed on demographics. Only primary tumors were used for survival analyses. Univariable and multivariable Cox proportional hazard analyses were performed for each tumor site to evaluate possible factors of influence on overall survival (OS). Subsequently, a univariable and three multivariable Cox proportional hazard models were constructed for all primary MPNSTs combined with tumor site as a separate variable. These three models were separated to appraise influences of different therapy regimens on overall survival and avoid correlation among variables included. P-values <0.05 were considered statistically significant. Bonferroni correction was applied to correct for multiple testing. Kaplan-Meier survival curves for overall survival and disease-specific survival (DSS) were constructed for MPNSTs per site. Statistical analyses were conducted using IBM® (Armonk, NY) Statistical Package for the Social Sciences (SPSS)® version 24 (IBM Inc., 2016) and Kaplan-Meier curves were created using R version 3.3.3 (R Core Team, 2017).

Results

Patient population

3267 patients with MPNSTs were identified in the SEER database: 167 intracranial (5.1%), 119 spinal (3.6%), 449 head and neck (13.7%), 1022 limb (31.3%), 1307 core (40.0%), and 203 NOS & unknown (6.2%, **Table 1**). The mean age was 47.6 years (SD: 21.0). The majority of patients were male (54.1%) and white (78.9%). Most patients were only treated surgically (46.8%), with a combination of surgery and radiation being the second most common treatment strategy (32.8%). 53.8% were of unknown tumor grade. Most often tumors were classified as grade IV (16.8%) and the median size of all tumors was

Table 1 Demographical differences between tumor sites.

Variable	Definition	Total	Intracranial	Spinal	H&N	Limbs	Core	NOS & Unknown	P
Number of patients		3267	167	119	449	1022	1307	203	
Age	<18	282 (8.6)	10 (6.0)	9 (7.6)	47 (10.5)	90 (8.8)	104 (8.0)	22 (10.8)	**<0.001**
	19-59	1970 (60.3)	105 (62.9)	67 56.3)	228 (50.8)	662 (64.8)	791 (60.5)	117 (57.6)	
	60+	1015 (31.1)	52 (31.1)	43 (36.1)	174 (38.8)	270 (26.4)	412 (31.5)	64 (31.5)	
	Mean (SD)	47.6 (21.0)	50.9 (20.1)	49.1 (21.7)	51.1 (22.5)	45.5 (20.8)	47.5 (20.3)	47.3 (21.9)	
Sex	Female	1501 (45.9)	83 (49.7)	51 (42.9)	180 40.1)	478 (46.8)	619 (47.4)	90 (44.3)	0.103
	Male	1766 (54.1)	84 (50.3)	68 (57.1)	269 (59.9)	544 (53.2)	688 (52.6)	113 (55.7)	
Race	White	2579 (78.9)	144 (86.2)	93 (78.2)	365 (81.3)	786 (76.9)	1020 (78.0)	171 (84.2)	**0.001**
	Black	417 (12.8)	16 (9.6)	12 (10.1)	45 (10.0)	163 (15.9)	163 (12.5)	18 (8.9)	
	Asian & other	253 (7.7)	5 (3.0)	13 (10.9)	38 (8.5)	64 (6.3)	119 (9.1)	14 (6.9)	
	Unknown	18 (0.6)	2 (1.2)	1 (0.8)	1 (0.2)	9 (0.9)	5 (0.4)	0 (0.0)	
Treatment	Sx only	1528 (46.8)	64 (38.3)	61 (51.3)	204 (45.4)	501 (49.0)	620 (47.4)	78 (38.4)	**<0.001**
	RTx only	144 (4.4)	24 (14.4)	5 (4.2)	15 (3.3)	19 (1.9)	73 (5.6)	8 (3.9)	
	Sx and RTx	1070 (32.8)	30 (18.0)	39 (32.8)	165 (36.7)	405 (39.6)	388 (29.7)	43 (21.2)	
	None	300 (9.2)	30 (18.0)	9 (7.6)	39 (8.7)	43 (4.2)	133 (10.2)	46 (22.7)	
	Unknown	225 (6.9)	19 (11.4)	5 (4.2)	26 (5.8)	54 (5.3)	93 (7.1)	28 (13.8)	
Tumor Grade	I	157 (4.8)	0 (0.0)	2 (1.7)	25 (5.6)	60 (5.9)	64 (4.9)	6 (3.0)	**<0.001**
	II	391 (12.0)	5 (3.0)	4 (3.4)	71 (15.8)	154 (15.1)	141 (10.8)	16 (7.9)	
	III	411 (12.6)	4 (2.4)	4 (3.4)	42 (9.4)	172 (16.8)	167 (12.8)	22 (10.8)	
	IV	549 (16.8)	8 (4.8)	9 (7.6)	62 (13.8)	216 (21.1)	240 (18.4)	14 (6.9)	
	Unknown	1759 (53.8)	150 (89.8)	100 (84.0)	249 (55.5)	420 (41.1)	695 (53.2)	145 (71.4)	
Tumor Size	≤50 mm	798 (24.4)	61 (36.5)	32 (26.9)	171 (38.1)	265 (25.9)	254 (19.4)	15 (7.4)	**<0.001**
	>50 mm	1283 (39.3)	15 (9.0)	14 (11.8)	91 (20.3)	482 (47.2)	625 (47.8)	56 (27.6)	
	Unknown	1186 (36.3)	91 (54.5)	73 (61.3)	187 (41.6)	275 (26.9)	428 (32.7)	132 (65.0)	
	Median (mm)	67.0	37.4	39.5	38.0	70.0	80.0	88.0	
	IQR (mm)	37.0-100.0	17.3-43.5	20.0-60.0	20.0-65.0	40.0-100.0	50.0-115.0	60.0-130.0	

GTR: gross total resection, IQR: interquartile range, mm: millimeters, NOS: not otherwise specified, SD: standard deviation

67 mm (IQR: 37-100 mm). The largest tumors were found in core (median 80 mm, IQR: 60-115 mm) and limb sites (70 mm, IQR: 40-100 mm), whereas intracranial (37.4 mm, IQR: 17.3-43.5 mm), spinal (39.5 mm, IQR: 20-60 mm), and head & neck sites (38 mm, IQR: 20-65 mm) were relatively smaller in size.

Treatment modalities

Most patients were treated with surgery (46.8%) which was followed by radiotherapy in 32.8% of patients. Intracranial tumors were less frequently resected (58.1%), whereas spinal tumors were treated surgically in 83.0% of cases. Gross total resection (GTR) was only achieved in 28.0% of cases and 30.0% of surgeries resulted in a subtotal resection (**Table 2**). GTR was most often achieved in spinal tumors (42.6%) and least frequently in core tumors (24.9%). Overall, 38.9% of patients were subjected to a form of radiation, and percentages varied slightly from 35.5% of intracranial cases to 41.8% of cases in extremities. Radiotherapy was given in a neoadjuvant setting in 4.2% and adjuvant in 28.0% of all cases. Preoperative radiation was most often used in limb sites (6.8%). Intraoperative radiation was administered in only 0.6% of cases. A combination of both pre- and postoperative radiotherapy was only given in 0.8% of all cases.

Univariable and multivariable analyses

Univariable analysis for intracranial MPNSTs showed that older age (>60 years), surgical procedure in the form of a biopsy, and larger size are associated with decreased survival (all $p<0.05$, **Supplemental Table 3**). In multivariable analyses, older age and larger size were significantly associated with decreased survival even after correction for multiple testing. In univariable analysis for spinal tumors, treatment strategies that included radiation and larger size are associated with worse survival ($p<0.05$ for both). Larger size lost significance in multivariable analyses. Treatment with radiotherapy only was significantly associated with worse survival even after Bonferroni correction. Older age, higher tumor grade (grade ≥3), and large size are associated with higher mortality in head and neck tumors (all $p <0.05$) in univariable analysis. These factors were still associated with poorer survival in multivariable analyses and correction for multiple testing. Older age, expectant management or radiation solely, large size, and higher grade are associated with higher mortality in limb tumors (all $p<0.05$, **Supplemental Table 4**) in univariable analysis and multivariable analyses with Bonferroni correction. Similar characteristics were associated with decreased survival in core MPNSTs. In the latter, patients that received radiation after surgery seemed to have a better overall survival in univariable analysis. In multivariable analyses older age, high tumor grade, large size, treatment modalities without surgery were all still significantly associated with worse overall survival, even after Bonferroni correction. Pediatric cases and those that received radiotherapy after surgery had an increased survival in multivariable analyses, but this was no longer significant after correction for multiple testing. In multivariable analysis of all primary MPNST cases, pediatric cases and intracranial

Table 2 Treatment differences between tumor sites.

Definition	Total	Intracranial	Spinal	H&N	Limbs	Core	NOS & Unknown	P
Number of patients	2732	141	94	344	878	1106	169	
No surgery	306 (11.2)	43 (30.5)	9 (9.6)	29 (8.4)	49 (5.6)	132 (11.9)	44 (26.0)	**<0.001**
Biopsy only	62 (2.3)	3 (2.1)	0 (0.0)	11 (3.2)	6 (0.7)	38 (3.4)	4 (2.4)	
Partial resection	820 (30.0)	4 (2.8)	9 (9.6)	129 (37.5)	317 (36.1)	334 (30.2)	27 (16.0)	
GTR	765 (28.0)	38 (27.0)	40 (42.6)	89 (25.9)	298 (33.9)	275 (24.9)	25 (14.8)	
Surgery NOS	658 (24.1)	37 (26.2)	34 (36.2)	73 (21.2)	195 (22.2)	270 (24.4)	49 (29.0)	
Unknown Sx	121 (4.4)	16 (11.3)	2 (2.1)	13 (3.8)	13 (1.5)	57 (5.2)	20 (11.8)	
No radiation	1591 (58.2)	88 (62.4)	59 (62.8)	195 (56.7)	477 (54.3)	660 (59.7)	112 (66.3)	**0.048**
Any form radiation	1064 (38.9)	50 (35.5)	34 (36.2)	141 (41.0)	367 (41.8)	421 (38.1)	51 (30.2)	
Unknown	77 (2.8)	3 (2.1)	1 (1.1)	8 (2.3)	34 (3.9)	25 (2.3)	6 (3.6)	
No RTx or no Sx	1802 (66.0)	112 (79.4)	64 (68.1)	216 (62.8)	523 (59.6)	758 (68.5)	129 (76.3)	**<0.001**
Adjuvant RTx	766 (28.0)	27 (19.1)	28 (29.8)	114 (33.1)	274 (31.2)	288 (26.0)	35 (20.7)	
Neoadjuvant RTx	116 (4.2)	0 (0.0)	1 (1.1)	6 (1.7)	60 (6.8)	45 (4.1)	4 (2.4)	
RTx b/a Sx	23 (0.8)	1 (0.7)	1 (1.1)	4 (1.2)	12 (1.4)	5 (0.5)	0 (0.0)	
Intraoperative RTx	16 (0.6)	1 (0.7)	0 (0.0)	3 (0.9)	6 (0.7)	6 (0.5)	0 (0.0)	
Unknown sequence	9 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	3 (0.3)	4 (0.4)	1 (0.6)	

b/a: before and after, GTR: gross total resection, H&N: head and neck, NOS: not otherwise specified, RTx: radiotherapy, Sx: surgery

tumors were independently associated with superior survival (both $p<0.05$, **Table 3 and 4**). MPNSTs originating from the head and neck or core sites showed significantly poorer survival (both $p<0.05$). Also, older age, male sex, black race, higher tumor grade (grade III and IV), and large tumor size were independently prognostic for worse survival (all $p<0.05$). Patients that did not receive surgical treatment or only a biopsy were significantly associated with worse survival (**Table 4**). The sequence of radiotherapy did not have any influence on the survival of patients (**Table 4**), nor did any addition of radiotherapy to surgery (all $p>0.05$, **Table 3**). After applying a Bonferroni correction to all three models, only large tumor size, high tumor grades, core site, and treatment modalities without surgery significantly reduced overall survival (all $p<0.002$).

Table 3 Univariable and multivariable Cox analysis of overall survival in all primary MPNST.

Variable	Definition	Univariable Analysis			Multivariable Analysis		
		HR	95% CI	P	HR	95% CI	P
Age	19-59	Ref.			Ref.		
	<18	0.84	0.70-1.02	0.071	0.80	0.66-0.97	**0.022**
	60+	1.65	1.49-1.84	**<0.001**	1.79	1.60-1.99	**<0.001**
Sex	Female	Ref.			Ref.		
	Male	1.18	1.07-1.30	**0.001**	1.15	1.04-1.27	**0.006**
Race	White	Ref.			Ref.		
	Black	1.19	1.03-1.37	**0.018**	1.22	1.05-1.41	**0.008**
	Asian & other	0.94	0.78-1.14	0.528	0.93	0.77-1.12	0.435
	Unknown	0.32	0.10-0.99	**0.047**	0.42	0.13-1.30	0.132
Therapy	Sx only	Ref.			Ref.		
	RTx only	2.50	2.01-3.11	**<0.001**	2.07	1.65-2.59	**<0.001**
	Sx and RTx	1.17	1.05-1.31	**0.006**	1.09	0.97-1.23	0.153
	None	1.63	1.35-1.96	**<0.001**	1.58	1.31-1.91	**<0.001**
	Unknown	1.71	1.42-2.06	**<0.001**	1.54	1.27-1.87	**<0.001**
Surgery	GTR	Ref.					
	PR	1.00	0.87-1.15	0.989			
	Biopsy	1.55	1.13-2.13	**0.006**			
	No Sx	1.88	1.58-2.25	**<0.001**			
	Sx NOS	1.09	0.95-1.25	0.238			
	Unknown	1.93	1.54-2.43	**<0.001**			
Radiation Sequence	No Sx or no RTx	Ref.					
	Adjuvant RTx	1.01	0.91-1.13	0.821			
	Neoadjuvant RTx	1.01	0.79-1.28	0.949			
	RTx b/a Sx	0.71	0.38-1.32	0.277			
	Intraoperative RTx	0.60	0.27-1.36	0.210			
	Unknown	1.20	0.54-2.68	0.658			
Tumor Location	Limbs	Ref.			Ref.		
	Intracranial	0.80	0.61-1.07	0.128	0.74	0.55-0.99	**0.045**
	Spinal	1.27	0.94-1.70	0.115	1.28	0.94-1.72	0.113
	H&N	1.18	1.00-1.40	0.052	1.27	1.07-1.52	**0.007**
	Core	1.68	1.49-1.89	**<0.001**	1.58	1.40-1.78	**<0.001**
	NOS & Unknown	2.07	1.69-2.54	**<0.001**	1.80	1.45-2.23	**<0.001**
Tumor Grade	I	Ref.			Ref.		
	II	1.34	0.94-1.89	0.102	1.33	0.94-1.89	0.106
	III	2.91	2.08-4.06	**<0.001**	2.74	1.96-3.84	**<0.001**
	IV	3.69	2.67-5.10	**<0.001**	3.24	2.33-4.49	**<0.001**
	Unknown	2.53	1.86-3.45	**<0.001**	2.34	1.71-3.19	**<0.001**
Tumor Size	≤50 mm	Ref.			Ref.		
	>50 mm	2.43	2.09-2.82	**<0.001**	2.26	1.93-2.64	**<0.001**
	Unknown	2.03	1.75-2.36	**<0.001**	1.91	1.63-2.22	**<0.001**

b/a: before and after, GTR: gross total resection, H&N: head and neck, HR: hazard ratio, intraop: intraoperatively, mm: millimeter, N: number, NA: not applicable, NOS: not otherwise specified, PR: partial resection, Ref.: reference, RTx: radiotherapy, Sx: surgery

Table 4 Multivariable Cox analysis of all primary MPNST including either radiation sequence of extent of surgery.

Variable	Definition	Univariable Analysis			Multivariable Analysis		
		HR	95% CI	P	HR	95% CI	P
Age	19-59	Ref.			Ref.		
	<18	0.79	0.66-0.97	**0.020**	0.80	0.66-0.97	**0.023**
	60+	1.79	1.60-1.99	**<0.001**	1.78	1.59-1.98	**<0.001**
Sex	Female	Ref.			Ref.		
	Male	1.15	1.04-1.27	**0.008**	1.16	1.05-1.28	**0.005**
Race	White	Ref.			Ref.		
	Black	1.27	1.09-1.46	**0.002**	1.23	1.06-1.42	**0.006**
	Asian & other	0.93	0.77-1.12	0.432	0.93	0.77-1.12	0.431
	Unknown	0.42	0.14-1.32	0.137	0.40	0.13-1.26	0.117
Surgery	GTR				Ref.		
	PR				1.10	0.96-1.27	0.174
	Biopsy				1.56	1.13-2.14	**0.007**
	No Sx				1.93	1.60-2.32	**<0.001**
	Sx NOS				1.16	1.00-1.35	0.055
	Unknown				1.97	1.53-2.52	**<0.001**
Radiation Sequence	No Sx or no RTx	Ref.					
	Adjuvant RTx	0.97	0.86-1.09	0.569			
	Neoadjuvant RTx	0.85	0.67-1.09	0.209			
	RTx b/a Sx	0.74	0.40-1.39	0.355			
	Intraoperative RTx	0.72	0.32-1.60	0.418			
	Unknown	0.98	0.44-2.19	0.958			
Tumor Location	Limbs	Ref.			Ref.		
	Intracranial	0.88	0.66-1.17	0.380	0.74	0.55-1.00	**0.046**
	Spinal	1.23	0.91-1.66	0.177	1.31	0.97-1.77	0.084
	H&N	1.32	1.11-1.58	**0.002**	1.28	1.08-1.53	**0.005**
	Core	1.62	1.44-1.83	**<0.001**	1.57	1.39-1.77	**<0.001**
	NOS & Unknown	1.99	1.61-2.45	**<0.001**	1.73	1.40-2.15	**<0.001**
Tumor Grade	I	Ref.			Ref.		
	II	1.33	0.94-1.88	0.113	1.35	0.96-1.92	0.101
	III	2.83	2.02-3.96	**<0.001**	2.82	2.02-3.95	**<0.001**
	IV	3.40	2.45-4.71	**<0.001**	3.40	2.45-4.71	**<0.001**
	Unknown	2.44	1.79-3.34	**<0.001**	2.32	2.32-1.69	**<0.001**
Tumor Size	≤50 mm	Ref.			Ref.		
	>50 mm	2.33	2.00-2.72	**<0.001**	2.33	1.99-2.72	**<0.001**
	Unknown	1.93	1.65-2.25	**<0.001**	1.82	1.55-2.13	**<0.001**

b/a: before and after, GTR: gross total resection, H&N: head and neck, HR: hazard ratio, intraop: intraoperatively, mm: millimeter, N: number, NA: not applicable, NOS: not otherwise specified, PR: partial resection, Ref.: reference, RTx: radiotherapy, Sx: surgery

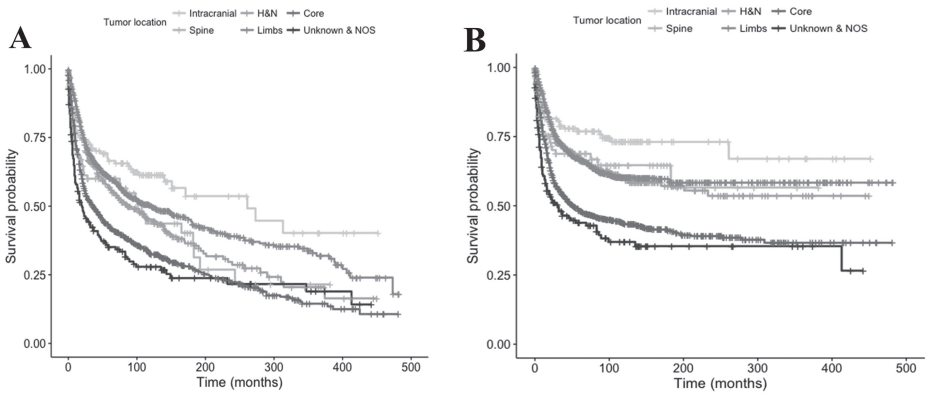

Figure 1 Kaplan-Meier curves per tumor site (A) overall survival (B) disease-specific survival

Overall and disease-specific survival

Patients with intracranial tumors showed superior overall survival followed by limbs, head and neck, and spine. Tumors arising from the core had the worse overall survival (overall difference between curves p<0.001, **Figure 1A**)**.** Differences across sites in disease-specific survival seem to be similar to overall survival, but disparities between limbs, head and neck, and spine were less obvious (overall difference between curves p<0.001, **Figure 1B**).

Discussion

Using the SEER database we identified that the site of origin is an independent prognostic factor for survival in MPNSTs. Intracranial tumors tend to have a better survival than those arising in extremities. Tumors arising from core sites are associated with the poorest survival; head and neck tumors were also associated with worse survival compared to limb sites. Pediatric cases were significantly associated with better survival compared to adult cases independent from tumor site, size, and treatment modality. Other factors associated with worse survival were older age, male gender, black race, higher tumor grade and large tumors. Treatment modalities appear to vary slightly across site of origin.

Intracranial MPNST

Literature on intracranial MPNSTs is scarce, consisting only of multiple case reports, small case series, and some systematic reviews. This analysis presents the largest group of intracranial MPNSTs reported in literature to date. Patients with intracranial MPNSTs are believed to have a short survival.[27–30] 1-year survival has been reported to be as little as 33%, while others found a 3-year overall survival of 64.0%.[27,28,31] The

survival of the 141 primary intracranial MPNSTs presented in this paper seems to be better than currently suggested in the literature. This difference could be the result of different grades of tumors included, treatment modalities used, and extent of resection achieved. On the other hand, lymphatic metastases have not been reported in intracranial MPNSTs, which may be associated with improved prognosis for this site of origin.[29,30] It is assumed that metastases from intracranial MPNSTs mainly occur as a consequence of cerebrospinal fluid dissemination that result in drop metastases.[29]

Head & Neck MPNST

MPNSTs arising from extracranial head and neck sites have previously been associated with a worse prognosis, but this rarely reached statistical significance, mainly due to small population sizes.[10,11,14,32] This is in line with findings of this study suggesting that they have worse survival compared to limb and intracranial sites. 5-year survival rates have been reported to vary from 20% to 47%.[14,32–34] Unlike intracranial MPNSTs, these tumors have been reported to metastasize to lymph nodes, but also to lungs.[34,35]

Spinal MPNST

Reports about spinal MPNSTs are as rare as those about intracranial tumors. Small case series have shown that survival in spinal tumors is generally unfavorable.[20,36–38] Reported 5-year survival rates vary from 16% to 44%.[20,37,38] Generally, MPNSTs of spinal origin are considered difficult to resect completely, because of close vital structures adjacent to the tumor site.[20,37,38] Although radiotherapy is recommended for local control in spinal MPNSTs, it has not been shown to have an effect on survival.[36,37] Likewise, this study did not find an additional benefit for radiotherapy in spinal tumors. Radiotherapy as a monotherapy was significantly associated with worse overall survival independent of tumor and patient specific characteristics. Since large amounts of radiation may induce myelopathy,[37,39] tumor control using radiotherapy must be executed in cases where tumor invasiveness causes symptoms.

Core MPNST

Core tumors are among the most frequent MPNSTs; prevalence reported in large series vary from 34-55%.[4,9–11,14,32,40] This is consistent with the SEER data which shows a prevalence of 40%. This location is more frequently affected in NF1 patients compared to sporadic MPNSTs.[4,40] Although generally seen as tumors with a less favorable outcome, only three large institutional studies have previously shown this difference to be significant.[11,14,32] This study supports their findings that core site tumors tend to have a worse prognosis.

Extremity MPNST

Extremities are also a common tumor site for MPNSTs with a prevalence in large series varying between 35% and 57%.[4,9–11,14,15,32,40] MPNSTs arising from extremities tend to be more easily completely resected compared to other tumor locations.[4,9,11,14,32] Therefore,

most authors believe that survival is better in these patients. All but intracranial tumors had a worse overall survival. In literature, 5-year overall survival range from 39% to 72%.[19,32] Although limb salvage treatment is possible, amputations are still not uncommon for large and deep tumors.[1]

Pediatric MPNST

Malignant peripheral nerve sheath tumors in pediatric patients have been described previously.[32,41–45] 5-year overall survival in children varies between 34.6% and 51%.[32,41,42,44,45] No institutional study has yet been able to find a difference in survival between pediatric and adult tumors. However, in two studies including only pediatric cases, a prolonged survival was seen in younger children compared to adults.[32,44] The SEER data suggests that pediatric patients tend to have a better survival in general, possibly by controlling for many risk factors previously shown to influence survival.

Strengths and limitations

This study has several, registry associated, limitations. Many data of interest were missing for instance data about tumor grade, tumor size, extent of resection, and site of origin. All missing groups were examined as separate entities and were associated with significantly worse outcomes. This may have resulted in over- or underrepresentation of certain variables. Also, it was not possible to conduct separate analyses for patients with NF1. While many studies found that NF1 patients show poorer survival,[4,10,22,26] more recent studies did not find this difference.[9,11,14] In a meta-analysis by Kolberg et al., NF1 negatively affected survival in studies published before 2000, but significance was lost in data after 2000.[15] Not only better surveillance may have had its impact on this difference, NF1 patients tend to present with larger tumors more frequently originating from trunk sites, both factors associated with worse survival.[10] 11.2% of all patients did not receive cancer-directed surgery, which mainly includes patients that were diagnosed at autopsy, but possibly a small heterogeneous group including clinical diagnoses as well. The latter may impede the interpretation of this group of patients. The SEER tumor grading system is also not completely comparable to WHO grading, which may make comparisons to other studies more difficult. Unfortunately, the registry does not contain any information on recurrence, progression-free survival; mode and dosage of radiotherapy are not registered either, nor is the indication of its use. This makes the interpretation of the impact that radiotherapy has, adjacent to surgery, difficult. It is possible that most patients receiving radiotherapy had positive margins, another variable that is not available in the SEER registry, which could skew data on survival. Furthermore, the use and regimen of chemotherapy cannot be extracted either. Nevertheless, the effect of chemotherapy is still subject of debate.[9,14,22,32,46,47] Despite these limitations, the SEER database allows for investigation of small subpopulations of rare tumors as MPNSTs, such as pediatric populations and rare tumor sites. Tumors that arise in different sites may be etiologically different from one another as location seems to be of great influence. Thoroughly examining clinical differences between different

sites of origin may, therefore, lead to a better understanding of these rare tumors. In the future, large databases with prospective registration could be set up that track all outcomes relevant to MPNSTs through multicenter interdisciplinary efforts. Exact clinicopathological differences between tumor sites and between pediatric and adult tumors should be investigated. This could help formulate specific treatment strategies to improve outcomes for these patients.

Conclusion

This study of the SEER database shows that intracranial and pediatric MPNSTs are associated with better overall survival, independent from treatment and other tumor specific factors. Worst prognosis is seen in core sites and tumors arising in the head and neck. Treatment modalities and extent of resection also vary slightly among tumor sites. Apart from tumor origin, older age, male gender, black race, higher tumor grade and large tumors may be associated with decreased survival.

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Supplemental Table 1 Recoding of tumor sites

Tumor site	ICD-O-3 code
Intracranial	C70.9-71.9, C72.3-72.8, C75.1, C75.3
Spinal	C41.2, C70.1, C72.0, C72.1
Head and Neck	C04.0-14.0, C30.0-31.9, C41.0, C41.1, C44.0-44.4, C47.0, C49.0, C69.6
Limbs	C40.0-40.2, C41.4, C44.6, C44.7, C47.1, C47.2, C49.1, C49.2
Core	C16.0-26.9, C34.0-38.4, C44.5, C47.3-47.6, C48.0-48.8, C49.3-49.6, C50.8-51.0, C51.9-67.9, C74.9
NOS/Unknown	C47.8, C47.9, C49.8, C49.9, C72.9, C72.9, C80.9

Supplemental Table 2 Recoding of extent of resection

Surgical Resection	SEER Code
No surgery	<1998: 00, 01; 1998+: 00
Biopsy	<1998: 02, 35, 38; 1998+: 27
Partial resection	<1998: 10, 18, 20, 40, 50, 55, 58; 1998+ 25, 26, 29, 31
Gross total resection	<1998: 30, 60, 68, 70 1998+: 30, 33, 36, 38, 40, 41,42,43,45, 46, 50, 51, 52, 53, 55, 60
Surgery not otherwise specified	<1998: 90; 1998+: 10, 15, 19, 20, 21, 22, 90
Unknown status of surgery	<1998: 05, 09, 80; 1998+: 99

Supplemental Table 3 Univariate Cox analyses of overall survival in intracranial, spinal, and head & neck tumor sites

Variable	Definition	Intracranial HR (95% CI)	P	Spinal HR (95% CI)	P	H&N HR (95%CI)	P
Age	19-59	Ref.		Ref.		Ref.	
	<18	1.30 (0.45-3.71)	0.628	0.88 (0.21-3.74)	0.862	0.75 (0.44-1.28)	0.298
	60+	2.18 (1.26-3.78)	**0.006**	1.52 (0.85-2.71)	0.159	1.86 (1.38-2.49)	**<0.001**
Sex	Female	Ref.		Ref.		Ref.	
	Male	1.37 (0.81-2.34)	0.243	1.51 (0.82-2.76)	0.184	1.08 (0.81-1.44)	0.604
Race	White	Ref.		Ref.		Ref.	
	Black	1.52 (0.65-3.58)	0.336	1.27 (0.54-3.01)	0.586	1.16 (0.74-1.84)	0.513
	Asian & other	*NA*	*NA*	0.25 (0.06-1.03)	0.056	0.87 (0.51-1.48)	0.616
	Unknown	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
Therapy	Sx only	Ref.		Ref.		Ref.	
	RTx only	1.91 (0.84-4.31)	0.122	8.68 (1.96-38.51)	**0.004**	1.67 (0.84-3.31)	0.144
	Sx and RTx	1.96 (0.91-4.21)	0.085	3.42 (1.86-6.29)	**0.000**	1.16 (0.85-1.58)	0.343
	None	1.85 (0.86-3.96)	0.117	0.71 (0.09-5.39)	0.741	0.84 (0.42-1.67)	0.620
	Unknown	1.45 (0.59-3.53)	0.416	4.18 (0.95-18.36)	0.058	0.98 (0.52-1.83)	0.944
Surgery	GTR	Ref.		Ref.		Ref.	
	PR	1.13	0.864	1.43 (0.56-3.63)	0.452	1.11 (0.76-1.62)	0.603
	Biopsy	7.81 (2.13-28.65)	**0.002**	*NA*	*NA*	0.74 (0.26-2.05)	0.558
	No Sx	1.37 (0.67-2.79)	0.391	1.20 (0.35-4.14)	0.770	1.47 (0.82-2.64)	0.201
	Sx NOS	0.91 (0.42-2.00)	0.819	1.23 (0.64-2.36)	0.536	1.16 (0.77-1.74)	0.483
	Unknown	1.06 (0.39-2.89)	0.904	6.46 (1.44-29.01)	**0.015**	1.07 (0.50-2.31)	0.856

Supplemental Table 3 Continued.

Variable	Definition	Intracranial HR (95% CI)	P	Spinal HR (95% CI)	P	H&N HR (95%CI)	P
Radiation Sequence	No Sx or no RTx	Ref.		Ref.		Ref.	
	RTx after Sx	1.96 (1.06-3.62)	**0.032**	3.23 (1.81-5.79)	**<0.001**	1.13 (0.84-1.53)	0.411
	RTx before Sx	*NA*	*NA*	4.83 (0.64-36.57)	0.127	0.96 (0.36-2.61)	0.942
	RTx b/a Sx	*NA*	*NA*	*NA*	*NA*	2.60 (0.96-7.07)	0.061
	Intraoperative RTx	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
	Unknown	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
Tumor Grade	I	Ref.		Ref.		Ref.	
	II	*NA*	*NA*	0.62 (0.06-6.82)	0.692	2.48 (0.86-7.12)	0.093
	III	*NA*	*NA*	5.69 (0.51-63.99)	0.159	5.30 (1.80-15.66)	**0.003**
	IV	*NA*	*NA*	1.69 (0.20-14.54)	0.631	6.66 (2.33-19.03)	**<0.001**
	Unknown	*NA*	*NA*	0.62 (0.08-4.36)	0.634	3.88 (1.43-10.54)	**0.008**
Tumor Size	≤50 mm	Ref.		Ref.		Ref.	
	>50 mm	3.49 (1.37-8.91)	**0.009**	5.26 (1.79-15.50)	**0.003**	2.25 (1.53-3.33)	**<0.001**
	Unknown	1.92 (1.00-3.72)	0.051	3.22 (1.35-7.67)	**0.008**	1.64 (1.17-2.29)	**0.004**

b/a: before and after, GTR: gross total resection, H&N: head and neck, HR: hazard ratio, intraop: intraoperatively, mm: millimeter, N: number, NA: not applicable, NOS: not otherwise specified, PR: partial resection, Ref.: reference, RTx: radiotherapy, Sx: surgery

Supplemental Table 4 Univariate Cox analyses of overall survival in limbs, core, and NOS & unknown tumor sites

Variable	Definition	Limbs HR (95% CI)	P	Core HR (95% CI)	P	NOS & Unknown HR (95%CI)	P
Age	19-59	Ref.		Ref.		Ref.	
	<18	0.92 (0.66-1.30)	0.648	0.78 (0.59-1.05)	0.097	0.82 (0.43-1.56)	0.545
	60+	1.96 (1.60-2.41)	**<0.001**	1.41 (1.20-1.65)	**<0.001**	1.59 (1.06-2.37)	**0.024**
Sex	Female	Ref.		Ref.		Ref.	
	Male	1.16 (0.96-1.40)	0.132	1.16 (1.01-1.35)	**0.042**	1.27 (0.88-1.85)	0.208
Race	White	Ref.		Ref.		Ref.	
	Black	1.22 (0.95-1.56)	0.125	1.17 (0.95-1.45)	0.142	1.90 (1.06-3.40)	**0.031**
	Asian & other	0.98 (0.66-1.44)	0.899	1.03 (0.80-1.32)	0.840	0.62 (0.27-1.42)	0.262
	Unknown	0.70 (0.22-2.17)	0.530	*NA*	*NA*	*NA*	*NA*
Therapy	Sx only	Ref.		Ref.		Ref.	
	RTx only	3.00 (1.67-5.38)	**<0.001**	2.74 (2.04-3.68)	**<0.001**	4.29 (1.85-9.94)	**0.001**
	Sx and RTx	1.17 (0.95-1.43)	0.131	1.04 (0.87-1.23)	0.681	1.66 (1.03-2.67)	**0.038**
	None	2.21 (1.44-3.41)	**<0.001**	1.88 (1.45-2.43)	**<0.001**	1.00 (0.58-1.74)	0.997
	Unknown	1.46 (0.95-2.23)	0.083	1.90 (1.45-2.48)	**<0.001**	2.66 (1.54-4.59)	**<0.001**
Surgery	GTR	Ref.		Ref.		Ref.	
	PR	0.91 (0.72-1.16)	0.438	0.94 (0.76-1.17)	0.588	1.04 (0.54-2.03)	0.899
	Biopsy	1.73 (0.71-4.23)	0.231	1.23 (0.82-1.86)	0.315	2.64 (0.88-7.91)	0.083
	No Sx	2.19 (1.48-3.24)	**<0.001**	2.56 (1.99-3.31)	**<0.001**	0.94 (0.50-1.76)	0.849
	Sx NOS	0.95 (0.73-1.23)	0.681	1.00 (0.81-1.24)	0.968	1.10 (0.62-1.96)	0.749
	Unknown	0.66 (0.29-1.51)	0.324	2.72 (2.00-3.70)	**<0.001**	2.35 (1.19-4.65)	**0.014**

Supplemental Table 4 Continued.

Variable	Definition	Limbs HR (95% CI)	P	Core HR (95% CI)	P	NOS & Unknown HR (95%CI)	P
Radiation Sequence	No Sx or no RTx	Ref.		Ref.		Ref.	
	RTx after Sx	1.04 (0.84-1.28)	0.733	0.83 (0.70-0.99)	**0.038**	1.35 (0.89-2.06)	0.160
	RTx before Sx	1.08 (0.74 (1.58)	0.686	0.97 (0.69-1.39)	0.883	0.83 (0.26-2.64)	0.758
	RTx b/a Sx	0.58 (0.25-1.82)	0.437	0.66 (0.16-2.64)	0.556	*NA*	*NA*
	Intraoperative RTx	1.17 (0.37-3.65)	0.789	0.65 (0.21-2.04)	0.464	*NA*	*NA*
	Unknown	2.33 (0.58-9.37)	0.234	0.89 (0.29-2.78)	0.845	1.43 (0.20-10.31)	0.723
Tumor Grade	I	Ref.		Ref.		Ref.	
	II	1.20 (0.62-2.32)	0.580	1.27 (0.79-2.06)	0.330	1.90 (0.41-8.85)	0.412
	III	3.63 (1.98-6.65)	**<0.001**	2.35 (1.47-3.74)	**<0.001**	3.38 (0.76-15.00)	0.109
	IV	4.02 (2.21-7.31)	**<0.001**	3.25 (2.09-5.05)	**<0.001**	4.62 (1.01-21.05)	**0.048**
	Unknown	2.69 (1.50-4.82)	**0.001**	2.51 (1.65-3.83)	**<0.001**	2.47 (0.60-10.10)	0.208
Tumor Size	≤50 mm	Ref.		Ref.		Ref.	
	>50 mm	2.32 (1.78-3.01)	**<0.001**	2.37 (1.87-3.00)	**<0.001**	1.53 (0.64-3.65)	0.339
	Unknown	1.58 (1.18-2.11)	**0.002**	2.28 (1.79-2.91)	**<0.001**	1.31 (0.57-3.01)	0.524

b/a: before and after, GTR: gross total resection, H&N: head and neck, HR: hazard ratio, intraop: intraoperatively, mm: millimeter, N: number, NA: not applicable, NOS: not otherwise specified, PR: partial resection, Ref.: reference, RTx: radiotherapy, Sx: surgery

3

A Nationwide Cohort Study on Treatment and Survival in Patients with Malignant Peripheral Nerve Sheath Tumors

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Abstract

Background Despite curative intents of treatment in localized malignant peripheral nerve sheath tumors (MPNST), prognosis remains poor. This study investigated survival and prognostic factors for overall survival in non-retroperitoneal and retroperitoneal MPNSTs in the Netherlands.

Methods Data were obtained from the Netherlands Cancer Registry and the Dutch Pathology Database. All primary MPNSTs were collected. Pediatric cases (age ≤18 years) and synchronous metastases were excluded from analyses. Separate Cox proportional hazard models were made for retroperitoneal and non-retroperitoneal MPNSTs.

Results A total of 629 localized adult MPNSTs (35 retroperitoneal cases, 5.5%) were included for analysis. In surgically resected patients (88.1%), radiotherapy and chemotherapy were administered in 44.2% and 6.7% respectively. In retroperitoneal cases significantly less radiotherapy and more chemotherapy were applied. In non-retroperitoneal MPNST, older age (60+), presence of NF1, size >5cm, and deep-seated tumors were independently associated with worse survival. In retroperitoneal MPNST male sex and age 60+ years old were independently associated with worse survival. Survival of R1 and R0 resections were similar for any location, while R2 resections were associated with worse outcome. Radiotherapy and chemotherapy administration were not associated with survival.

Conclusion In localized MPNST, risk stratification for survival can be done using several patient- and tumor specific characteristics. Resectability is the most important predictor for survival in MPNST. No difference is present between R1 and R0 resections in both retroperitoneal and non-retroperitoneal MPNSTs. The added value of radiotherapy and chemotherapy is unclear.

Introduction

Malignant peripheral nerve sheath tumors (MPNSTs) are rare and aggressive soft tissue sarcomas (STS), accounting for 2% of all STS.[1] While 23-51% of MPNSTs occur in neurofibromatosis type 1 (NF1) patients, they can also be sporadic or radiation-induced.[2–5] MPNSTs can originate within a neurofibroma which can lead to diagnostic challenges, particularly in NF1 patients.[6,7] MPNSTs can also present with heterologous elements such as rhabdomyoblastic differentiation, so-called Triton tumors, which reportedly have been associated with poorer survival.[8,9]

To date, surgery is the only proven therapy increasing survival in localized MPNST.[3,10] As in other STS, radiotherapy is commonly administered in order to improve local control, but no effect has been shown on survival.[3,11,12] Neoadjuvant administration of radiotherapy is increasing in popularity as it decreases radiation fields and dosage which results in lower long-term toxicities, yet postoperative wound complications are more common.[13,14] Recent studies have shown that neoadjuvant chemotherapy may be considered in high-grade, large, and deep MPNSTs.[15,16]

Despite curative intents of treatment in localized MPNST survival remains poor.[2,3,10] Understanding factors associated with survival of this rare sarcoma may ameliorate clinical decision-making. Using a Dutch nationwide cohort of patients, this study aims to investigate overall survival and prognostic factors for overall survival in non-retroperitoneal and retroperitoneal MPNSTs.

Methods

Patient population

Data of patients treated between 1989- 2017 were obtained from the nationwide Netherlands Cancer Registry (NCR), which is managed by the Netherlands Comprehensive Cancer Organisation (IKNL). The NCR is a population-based registry that gets notified of all newly diagnosed malignancies in the Netherlands by automated pathological archive (PALGA) and the National Registry of Hospital Discharge Diagnosis (LMR). Patient and tumor characteristics and initial treatment information are routinely extracted from medical records by uniformly trained registrars and enhanced by computerized consistency checks at both regional and national levels. Full pathological reports were also requested from PALGA.[17] The data request was approved by the scientific and privacy committees of IKNL. MPNSTs from any site were obtained from the registry. Cases were matched to PALGA by means of a trusted third party, which allows all pathological reports from a single patient to be matched. All pathological reports were reviewed to see if a final diagnosis of MPNST was made in each patient;

whenever diagnoses were mentioned as doubtful or the diagnosis changed after e.g. (metastasis) resection, cases were excluded.

Covariates

Covariates extracted for analysis were: year of diagnosis (1989-2005/2006-2017), sex, age, established diagnosis of NF1, tumor site, tumor stage (presence of metastasis/no metastasis), tumor size (≤5/>5cm), tumor depth (superficial/deep of the fascia), tumor morphology (Triton tumor/within neurofibroma), obtained surgical resection margin (R0/R1/R2), the use of other treatment modalities, and sequence of treatment. NF1 status was extracted from pathological reports and was concluded either when stated as such in the report or when a pathology report of previous plexiform neurofibroma resections or two or more neurofibromas was present. Tumor sites were categorized as: head & neck, extremities, trunk (including thorax, abdomen, and pelvis), retroperitoneal, and not otherwise specified (NOS). Resection margins were regarded as tumor-free (R0), microscopically positive (R1, <1mm margin), and macroscopically positive (R2). Tumor grade is not registered in the NCR and its reporting is inconsistent in pathological reports. Vital status and date of death are routinely obtained from municipal demographic registries in the Netherlands. Pediatric and synchronous metastatic cases were excluded from all statistical analyses as they are treated differently.

Statistical analysis

Overall, analyses were stratified between retroperitoneal and non-retroperitoneal localized MPNSTs as they are generally treated differently. Estimated median survival was calculated using the Kaplan-Meier method for several covariates of interest and differences were assessed with log-rank tests. A conditional inference tree was constructed for localized non-retroperitoneal MPNST using the R package "partykit" to evaluate the most important predictors for survival.[18] A conditional inference tree generates a decision tree that splits the population of interest into subpopulations by means of recursive partitioning. At each partition, the best predictor separates one node into two child nodes. The decision tree extends until it cannot find any predictor that can significantly divide a node. Two separate Cox proportional hazard models were constructed for localized non-retroperitoneal MPNSTs and retroperitoneal MPNSTs by backward selection. Adjusted survival curves were made for individual prognostic factors, based on the final model.[19] Statistical analyses and data visualization were conducted using R version 3.6.0 (R Core Team, 2019).

Results

Patient population

A total of 875 patients were registered in the NCR database, of which 784 had a definitive pathological diagnosis of MPNST during the study period (from 1989-2017) (**Table 1**). There was a slight male predilection (53.7%) and 26.8% of all patients were known to have NF1. On average patients were 49 years old, and NF1 patients tended to be younger (mean: 39.8±18.0) compared to non-NF1 patients (mean: 52.4±21.3, **Figure 1**). Most tumors were large (>5cm, 67.9%) and deep-seated (75.2%). Most MPNSTs arose in truncal sites (45.2%) of which 43 (5.5%) were situated retroperitoneal. In 72 cases (9.2%), the pathology report described the presence of MPNSTs within preexistent neurofibromas. Triton tumors made up 6.1% of all MPNSTs. In 11.5% of all cases, patients presented with synchronous metastases.

Table 1 Clinicopathologic characteristics of study population.

Variable		**Overall**	
Number of patients		784	
Age (years)			
	0-18	70	(8.9%)
	19-59	434	(55.4%)
	60+	280	(35.7%)
	Mean (SD)	49.0 (±21.2)	
Male gender		421	(53.7%)
NF1		210	(26.8%)
Site			
	Extremities	303	(38.6%)
	Trunk	312	(39.8%)
	Retroperitoneum	43	(5.5%)
	Head & Neck	100	(12.8%)
	NOS	26	(3.3%)
Tumor size			
	≤5cm	190	(32.1%)
	>5cm	402	(67.9%)
	NA	192	
Tumor depth			
	Superficial	139	(24.8%)
	Deep	421	(75.2%)
	NA	224	
Triton tumor		48	(6.1%)
Within neurofibroma		72	(9.2%)
Synchronous metastasis		90	(11.5%)
Time period			
	1989-2005	454	(57.9%)
	2006-2017	330	(42.1%)

Cm: centimetre, NA: not avalaible, NF1: neurofibromatosis type 1, NOS: not otherwise specified

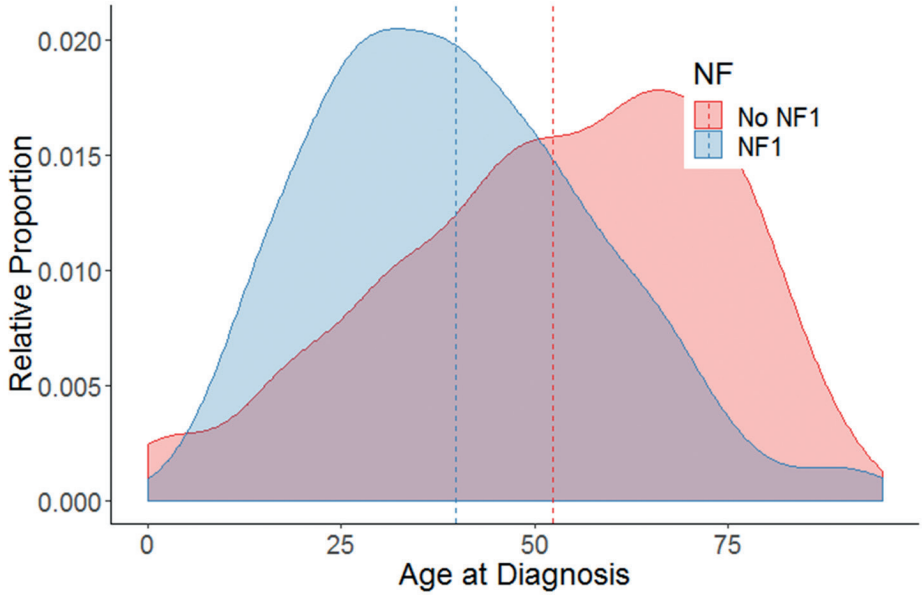

Figure 1 Relative age distribution of neurofibromatosis type 1 (NF1) and sporadic patients

Treatment of localized adult MPNST

Surgical resection was performed in 88% of localized MPNSTs (**Table 2**). Surgical margin involvement did not differ significantly between retroperitoneal and non-retroperitoneal tumors (p>0.05). Overall, a microscopically radical resection (R0) was achieved in 66.3% of the patients, while R1 and R2 resections were present in 27.5% and 6.1% respectively. Overall, additional radiotherapy was administered in 44.2% of the patients and less frequently in patients with a retroperitoneal MPNST (29.6%, p<0.05). Postoperative administration was more common than preoperative administration of radiotherapy (88.4%), but overall, postoperative radiotherapy use was not more common after R1 resections (42.5%) compared to R0 (39.9%, p>0.05). Preoperative use of radiotherapy is becoming more common at the end of the study period; in patients receiving radiotherapy after 2006, preoperative administration was performed in 22.7%. In surgically treated patients, chemotherapy was more commonly administered in retroperitoneal MPNST (18.5% vs. 6.1%, p<0.05). In patients who were not operated, radiotherapy and chemotherapy were administered in 33.3% and 24.0% of the patients respectively. No differences were present between non-retroperitoneal and retroperitoneal MPNST (both p>0.05).

Table 2 Treatment of localized MPNST in adults.

	Variable		Overall		nRP MPNST		RP MPNST		P
Surgically treated	**Surgical Margin**								
		R0	306	(55.2%)	294	(55.8%)	12	(44.4%)	0.180
		R1	127	(22.9%)	118	(22.4%)	9	(33.3%)	
		R2	28	(5.1%)	26	(4.9%)	2	(7.4%)	
		Unknown margin	93	(16.8%)	89	(16.9%)	4	(14.8%)	
	Radiotherapy Sequence								
		No Radiotherapy	313	(55.8%)	295	(55.0%)	19	(70.4%)	**0.044**
		Preoperative Radiotherapy	28	(5.1%)	25	(4.7%)	3	(11.1%)	
		Postoperative Radiotherapy	213	(39.2%)	208	(40.2%)	5	(18.5%)	
	Chemotherapy								
		No	517	(93.3%)	495	(93.9%)	22	(81.5%)	**0.012**
		Yes	37	(6.7%)	32	(6.1%)	5	(18.5%)	
Biopsy only	**Radiotherapy**								
		No	50	(66.7%)	43	(64.2%)	7	(87.5%)	0.26
		Yes	25	(33.3%)	24	(35.8%)	1	(12.5%)	
	Chemotherapy								
		No	57	(76.0%)	52	(77.6%)	5	(62.5%)	0.39
		Yes	18	(24.0%)	15	(22.4%)	3	(37.5%)	

MPNST: malignant peripheral nerve sheath tumor, nRP: non-retroperitoneal, RP: retroperitoneal

Survival in localized non-retroperitoneal MPNST

Overall estimated median survival of localized non-retroperitoneal MPNSTs was 6.0 years. Median survival of patients older than 60 was 4.5 years compared to 14.5 years in their younger counterparts ($p<0.05$, **Figure 2**). The median survival of R0 resections was 14.7 years, 5.8 years in R1, and less than a year in R2 and unresected patients ($p<0.05$). Although median survival of NF1 patients was shorter compared to non-NF1 patients (3.2 vs. 6.4 years respectively), this difference was not statistically significant ($p>0.05$). MPNSTs arising within neurofibromas had a significantly longer median survival of 14.4 years compared to 5.3 years in patients with de novo neoplasms ($p<0.05$). Time period of diagnosis was not significantly different ($p>0.05$), yet a trend is seen in longer survival for cases presenting after 2005 (7.5 vs. 5.2 years). The conditional inference tree found resectability (R0/R1) to be the strongest predictor for survival in any localized adult non-retroperitoneal MPNST ($p<0.05$, **Figure 3**). Whenever R0 or R1 resections were performed, patient age was the most significant factor associated with survival ($p<0.05$). In older patients (60+ years) with at least an R1 resection only tumor depth was significantly associated with survival ($p<0.05$). In younger adults (<60 years) larger tumor

size (>5cm) was then the strongest predictor of poorer survival (p<0.05). However, when tumor sizes were smaller than 5cm, only the patient's gender remained a critical factor significantly associated with survival; female patients had a worse prognosis (p<0.05).

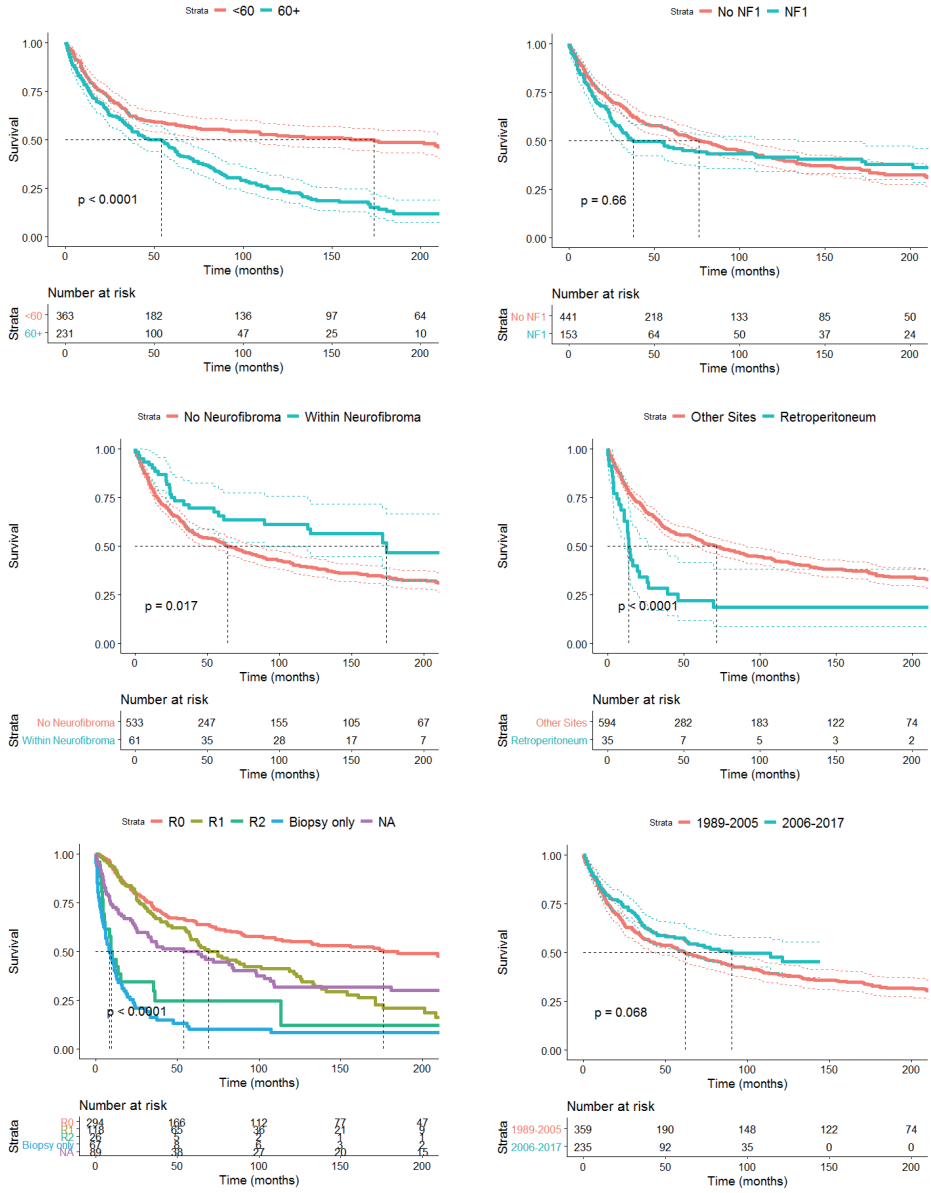

Figure 2 Kaplan-Meier curves of overall survival in localized adult non-retroperitoneal MPNSTs. A) Older versus younger adults. B) NF1 versus non-NF1 patients C) MPNSTs arising within a neurofibroma versus not arising within a neurofibroma D) Retroperitoneal versus non-retroperitoneal sites E) Resection margins F) Time period of diagnosis

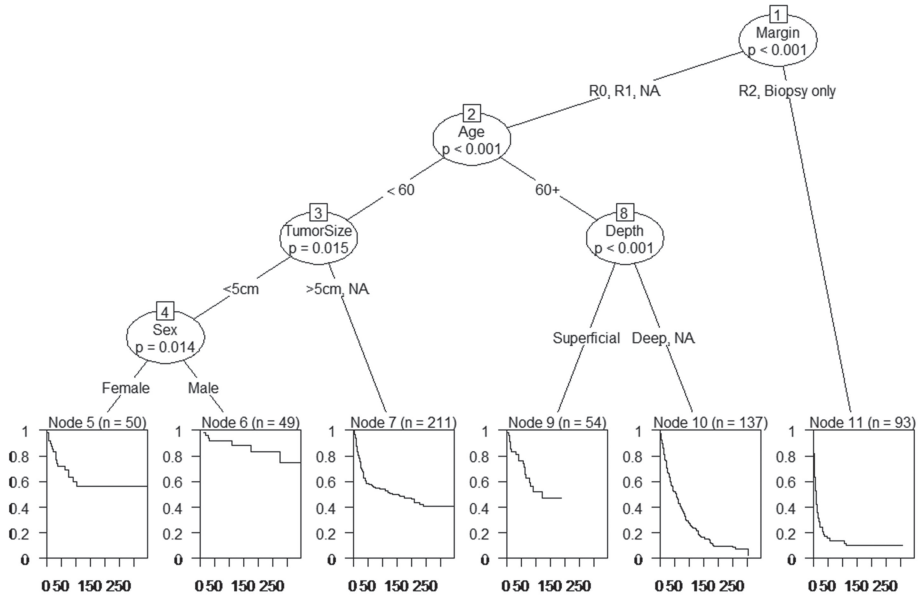

Figure 3 Conditional inference tree of overall survival in localized non-retroperitoneal adult MPNSTs.

Predictors for survival in localized non-retroperitoneal MPNST

On multivariate analysis age 60+ years, lesions in NF1 patients, large (>5cm) and deep-seated tumors were significantly associated with a poor survival in localized non-retroperitoneal MPNSTs (all p<0.05, **Figure 4 and 5**). Tumor site, Triton tumors, and time period of diagnosis were not significantly associated with survival (all p>0.05). There was a trend for MPNSTs arising within neurofibromas to be associated with increased survival ($p \approx 0.08$). Surgical margins were the only treatment related factor significantly associated with survival. Both R2 resections and biopsies only were significantly associated with worse survival (both p<0.05). R1 resections were not significantly associated with worse survival compared to R0 (p>0.05). Both the use of radiotherapy and chemotherapy were not independently associated with survival (both p>0.05).

Survival and predictors for survival in localized retroperitoneal MPNST

Retroperitoneal MPNSTs had a significantly worse outcome: median survival of 1.1 years compared to 6.0 years in patients with MPNST in other tumor sites (p<0.05, **Figure 2D**). The multivariate model for retroperitoneal MPNST specifically showed that older age and R2 and no resections were also associated with poorer survival in this subset of MPNSTs (both p<0.05, **Figure 6**). Additionally, male gender was significantly associated with poorer survival (p<0.05), without any known demographical differences compared to their female counterparts. Both radiotherapy and chemotherapy use were not significantly associated with survival (p>0.05).

Variable		N	Hazard ratio	p
Age	<60	363	Reference	
	60+	231	2.22 (1.75, 2.82)	<0.001
Sex	Female	272	Reference	
	Male	322	1.13 (0.91, 1.40)	0.282
NF	No NF1	441	Reference	
	NF1	153	1.39 (1.05, 1.83)	0.020
Neurofibroma	No neurofibroma	533	Reference	
	Within neurofibroma	61	0.68 (0.44, 1.05)	0.079
Triton	MPNST	559	Reference	
	Triton Tumor	35	1.41 (0.91, 2.19)	0.122
Site	Extremities	252	Reference	
	Trunk	243	1.01 (0.79, 1.31)	0.912
	Head & neck	82	1.11 (0.80, 1.55)	0.532
	NOS	17	1.45 (0.83, 2.55)	0.194
TumorSize	<5cm	169	Reference	
	>5cm	297	1.74 (1.28, 2.36)	<0.001
	NA	128	1.76 (1.25, 2.49)	0.001
Depth	Superficial	121	Reference	
	Deep	292	1.79 (1.20, 2.66)	0.004
	NA	181	1.56 (1.02, 2.38)	0.040
Margin	R0	294	Reference	
	R1	118	1.20 (0.90, 1.62)	0.216
	R2	26	2.54 (1.52, 4.24)	<0.001
	Biopsy only	67	4.01 (2.85, 5.64)	<0.001
	NA	89	1.36 (0.98, 1.89)	0.062
Radiotherapy	No	333	Reference	
	Yes	261	0.96 (0.76, 1.21)	0.735
Chemotherapy	No	547	Reference	
	Yes	47	0.99 (0.66, 1.48)	0.961
Period	1989-2005	359	Reference	
	2006-2017	235	1.01 (0.77, 1.33)	0.940

Figure 4 Cox proportional hazard model for overall survival in localized non-retroperitoneal adult MPNSTs. C-statistic: 0.715, N: number of patients, NA: not available.

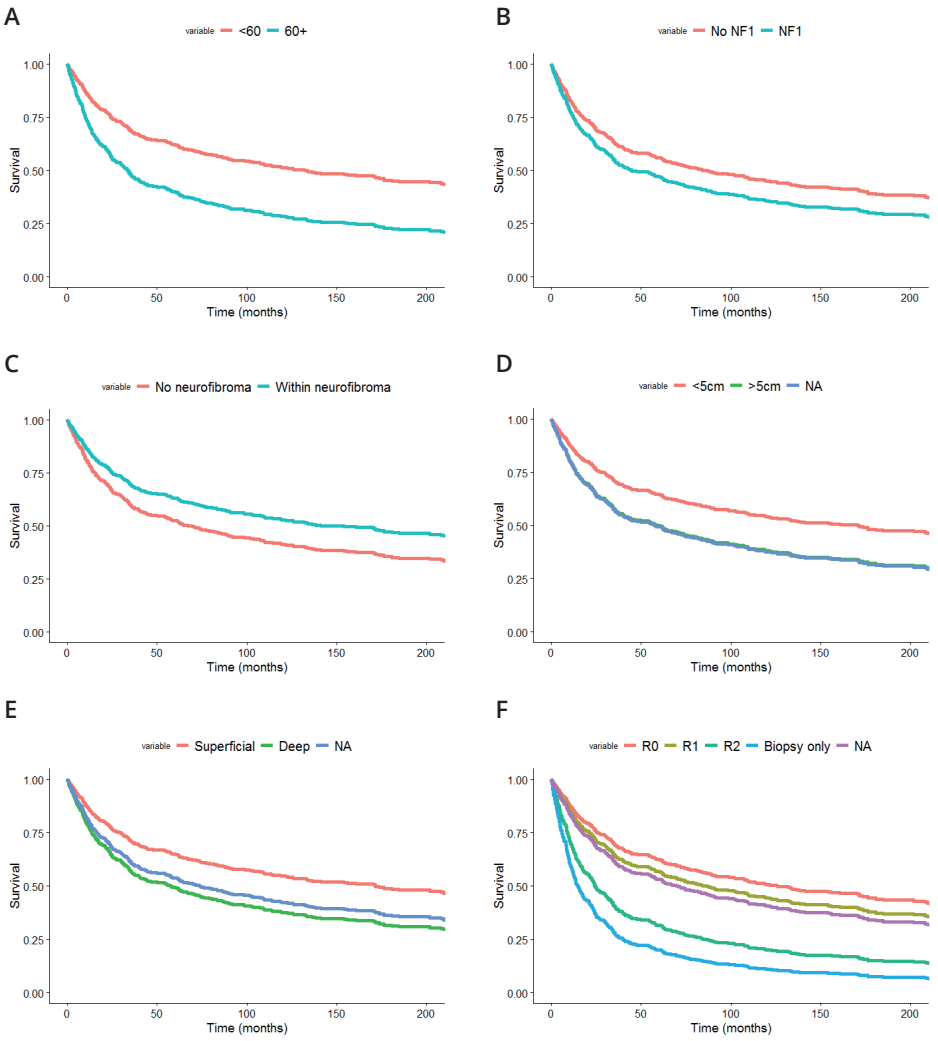

Figure 5 Adjusted survival curves of prognostic factors in localized non-retroperitoneal MPNSTs. A) Older versus younger adults B) NF1versus non-NF1 patients C) MPNSTs arising within a neurofibroma versus not arising within a neurofibroma D) Larger (>5 cm) versus smaller (≤5 cm) tumors E) Deep-seated versus superficial tumors F) Resection margins

Discussion

Using a large nationwide unselected group of MPNSTs several patient-, tumor-, and treatment-related prognostic factors were identified. In localized non-retroperitoneal MPNST, older age, presence of NF1, and large, deep-seated tumors are patient- and tumor-specific factors significantly associated with poor survival. Resectability is the most important predictor for survival. In retroperitoneal MPNSTs, older age, male sex, and R2 or absence of surgery were associated with poor survival. There was no statistically significant difference in survival between R1 and R0 resections in both retroperitoneal and non-retroperitoneal localized MPNSTs.

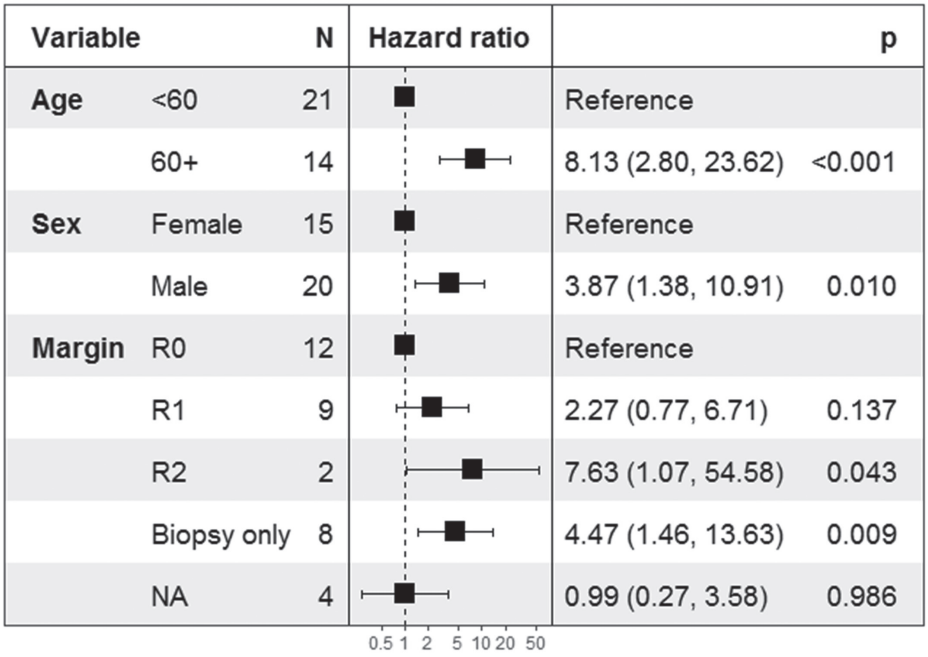

Figure 6 Cox proportional hazard model for overall survival in localized retroperitoneal adult MPNSTs. C-statistic: 0.811, N: number of patients, NA: not available

Tumor and patient-specific predictors of survival in MPNST

Factors independently found to be associated with overall survival in this study have been variously reported in other series. Whether or not presence of NF1 is inherently associated with worse survival compared to their sporadic counterparts has been subject to debate. While a meta-analysis contradicted this correlation when performing univariate analyses of series published after 2000,[20] our cohort and three other recent large series still reported this correlation when accounting for other confounders (**Table 3**).[5,21,22] Tumor biology between NF1 and sporadic MPNST may differ significantly and further studies are needed on how to translate these differences into optimal

treatment regimens.[5,23] Age has been reported as an independent predictor in one cohort only.[5] A study using registry data from the Surveillance, Epidemiology, and End Result (SEER) database also showed a significant correlation in which pediatric cases had the best prognosis, while older patients did significantly worse.[24] Larger tumor size has repeatedly been reported to affect survival,[2–5,21,22,25] while tumor depth has only been shown an independent predictor of survival in one study.[10] Tumor site has been reported varyingly as a predictor of survival, where truncal location, and in some series head and neck MPNSTs were independently associated with worse survival compared to extremity sites.[3–5,22,24,26] In this study, this correlation was not found, but results from other studies may be impeded as retroperitoneal cases were not evaluated as separate entities. The finding of a trend for MPNSTs encased by neurofibromas having a better survival compared to de novo tumors, despite the largest proportion being NF1 patients, may possibly be explained by tumor grade.[27] However, an exact explanation could not be found in this study and is therefore of interest in future studies.

Table 3 Common independent predictors of survival in previous large cohort studies.

Study	N	5-year OS	Factors influencing survival[a]					
			Age	NF1	Size	Depth	Site	R2
Current study[b]	594	50.8%	+	+	+	+	-	+
Miao 2019[b]	251	56.5%	+	+	+	*NA*	+	+
Yuan 2017[b]	140	45.0%	-	-	-	-	-	*NA*
Valentin 2016[b]	294	59.4%	-	-	-	+	-	+
Watson 2016[c]	289	52.0%	-	-	-	-	+	+
Fan 2014	146	57.0%	-	-	-	-	-	-
LaFemina 2013[c]	105	*NR*	-	-	+	*NA*	-	+
Stucky 2012[c]	175	60.0%	-	-	+	-	+	-
Porter 2009	123	51.0%	*NA*	+	+	-	-	*NA*
Zou 2009[c,d]	140	38.7%	-	-	+	*NA*	-	*NA*
Anghileri 2006[b,c]	205	39.9%	-	-	+	*NA*	+	+
Carli 2005[e]	167	51.2%	-	+	+	*NA*	+	*NA*
Wong 1998[b]	134	52.0%	*NA*	-	-	*NA*	-	+

[a]: significantly associated (+), not significantly associated (-), not evaluated (NA), [b]: localized disease only, [c]: analyses on disease-specific survival, [d]: multivariate analyses on completely resected cases only, [e]: includes pediatric cases only, N: number of patients, NF1: neurofibromatosis type 1, OS: overall survival

Treatment of localized MPNST

Macroscopically positive surgical margins have repeatedly been shown to have a strong correlation with poor survival in other series as well.[4,5,10,25,26,28] The conditional inference tree showed that it was even the strongest predictor for survival in localized disease. While R1 resections are not associated with worse prognosis, radiotherapy may be indicated to reduce the risk for local recurrence.[3,11,12] In both retroperitoneal as well as non-retroperitoneal MPNSTs, close margins may achieve similar survival outcomes, yet

decrease morbidity. This is of special interest for tumors situated in extremities and the retroperitoneum. To date, no rationale has yet been proven for treating MPNSTs differently from other STS when using chemotherapy.[15] In localized disease there may be a role for neoadjuvant chemotherapy in high-risk MPNSTs.[15,16] In individual cases neoadjuvant administration of chemotherapy may help initially deemed irresectable tumors to become resectable.[22,29] As retroperitoneal STS are more difficult to treat because of their relation to critical organs and structures, only recently guidelines have stated macroscopically complete resections to be necessary and just.[30] This study also supports the survival benefit of such resections. Neither radiotherapy nor chemotherapy has yet shown a significant benefit for survival in retroperitoneal STS.[31–33] Several ongoing trials are currently however still investigating the exact role of chemotherapy in retroperitoneal STS.[34] As retroperitoneal MPNSTs have one of the highest risks for local and distant recurrence and early death, the additional value of multimodal treatment is especially of interest in these patients.[35,36]

Strengths and limitations

Limitations are inevitable as in part only registry data was available. As NF1 status is not routinely registered in the NCR, the total amount of NF1 patients is possibly underestimated. However, the incidence rate in this study is in concordance to other series.[3–5,10] Furthermore, tumor grade could not be analyzed because of heterogeneity in reporting. However, the definition of low-grade tumors has only recently been assessed in a consensus meeting.[37] Unfortunately, local recurrence and distal metastasis rates were not recorded either, hindering further analyses for the role of multimodal treatment in localized MPNST. Nevertheless, this study is to the authors' knowledge the first nationwide study on MPNSTs. This design makes the data and models more generalizable as there is no form of selection or referral bias. As such, a model for a relatively homogenous group of localized adult non-retroperitoneal MPNSTs could be constructed specifically. The SEER database also allows for analyses of large patient cohorts, but lacks data on NF1 status, tumors within neurofibromas, R0/R1/R2 resection margins, the use of chemotherapy, and pathology review.[24] As STS patients present as a very heterogeneous group of patients, research on a single histological subtype level is necessary to aid in tailoring ideal treatment and outcomes and to increase our knowledge of their behavior. Especially as there may be important clinical variety within a single entity such as in MPNSTs, like NF1 patients, malignant transformation within neurofibromas, or tumors associated with large nerve bundles such as the brachial and sacral plexus. However, complete excision is necessary in all of these patients, yet R1 resections may suffice in order to preserve functionality, as MPNSTs have reported rates of motor deficits in over 30%.[38] Further understanding of ideal patient-tailored approaches in rare STS such as MPNSTs can only be made possible by large international collaborations including all medical specialties involved in their multimodal treatment.

Conclusion

In localized MPNST, risk stratification for survival can be done using several patient- and tumor specific characteristics. Controlling for several confounders, no difference in survival is seen between R0 and R1 resections. This is true for both retroperitoneal and non-retroperitoneal MPNSTs. The added value of radiotherapy and chemotherapy is unclear.

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Neurofibromatosis-associated Malignant Peripheral Nerve Sheath Tumors in Children Have a Worse Prognosis: a Nationwide Cohort Study

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Abstract

Background Malignant peripheral nerve sheath tumors (MPNST) are rare and aggressive non-rhabdomyoblastic soft tissue sarcomas (NRSTS) in children. This study set out to investigate clinical presentation, treatment modalities, and factors associated with survival in pediatric MPNST using Dutch nationwide databases.

Methods Data were obtained from the Netherlands Cancer Registry (NCR) and the Dutch Pathology Database (PALGA) from 1989-2017. All primary MPNSTs were collected. Demographical differences were analyzed between adult and pediatric (age ≤18 years) MPNST. In children, demographical and treatment differences between NF1 and non-NF1 were analyzed. A Cox proportional hazard model was constructed for localized pediatric MPNSTs.

Results A total of 70/784 MPNST patients were children (37.1% NF1). Children did not present differently from adults. In NF1 children, tumor size was more commonly large (>5cm, 92.3% vs. 59.1%). Localized disease was primarily resected in 90.6% and radiotherapy was administered in 37.5%. Non-NF1 children tended to receive chemotherapy more commonly (39.5% vs. 26.9%). Overall, estimated 5-year survival rates of localized NF1-MPNST was 52.4% (SE: 10.1%) compared to 75.8% (SE: 7.1%) in non-NF1 patients. The multivariate model showed worse survival in NF1 patients (HR: 2.98, 95%CI: 1.17-7.60, p = 0.02) and increased survival in patients diagnosed after 2005 (HR: 0.20, 95%CI: 0.06-0.69, p = 0.01). No treatment factors were independently associated with survival.

Conclusion Pediatric MPNSTs present similar to adult MPNSTs. In children, NF1 patients present with larger tumors, but are treated similarly to non-NF1 MPNSTs. In localized pediatric MPNST, NF1 is associated with worse survival. Promisingly, survival has increased for pediatric MPNSTs after 2005.

Introduction

Malignant peripheral nerve sheath tumors (MPNSTs) are rare and aggressive soft tissue sarcomas (STS), accounting for 2% of all STS.[1] A significant amount of MPNSTs occur in neurofibromatosis type 1 (NF1) patients, others occur sporadically, and in adults some are induced by radiation.[2,3] Despite the rare nature of MPNSTs, these sarcomas are among the most common non-rhabdomyosarcomatous STS (NRSTS) in pediatric patients, encompassing approximately 10% of all NRSTS.[4–6]

Besides clinically diverse presentations of MPNSTs based on tumor location, tumors will also present with different histological aspects. MPNSTs can arise within a neurofibroma as a malignant transformation, which is especially troublesome in the NF1 population.[7,8] Rarely, MPNSTs may also present with rhabdomyoblastic differentiation, so-called Triton tumors, which have been reported to be associated with poorer survival.[9,10]

To date, surgery remains the key to improve survival in any localized MPNST.[3,11] However, MPNSTs have been reported unresectable in 17-53%, which is higher than other NRSTS.[6,12–15] Also, when unresectable, clinical response to neoadjuvant chemotherapy is lowest in MPNSTs compared to other NRSTS, especially in NF1 patients.[15,16] As in other STS, radiotherapy is commonly administered in order to improve local control, but no effect has been shown on survival.[3,17,18] However, long-term morbidity of radiotherapy in a pediatric population needs particular attention. Despite the curative intent of treatment in localized MPNST, local recurrences and distant metastases are very common and survival remains poor.[2,3,11] Overall survival in MPNSTs is also poorer compared to other NRSTS.[19] Additionally, factors influencing survival are not evident yet in pediatric MPNSTs. Recently, the influence of NF1 on survival has been subject of debate as studies report conflicting results.[11,15,20,21]

As pediatric NRSTS are rare they have historically been treated as rhabdomyosarcomas, yet the low chemosensitivity and aggressive nature of MPNSTs pose difficulties in selecting ideal treatment regimens. More needs to be learned on prognostic factors of survival in pediatric MPNSTs particularly, as it may help tailoring clinical decision-making. This study aims to investigate differences in clinical presentation between adult and pediatric MPNST patients. It also aims to evaluate overall survival, treatment modalities used, and factors associated with survival in pediatric MPNSTs only using a Dutch nationwide cohort of patients.

Methods

Data Source

Data were obtained from the nationwide Netherlands Cancer Registry (NCR), which is managed by the Netherlands Comprehensive Cancer Organisation (IKNL). The NCR is a population-based registry that gets notified of all newly diagnosed malignancies in the Netherlands by automated pathological archive (PALGA) and the National Registry of Hospital Discharge Diagnosis (LMR). Patient and tumor characteristics and initial treatment information are routinely extracted from medical records. Their quality is high due to thorough training of the registration team and computerized consistency checks at both regional and national levels. Full pathological reports were also requested from PALGA.[22] Cases were matched to PALGA by means of a trusted third party. Malignant peripheral nerve sheath tumors (ICD-O-3: 9540, 9560, 9561) from any site were obtained. Cases from the NCR were obtained from 1989-2017. The data requested was approved by the scientific and privacy committees of IKNL.

Covariates

Covariates extracted for analysis were: year of diagnosis (1989-2005/2006-2017), sex, age (pediatric ≤18 years vs. adult >18 years), NF1 status, tumor site, tumor stage (metastasis/no metastasis at diagnosis), tumor size (≤5/>5cm), tumor depth (superficial/deep to the fascia), tumor morphology, resection margin (R0/R1/R2/biopsy only), other treatment modalities, and sequence of treatment. A cut-off between 2005 and 2006 was chosen because of the publication of the Italian and German Soft Tissue Sarcoma Cooperative Group in 2005 showing highest treatment effect of doxorubicin and ifosfamide regimens.[6] NF1 status was extracted based on pathology reports. The diagnosis was concluded either when explicitly reported in the pathological reports or whenever a pathology reports existed of previous plexiform neurofibroma resections or two or more neurofibromas. Tumor sites were recoded into: head and neck, extremities, trunk (including thorax, abdomen, and pelvis), retroperitoneal, and not otherwise specified (NOS). Resection margins were classified as tumor-free (R0), microscopically positive (R1, less than 1mm margins), and macroscopically positive (R2). Tumor grade was not obtained as it is not registered in the NCR and pathological reports inconsistently report it. Vital status and date of death are routinely obtained from municipal demographic registries in the Netherlands.

Statistical analysis

All pathological reports of a patient registered in the NCR were screened for the final diagnosis of MPNST; all cases with doubtful diagnoses were excluded. Demographical differences were compared between adult and pediatric MPNSTs and in pediatric patients between NF1 and non-NF1 MPNST. Treatment modalities were compared between NF1 and non-NF1 pediatric patients excluding those who presented with metastatic disease. 5-year survival rates were estimated using the Kaplan-Meier

method to compare adult and pediatric MPNSTs, metastatic and non-metastatic pediatric MPNST, and in localized pediatric patients for NF1 status, tumor depth, tumor size, resection margin, and time period of diagnosis. Kaplan-Meier curves were made for all comparisons of localized pediatric patients only, except for the comparison of metastatic versus localized disease at presentation. Differences were assessed using the log-rank test. A multivariate Cox proportional hazard model was constructed by backward selection for localized pediatric MPNSTs only. P-values <0.05 were considered statistically significant. In order to create a parsimonious model, a ratio of five events per degree of freedom was chosen. Additionally, adjusted survival curves were constructed for individual prognostic factors based on the final model.[23] Statistical analyses and data visualization were conducted using R version 3.6.0 (R Core Team, 2019).

Table 1 Clinicopathologic differences between adult and pediatric patients

Variable		**Overall**		**Pediatric**		**Adult**		**P**
Number of patients		784		70		714		
Male gender		421	(53.7%)	38	(54.3%)	383	(53.6%)	1.00
NF1		210	(26.8%)	26	(37.1%)	184	(25.8%)	0.06
Site								
	Extremities	303	(38.6%)	24	(34.3%)	279	(39.1%)	
	Trunk	312	(39.8%)	29	(41.4%)	282	(39.5%)	
	Retroperitoneum	43	(5.5%)	3	(4.3%)	40	(5.6%)	0.78
	Head & Neck	100	(12.8%)	11	(15.7%)	89	(12.5%)	
	NOS	26	(3.3%)	3	(4.3%)	24	(3.4%)	
Tumor size								
	≤5cm	190	(32.1%)	10	(28.6%)	180	(32.3%)	0.65
	>5cm	402	(67.9%)	25	(71.4%)	377	(67.7%)	
	NA	192		35		157		
Tumor depth								
	Superficial	6	(14.0%)	3	(12.0%)	3	(16.7%)	
	Deep	37	(86.0%)	22	(88.0%)	15	(83.3%)	0.68
	NA	27		19		8		
Triton tumor		48	(6.1%)	3	(4.3%)	45	(6.3%)	0.68
Synchronous metastasis		90	(11.5%)	6	(8.6%)	84	(11.8%)	0.56
Time period								
1989-2005		454	(57.9%)	43	(61.4%)	411	(57.6%)	0.62
2006-2017		330	(42.1%)	27	(38.6%)	303	(42.4%)	

cm: centimeters, MPNST: malignant peripheral nerve sheath tumor, NA: not available, NF1: neurofibromatosis type 1, NOS: not otherwise specified

Results

Patient population

From a total of 879 patients registered in the NCR database, 784 had the final diagnosis of MPNST. Of this group 70 patients were children (8.9%, **Table 1**). Demographically there were no statistically significant differences between presentation of adult and pediatric MPNSTs (all p>0.05). There was a trend for a higher incidence of NF1 in pediatric patients (37.1% vs. 25.8%, p = 0.06). In pediatric patients there was a slight male predilection (54.3%). Tumors were usually large (>5cm, 71.4%) and most commonly located in truncal sites (45.7%); three of which had a retroperitoneal MPNST (4.3%). Tumors tended to be larger in NF1 patients compared to non-NF1 pediatric patients, 92.3% and 59.1% respectively (p = 0.05, **Table 2**). Tumor site, tumor depth, and presence of rhabdomyoblastic differentiation did not differ significantly between pediatric NF1 and non-NF1 patients (all p>0.05). A total of six children (8.6%) initially presented with metastatic disease, of which all were in non-NF1 patients.

Table 2 Clinicopathologic differences between NF1 and non-NF1 pediatric patients.

Variable		**Pediatric**		**Non-NF1**		**NF1**		**P**
Number of patients		70		44		26		
Male gender		38	(54.3%)	27	(61.4%)	11	(42.3%)	0.19
Site								
	Extremities	24	(34.3%)	15	(34.1%)	9	(34.6%)	
	Trunk	29	(41.4%)	16	(36.4%)	13	(50.0%)	
	Retroperitoneum	3	(4.3%)	2	(4.5%)	1	(3.8%)	0.65
	Head & Neck	11	(15.7%)	9	(20.5%)	2	(7.7%)	
	NOS	3	(4.3%)	2	(4.5%)	1	(3.8%)	
Tumor size								
	≤5cm	10	(28.6%)	9	(40.9%)	1	(7.7%)	
	>5cm	25	(71.4%)	13	(59.1%)	12	(92.3%)	**0.05**
	NA	35		22		13		
Tumor depth								
	Superficial	6	(14.0%)	3	(12.0%)	3	(16.7%)	
	Deep	37	(86.0%)	22	(88.0%)	15	(83.3%)	0.68
	NA	27		19		8		
Triton tumor		3	(4.3%)	1	(2.3%)	2	(7.7%)	0.55
Synchronous metastasis		6	(8.6%)	6	(13.6%)	0	(0.0%)	0.08
Time period								
1989-2005		43	(61.4%)	26	(59.1%)	17	(65.4%)	0.62
2006-2017		27	(38.6%)	18	(40.9%)	9	(34.6%)	

cm: centimeters, NA: not available, NF1: neurofibromatosis type 1, NOS: not otherwise specified

Table 3 Treatment of localized pediatric MPNST.

Variable		Overall		Non-NF1		NF1		P
Surgery								
	Surgical excision	58	(90.6%)	36	(94.4%)	22	(84.6%)	0.21
	Biopsy only	6	(9.4%)	2	(5.6%)	4	(15.4%)	
Surgical Margin								
	R0	32	(59.3%)	20	(60.6%)	12	(57.1%)	0.53
	R1	15	(27.8%)	10	(30.3%)	5	(23.8%)	
	R2	1	(1.9%)	1	(3.0%)	0	(0.0%)	
	Biopsy only	6	(11.1%)	2	(6.0%)	4	(19.0%)	
	Resection, unknown margin	10		5		5		
Radiotherapy Sequence								
	No Radiotherapy	40	(62.5%)	26	(68.4%)	14	(53.8%)	0.44
	Preoperative Radiotherapy	5	(7.8%)	2	(5.3%)	3	(11.5%)	
	Postoperative Radiotherapy	19	(29.7%)	10	(26.3%)	9	(34.6%)	
Chemotherapy								
	No	42	(65.6%)	23	(60.5%)	19	(73.1%)	0.42
	Yes	22	(34.4%)	15	(39.5%)	7	(26.9%)	
Chemotherapy Sequence								
	No Chemotherapy	42	(65.6%)	23	(60.5%)	19	(73.1%)	0.64
	Preoperative Chemotherapy	8	(12.5%)	5	(13.2%)	3	(11.5%)	
	Postoperative Chemotherapy	12	(18.8%)	9	(23.7%)	3	(11.5%)	
	Chemotherapy only	2	(3.1%)	1	(3.0%)	1	(3.8%)	

MPNST: malignant peripheral nerve sheath tumor, NF1: neurofibromatosis type 1

Treatment of localized pediatric MPNST

Overall, surgical excision was part of initial treatment in 90.6% of localized pediatric MPNSTs (**Table 3**). R0 resections were achieved in 66.7%, without any differences between NF1 and non-NF1 patients (p>0.05). R1 resections were achieved in 31.3% and only one child had an R2 margin as final surgical margin. Radiotherapy was administered in 37.5% of all patients, but not more commonly in NF1 patients (47.2% vs. 31.6%, p>0.05). No patient received salvage radiotherapy only. Chemotherapy was administered in 34.4% as an adjunct to surgical excision, of which 40% was administered in a neoadjuvant setting. Rates of chemotherapy use were non-significantly higher in non-NF1 patients (39.5% vs. 26.9%, p>0.05). Two patients received chemotherapy without any further surgical excision. No patient received both adjuvant and neoadjuvant chemotherapy.

Survival and factors associated with survival in pediatric MPNST

In the complete nationwide cohort, the estimated 5-year survival rate of any pediatric MPNST was 62.0% (SE: 5.9%) compared to 46.2% (SE: 1.9%) in adult MPNST (p<0.05). In localized disease only, 5-year survival rates were 66.3% (SE: 6.0%) and 51.6% (SE: 2.1%) respectively (p<0.05). Pediatric patients initially presenting with metastatic

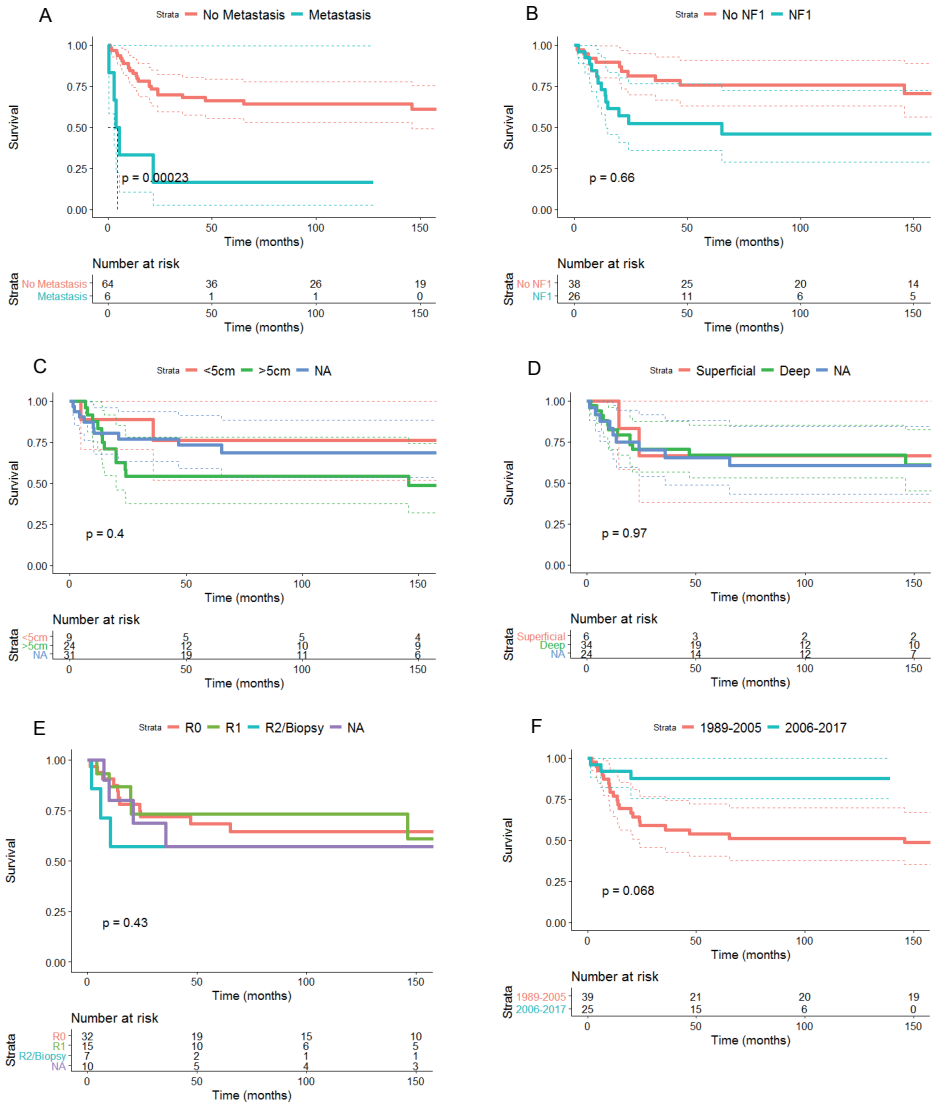

Figure 1 Kaplan-Meier curves for overall survival in localized pediatric MPNST. A) Tumor stage at presentation (metastatic vs localized) B) NF1 status C) tumor size (≤5 cm vs > 5 cm) D) tumor depth (superficial vs deep of the fascia) E) resection margin (R0 vs R1 vs R2/biopsy) F) time period (1989-2005 vs 2006-2017)

disease had a 1-year survival rate of 33.3% (SE: 19.2%) compared to 82.8% (SE: 4.7%, P<0.05) presenting with localized disease (**Figure 1**). In localized pediatric patients only, NF1 patients had lower 5-year survival rates (52.4%, SE: 10.1%) compared to non-NF1 children (75.8%, SE: 7.1%, p<0.05). Also, estimated 5-year survival rates were

higher in children diagnosed after 2005 (87.6% SE: 6.7% vs. 53.9% SE: 8.0%, p<0.05). On multivariate analysis of localized pediatric MPNST, NF1 status was the only patient- and tumor-specific variable independently associated with survival (HR: 2.98, 95% CI: 1.17-7.60, p<0.05, **Figure 2 and 3**). Additionally, patients presenting after 2005 were significantly associated with increased survival (HR: 0.20, 95% CI: 0.06-0.69, p<0.05), without demographical or overall treatment differences between these time periods. Surgical margins, the use of chemotherapy, radiotherapy, and any sequence of multimodal treatment were not significantly associated with survival in localized pediatric MPNST (all p>0.05).

Variable		N	Hazard ratio	p
NF	No NF1	38	Reference	
	NF1	26	2.98 (1.17, 7.60)	0.02
Margin	R0	32	Reference	
	R1	15	1.40 (0.45, 4.41)	0.56
	R2/Biopsy	7	2.07 (0.61, 6.97)	0.24
	NA	10	0.83 (0.25, 2.72)	0.75
Chemotherapy	No	42	Reference	
	Yes	22	1.96 (0.82, 4.70)	0.13
Period	1989–2005	39	Reference	
	2006–2017	25	0.20 (0.06, 0.69)	0.01

Figure 2 Cox proportional hazard model in localized pediatric MPNST

Discussion

In this large, nationwide, unselected group of MPNST, pediatric patients presented similarly compared to adult MPNST. In children, NF1 patients more commonly had large tumors, but were treated similarly compared to non-NF1 patients. In localized pediatric MPNST, only NF1 status was independently associated with poor survival. No treatment related factors were independently associated with survival. Also, patients presenting after 2005 were independently associated with increased survival.

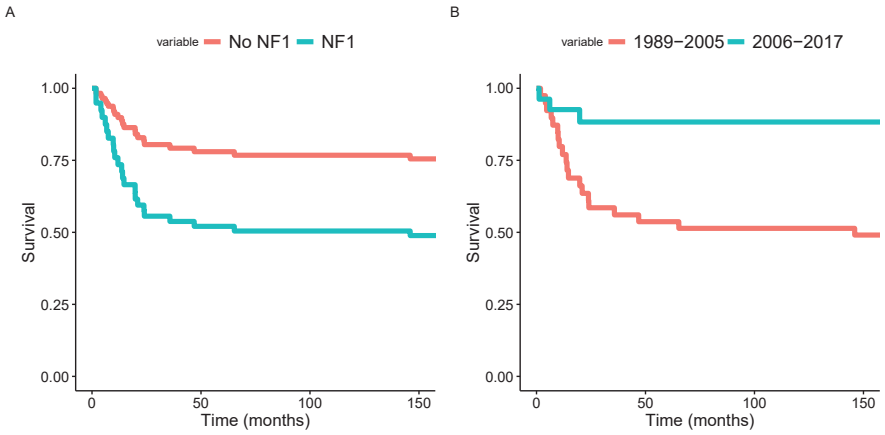

Figure 3 Adjusted survival curves for prognostic factors in localized pediatric MPNST. A) NF1 status B) time period (1989-2005 versus 2006-2017)

Survival in pediatric MPNST

Historically, pediatric MPNSTs have been associated with poor prognosis, with 5-year survival rates ranging from 34.6-65%.[6,24,25] Earlier series reported even worse survival rates.[26–28] However, a trend towards increased survival in pediatric MPNST has been suggested in a study using data from the Surveillance, Epidemiology, and End Results Program (SEER) database.[29] Anthracycline-based regimens with or without additional ifosfamide have shown superior results in a large cohort of pediatric patients in a study published in 2005.[6] The European Pediatric Soft Tissue Sarcoma Group (EpSSG) consequently published results of their 2005-2016 cohort in which doxorubicin and ifosfamide was used whenever chemotherapy was administered.[15] The study by the EpSSG showed higher 5-year survival rates compared to the earlier publication of the Italian and German Soft Tissue Sarcoma Cooperative Group. This may explain at least in part the increasing survival rates observed in this study after 2005, as doxorubicin and ifosfamide use may have risen compared to other regimens since the first publication in 2005. Furthermore, in other sarcoma trials, such as the EpSSG rhabdomyosarcoma 2005 trial also showed increase in survival in both study arms, indicating that survival of sarcomas in children generally may be improving over the years. This may in turn be due to centralization of their healthcare. While survival rates in pediatric MPNST from previous studies show comparable results as in adult MPNST,[2,30,31] another study using SEER data showed that children had a better prognosis when controlling for known confounders.[4] Few other studies have found factors associated with survival in pediatric MPNST.[6,15,27] NF1 status has previously been reported as well to be independently associated with worse survival in children.[6,15,27] It is not yet completely clear what NF1-related factors cause this difference. Demographically, all but initial tumor size differed in this study between NF1 and non-NF1 patients and no differences in treatment modalities were observed, especially in final surgical margins.

And although not independently associated with survival in this study, larger tumor size and non-extremity tumor site have also been associated with worse survival in pediatric MPNST.[6,27] However, the model did not improve by adding any of the two factors, and the association of NF1 status with survival was independent of both factors. In part, it may be due to lower chemosensitivity which has been suggested in NF1 patients.[6,16,32,33] However, in the EpSSG study, similar response rates were seen between NF1 and non-NF1 children.[15] The impact of NF1 status on survival in adults has been controversial as well. While a meta-analysis suggests there is no influence seen in studies published after 2000,[20] several large recent studies do find NF1 status to be independently associated with worse survival.[21,34,35] Some immunohistochemical markers have been proposed predictors of poor survival as well as they may reflect more aggressive biology of the tumor, such as loss of p53,[2,36] negative S100 staining,[37] or loss of H3K27 tri-methylation.[38]

Treatment of pediatric MPNST

Although this study did not find a significant difference in survival between R2 resections and biopsies only compared to complete resections, results from previous studies in adults have shown a strong benefit on survival if performed.[11,30,31,34,39,40] In pediatric MPNST, Intergroup Rhabdomyosarcoma Study (IRS) groups III/IV (translating to R2 and metastatic cases respectively) have been associated with worse survival as well,[6,26] yet this effect may partially be due to the inclusion of metastatic patients in these analyses. Also, previous studies in pediatric MPNSTs showed higher rates of IRS III/R2 patients compared to this study possibly indicating a selection bias in larger pediatric sarcoma centers.[6,24–28,41] It may also imply that the subgroup was underpowered as only seven patients had R2 resections or biopsies only. As MPNSTs are aggressive in general and surgery is the only treatment proven effective, R0/R1 resections should still be strived after.[42] While R1 resections have been associated with increased risks for local recurrence, they have not been associated with worse survival in both adult and pediatric MPNST.[3,6,17,21] This may provide an opportunity for the adoption of planned positive margins in MPNSTs as well, thus decreasing morbidity in some patients.[43,44] The role of both chemotherapy and radiotherapy is controversial in MPNST, even more so in pediatric patients. Radiotherapy is generally administered for local control, either preoperatively or after R1 resection.[3,17,18,42] Guidelines usually follow adult doses, which is generally equal to 50Gy preoperatively and 60-66Gy postoperatively.[17,42,45,46] However, in children, keeping long-term radiation complications to a minimum is important and has resulted in lower radiation dose of 50.4-54Gy in the EpSSG guidelines. Although R1 resections may decrease postoperative morbidity by avoiding resection of adjacent functional structures, close margin surgery will necessitate the use of radiotherapy, which in turn may also impair function. Careful preoperative planning including a reconstructive surgeon and shared decision making are therefore crucial. The use of chemotherapy in unresectable cases may benefit patients as some may become resectable and thus downstage the tumor,[6,32] and is

therefore incorporated in both the EpSSG and the Children's Oncology Group (COG) guidelines. The benefit of chemotherapy in an adjuvant setting is however less clear. Some studies have suggested its use in large, high-grade STS including MPNSTs.[14,42,47] Ideal cytotoxic regimens include a combination of doxorubicin and ifosfamide as they have shown to give the best effect in both adult and pediatric MPNST.[6,32,33,48] Yet response rates in MPNSTs are still very low, even more so in NF1 patients.[6,16,32,33] Given the low chemosensitivity of MPNSTs, novel therapies are desperately warranted. Currently, multiple new therapies are under investigation, including targeted therapies, immunotherapy, and oncolytic viruses.[49] However, to date no targeted therapy has been proven effective in MPNST patients.[50–55]

Strengths and limitations

This study is based on registry and pathological data only and subsequently resulting in some limitations. NF1 status is not routinely registered in the NCR and all diagnoses were made based on pathological reports. This has possibly resulted in an underestimation of the total amount of NF1 patients. However, the incidence rate in this study is in concordance to other series.[6,15,24,25] Tumor size was also commonly missing, which may have underestimated the effect of tumor size on survival in this study. Tumor grade could also not be analyzed because of its heterogeneity in reporting. Nonetheless have low-grade tumors only recently been defined following a consensus meeting.[56] Other clinical information such as the efficacy of chemotherapy or radiotherapy on disease-free survival were not available for this study. Nevertheless, using a nationwide cohort of patients, a model for localized pediatric MPNST could be constructed. The advantage of such data is that models may be more generalizable as there is no form of selection or referral bias. The SEER database also allows for analyses of large patient cohorts, but lacks data on NF1 status, tumor depth, R0/R1/R2 resection margins, and the use of chemotherapy.[29,57] It becomes increasingly clear that STS can present very heterogeneously and single histological subtypes may present differently, having additional risk factors which warrant attention. As MPNSTs carry a high risk for postoperative morbidity and oncological treatment failure, more knowledge needs to be gathered from their adult counterparts as well as other high-risk pediatric NRSTS. As such, ideal patient-tailored treatments may be elucidated balancing both oncological and functional outcomes.

Conclusion

Pediatric MPNST present similarly compared to adult MPNST. In children, NF1 patients will generally present with larger tumors, but are treated similarly compared to non-NF1 MPNSTs. In localized pediatric MPNST, NF1 status is independently associated with poor survival. No treatment related factor was independently associated with survival. Life expectancy has significantly increased in pediatric MPNSTs after 2005.

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5

Oncological Treatment Considerations Differ Across Surgical Subspecialties Treating Malignant Peripheral Nerve Sheath Tumors: an International Survey

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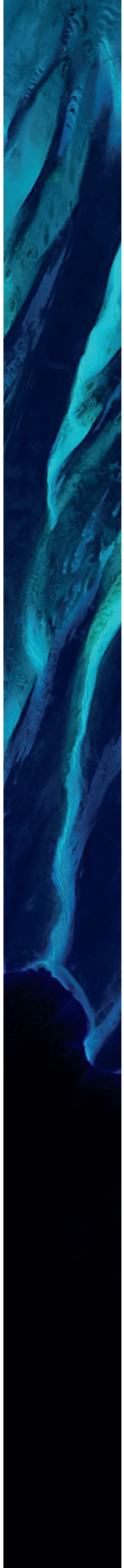
Sarcoma. 2020 Feb, 2020: 6406439.



Abstract

Background Malignant peripheral nerve sheath tumors (MPNSTs) are rare and aggressive soft tissue sarcomas (STS) that, because of their origin, are operated by several surgical subspecialties. This may cause differences in oncologic treatment recommendations based on presentation. This study investigated these differences both within as between subspecialties.

Methods A survey was distributed among several (inter)national surgical societies. Differences within and between subspecialties were analyzed by χ^2-tests.

Results In total, 30 surgical oncologists, 30 neurosurgeons, 85 plastic surgeons, and 29 'others' filled out the survey. Annual caseload, tumor sites operated, and fellowship training differed significantly between subspecialties. While most surgeons agreed upon preoperative use of MRI, the use of radiological staging and FDG-PET use differed between subspecialties. Surgical oncologists agreed upon core needle biopsies as ideal type of biopsy while other subspecialties differed in opinion. On average, 53% of surgeons always consider preservation of function preoperatively, but 42% would never perform less extensive resections for function preservation. Respondents agreed that radiotherapy should be considered in tumor sizes >10cm, microscopic, and macroscopic positive margins. Preferred sequence of radiotherapy administration differed between subspecialties. There was no consensus on indications and sequence of administration of chemotherapy in localized disease.

Conclusion Surgical oncologists generally agree on preoperative diagnostics, other subspecialties do not. Considering preservation of function differed among all subspecialties. Surgeons do agree on some indications for radiotherapy, yet the use of chemotherapy in localized MPNSTs lacks consensus. Preferred sequence of multimodal therapy differs between and within surgical subspecialties, but surgical oncologists prefer neoadjuvant radiotherapy.

Introduction

Malignant peripheral nerve sheath tumors (MPNSTs) are aggressive soft tissue sarcomas (STS) that can occur at any anatomical site.[1] Approximately 25-50% of all patients are known to have neurofibromatosis type 1 (NF1).[2–6] The diagnosis of an MPNST can be difficult as patients may present with similar symptoms compared to their benign counterparts and MRI studies cannot distinguish a malignancy with high precision.[7–9] This can especially be troublesome in patients with NF1 that develop multiple benign nerve sheath tumors.

Surgical resection is the only curative treatment option in localized MPNSTs.[4,10] Radiotherapy has an important role in decreasing local recurrence rates, but does not affect survival.[4,11,12] The exact role for chemotherapy is also subject of controversy, but is advocated by some as adjuvant treatment in large and deep MPNSTs.[13,14] Unfortunately, despite curative aims of aggressive treatment including clear surgical margins, MPNSTs regularly recur and metastasize in up to 60% of patients.[2–4,15,16]

MPNSTs are rare tumors and exact treatment strategies may differ between surgeons, because patients can present at different surgical subspecialties due to their origin in nervous tissue and occurrence in NF1. While surgical oncologist consider MPNSTs as part of their sarcoma population requiring radical excision,[17,18] plastic surgeons and neurosurgeons operating peripheral nerve lesions regard them as a malignant form of nerve sheath tumor, which are treated by nerve-sparing surgery.[19,20] Such a difference in perspective could affect clinical decision-making. This study investigated treatment recommendations and differences in opinions between surgical subspecialties treating MPNSTs on preoperative diagnostics, surgical decision-making, and the use of multimodal therapy in localized MPNSTs.

Methods

Study design and survey instrument

A survey was constructed by two authors (E.M. and J.H.C.) and tested internally with all co-authors from different surgical subspecialties. A secure electronic data capturing tool (REDCap) provided by the Dutch Plastic Surgery Society (NVPC) was used to construct the survey. This study is part of a larger survey addressing both oncological and reconstructive treatment considerations for localized MPNST. A total of 18 questions (30 in total) were used for this study, of which seven were for demographical purposes. The complete survey can be found in **Supplementary File 1**. Approval for this study was obtained from our institutional review board.

Study population

Several national and international surgical societies were asked to distribute the survey among their members with an accompanying text explaining the purpose of the research. Surgeons involved in the surgical management of MPNSTs were asked to fill out the survey. A reminder email was sent thereafter. The survey was sent to the members of the Dutch Society of Surgical Oncology (NVCO), the Dutch Society for Surgery of the Hand (NVVH), the peripheral nerve section of the Dutch Society for Neurosurgery (NVVN), the American Society for Peripheral Nerve (ASPN), the peripheral nerve section of the European Association of Neurosurgical Societies (EANS), and the Soft Tissue and Bone Sarcoma Group of the European Organization for Research and Treatment of Cancer (EORTC). Survey responses were filled out anonymously and no person identifying data was inquired.

Statistical analysis

Responses were summarized per surgical subspecialty: oncologic surgery, neurosurgery, plastic surgery, and other surgical subspecialties. Differences were calculated with χ^2-tests for categorical data. P-values <0.05 were considered statistically significant. Statistical analyses and data visualization were conducted using R version 3.6.0 (R Core Team, 2019).

Results

Demographics of survey responders

In total, 174 respondents filled out the survey: 30 surgical oncologists, 30 neurosurgeons, 85 plastic surgeons, and 29 surgeons from other surgical subspecialties. Most respondents were European (**Figure 1**). The 'other' surgical subspecialty group consisted mainly of non-oncologic orthopedic surgeons and general surgeons with a hand surgery subspecialization. The largest proportion of surgeons had less than 10 years of experience as a consultant surgeon (38%, **Table 1**). Fellowship experience differed between subspecialties ($p<0.001$); surgical oncologists commonly had completed a sarcoma fellowship (85%), while other respondents more commonly did a fellowship in peripheral nerve surgery (32-56%). Highest caseloads were performed by surgical oncologists ($p<0.001$). The majority of respondents operated extremity site tumors (87%, $p>0.05$), but most other tumor sites differed between surgical subspecialties.

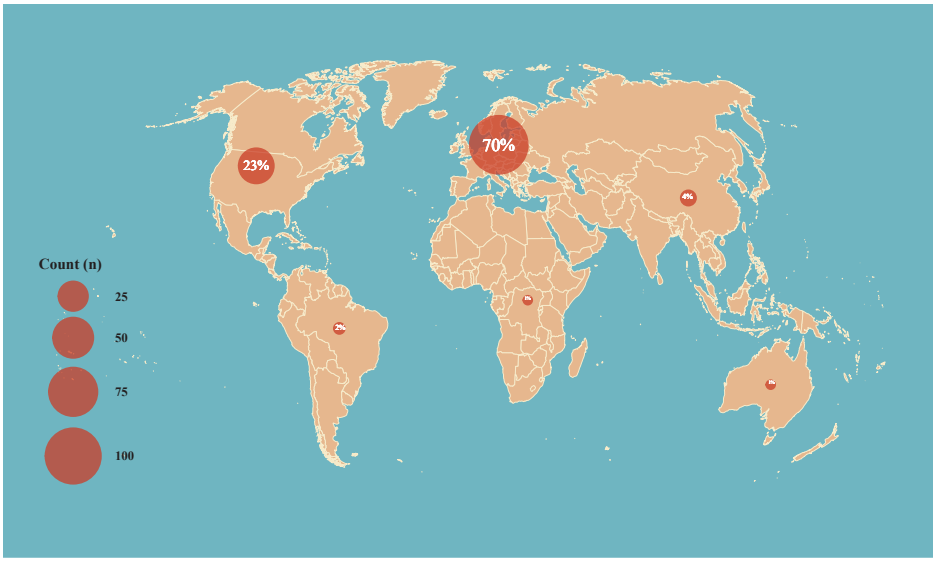


Figure 1 World map showing the geographical distribution of survey respondents per continent. The surface of the bubbles corresponds to the number of respondents.

Preoperative diagnostics

Opinions regarding preoperative work-up of soft tissue tumors that may originate from peripheral nerves differs between surgical subspecialties (**Figure 2**). The majority of respondents would perform radiological imaging and a biopsy before operating (65%), and surgical oncologists strongly agreed on this (92%, $p<0.05$). Regarding preoperative imaging studies, surgeons agreed that an MRI is necessary (95%, $p>0.05$). FDG-PET scans which can be used both for staging and possible differentiation of benign and malignant lesions are more commonly performed by neurosurgeons (67%) and surgical oncologists (48%, $p<0.05$). Preoperative staging was carried out by 44% of respondents, most commonly by surgical oncologists (80%, $p<0.001$). A CT-thorax is used by 25%, of which more than half would be in conjunction with an FDG-PET scan. A total of 10% would also carry out other radiologic diagnostics preoperatively. Preferred type of biopsy differed significantly between the surgical subspecialties ($p<0.001$). Overall, core needle biopsy was the preferred type of biopsy, especially among surgical oncologists (96%). Plastic surgeons and 'other' surgeons commonly also preferred open biopsies. Plastic surgeons were also most likely not to have a preferred biopsy technique (17%). Respondents that did not regard a preoperative biopsy necessary commonly reported that they considered the chances of tumor spread too high and would therefore directly proceed to surgery.

Table 1 Demographical data of survey participants

Variable		Oncologic Surgery	Neuro-surgery	Plastic Surgery	Other Specialties	P
Number of participants		30	30	85	29	
Experience	Mean (SD)	15.64 (9.31)	13.26 (8.64)	13.49 (9.81)	15.64 (10.13)	0.603
	<10 Years	28.6%	37.0%	43.1%	36.0%	
	10-20 Years	50.0%	37.0%	34.7%	28.0%	0.585
	>20 Years	21.4%	25.9%	22.2%	36.0%	
Fellowship training	Sarcoma	81.5%	0.0%	2.8%	8.0%	**<0.001**
	PNS	0.0%	55.6%	29.2%	56.0%	
	Sarcoma & PNS	3.7%	0.0%	2.8%	0.0%	
	Other or none	14.8%	44.4%	65.3%	36.0%	
Annual caseload	0-1	18.5%	50.0%	70.4%	66.7%	**<0.001**
	2-3	22.2%	34.6%	22.5%	12.5%	
	3-5	33.3%	15.4%	2.8%	12.5%	
	>5	25.9%	0.0%	4.2%	8.3%	
Tumor sites operated	Intracranial	0.0%	34.6%	0.0%	0.0%	**<0.001**
	Head & neck	18.5%	42.3%	14.1%	8.3%	**0.007**
	(Para)spinal	22.2%	76.9%	1.4%	4.2%	**<0.001**
	Superficial thoracic	55.6%	34.6%	8.5%	8.3%	**<0.001**
	Intrathoracic	37.0%	15.4%	0.0%	0.0%	**<0.001**
	Abdominal	74.1%	23.1%	5.6%	4.2%	**<0.001**
	Retroperitoneal	74.1%	46.2%	4.2%	0.0%	**<0.001**
	Pelvic	81.5%	38.5%	1.4%	8.3%	**<0.001**
	Extremities	85.2%	84.6%	93.0%	75.0%	0.136
	Brachial plexus	37.0%	65.4%	35.2%	41.7%	0.059

PNS: peripheral nerve surgery, SD: standard deviation

Surgical treatment and postoperative morbidity

On average, 53% of all respondents always consider preservation of function before performing a resection; most commonly plastic surgeons did so (66%, p>0.05, **Figure 3**). Less than 8% would consider preservation of function given particular circumstances: based on localization (n = 3), in low-grade MPNSTs (n = 1), in case it does not interfere with oncological resection (n = 1), when multiple lesions are present (n = 1), or if a main nerve bundle is separable from the tumor (n = 1). Contrarily, 42% of all surgeons would never perform less extensive resections to preserve functionality and possibly compromise oncological result, and this did not differ between surgical subspecialties (p>0.05). Others would only resect less if achieving free margins was not presumed feasible (36%), while a minority would consider it in other cases as well (22%). The majority of respondents always look for the nerve of origin peroperatively (74%). In the hypothetical situation of a microscopically complete resectable MPNST, 47% of respondents had the opinion that there is a beneficial effect of resecting more of the originating nerve to decrease local recurrence as microscopic satellite lesions within or along the nerve may be present.

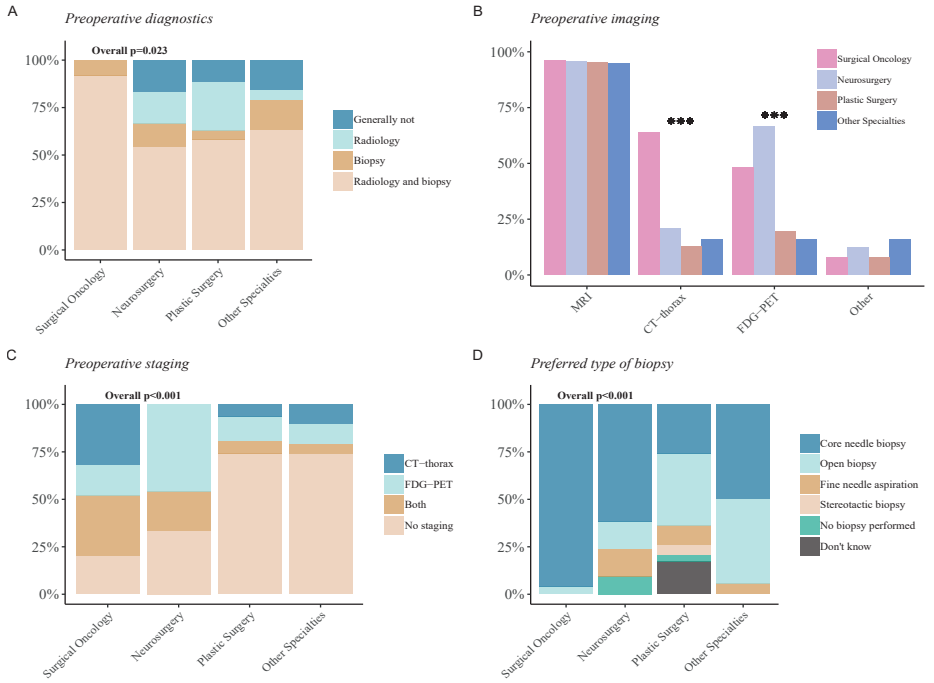


Figure 2 Preoperative diagnostics performed. A) Overall preoperative diagnostics per surgical subspecialty B) Percentage per surgical subspecialty of different imaging techniques used C) Use of preoperative staging modalities per surgical subspecialty D) Preferred type of biopsy per surgical subspecialty. p values: ***≤ 0.001.

Radiotherapy

Opinions of indications for the use of radiotherapy in localized disease did not differ significantly among surgical subspecialties (all p>0.05, **Figure 4**). While opinions were divided on whether to use radiotherapy in tumors 5-10cm of size, 78% of respondents would advise radiotherapy in patients with tumors larger than 10cm of size. Microscopic positive margin was regarded as an indication for radiotherapy by the majority of respondents (86%), and by an even larger proportion of the surgical oncologists (96%). Forty-three percent of respondents are of the opinion that radiotherapy is routinely indicated in any localized MPNST. Preferred sequence of radiotherapy in any localized MPNST differed significantly among surgical subspecialties (p<0.05). Surgical oncologists preferred neoadjuvant administration (72%), while other subspecialties either preferred adjuvant administration (36-53%) or had no preference (21-43%).

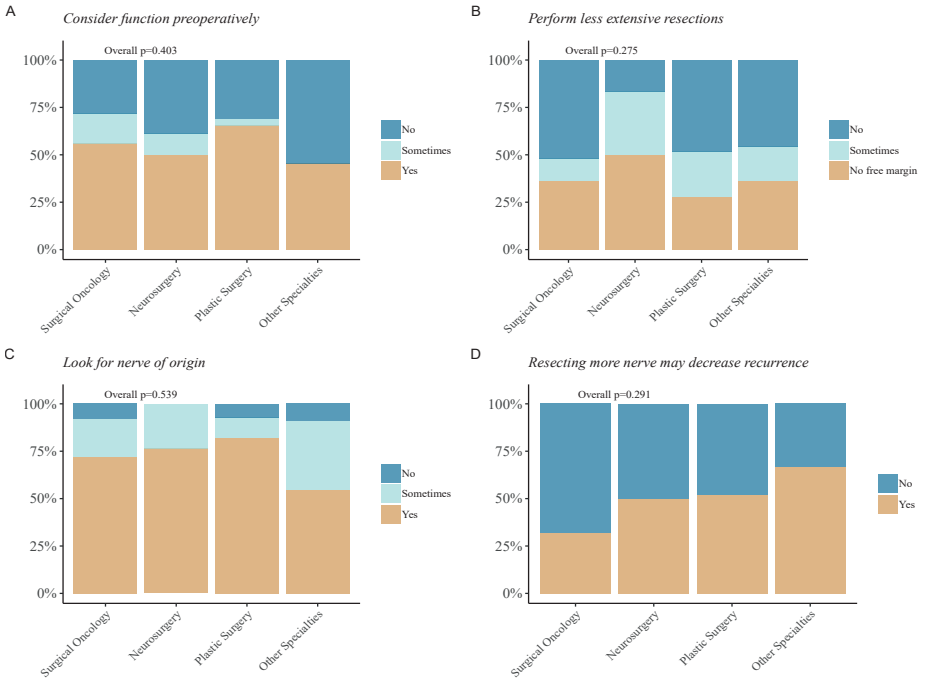


Figure 3 Surgical considerations per surgical subspecialty. A) Considering the preservation of function preoperatively B) Performing less extensive resections to preserve function C) Look for originating nerve intraoperatively D) Resecting more nerve may lead to a decrease in recurrences.

Chemotherapy

Overall, respondents felt that chemotherapy was usually not indicated in localized disease (**Figure 4**). Only tumor sizes larger than 10cm (54%) and macroscopically positive margins (51%) were regarded as an indication by more than half of all respondents. While tumor sizes 5-10cm was seen as an indication for the use of chemotherapy by 29% of respondents, neurosurgeons and 'other' surgical subspecialties more commonly viewed this as an indication for its use ($p<0.05$). A total of 26% of all respondents were of the opinion that chemotherapy should always be used in localized disease; this differed significantly among surgical subspecialties ($p<0.05$). Neurosurgeons most commonly recommended the latter (47.4%). Preferred sequence of chemotherapy in any localized MPNST did not differ between surgical subspecialties ($p>0.05$), but no consensus was present. Overall, 24% of respondents did not see a role for chemotherapy in any localized MPNST.

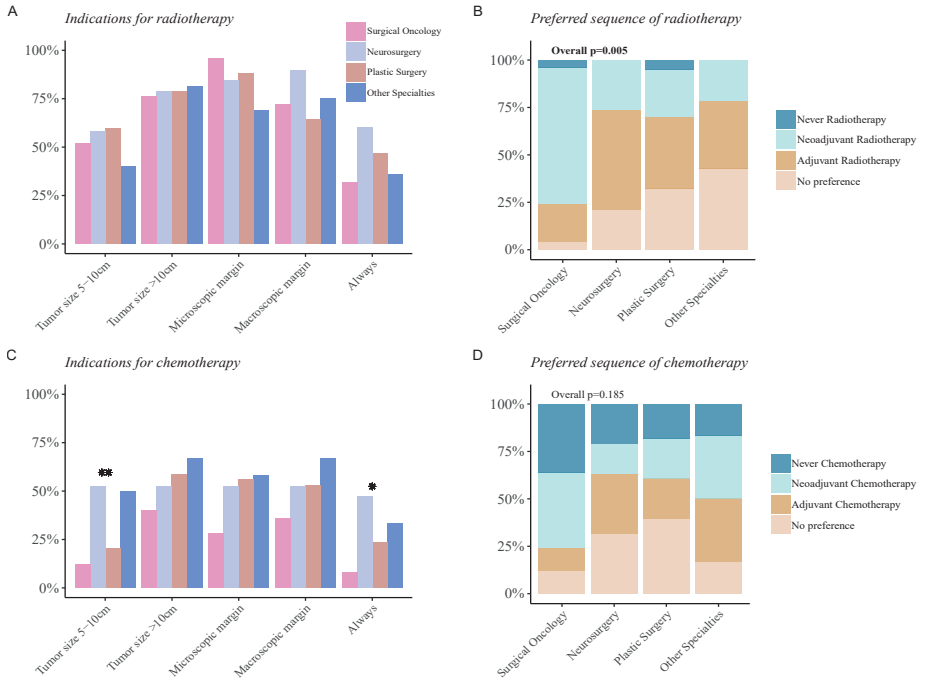


Figure 4 Use of multimodal therapy. A) Percentage per surgical subspecialty of indications for radiotherapy B) A preferred sequence of radiotherapy per surgical subspecialty C) Percentage per surgical subspecialty of indications for chemotherapy D) A preferred sequence of chemotherapy per surgical subspecialty. p values: *≤ 0.05, **≤ 0.01.

Discussion

In patients who are referred for soft tissue tumors that are possibly MPNSTs, the reported use of preoperative imaging studies and biopsies differs between surgical subspecialties; the vast majority of surgical oncologists routinely perform both. Some surgical considerations such as extent of resection margins for preservation of function in selected cases differ within surgical subspecialties. Moreover, assumed indications for the use of radiotherapy and chemotherapy in localized MPNST differ among surgical subspecialties, as well as their ideal timing of administration.

Preoperative diagnostics in MPNST

Ideally, MPNSTs are resected with a wide margin to obtain an R0 margin.[4,10,21,22] As a result, surgery can be very disabling, underlining the need for correct preoperative diagnosis as benign nerve sheath tumors can be resected without margins. Additionally, obtaining a preoperative diagnosis facilitates the opportunity to administer preoperative radiotherapy or chemotherapy. Therefore, guidelines for

treating STS and NF1 both recommend performing MRI imaging and core needle biopsies to obtain a histopathological diagnosis.[21–23] Although radiological features and presenting symptoms are not specific for malignancy, some general indications should make surgeons aware of a potential malignancy. Irregular shape and border, lobed aspect, cystic changes, heterogeneous structure, absence of a target sign (distinctive for neurofibromas), and peritumoral edema on MRI may indicate malignant transformation in MPNSTs.[8,9,24] Tumors larger than 5cm or deep to the fascia definitely justify imaging and biopsy.[21,23] However, preoperative identification of malignancy in NF1 patients is particularly difficult, as atypical and plexiform neurofibromas can present similarly to MPNSTs. Recent research has shown that FDG-PET scans can be helpful in distinguishing malignant from benign lesions, differentiating MPNSTs from neurofibromas with a 80% specificity and almost 100% sensitivity,[25,26] which is why an NF1 consensus does recommend performing it.[22] Others have shown that diffusion-weighted imaging sequences in MRI can differentiate malignancy with 100% specificity, however these techniques are not standard of care in many centers.[24] As neurosurgeons see neurofibromas commonly, it may explain the high proportion of neurosurgical respondents performing FDG-PET scans preoperatively. While surgical oncologists more commonly adhere to guidelines recommending core needle biopsies as preferred biopsy,[21–23] a larger proportion in other subspecialties favor open biopsies as well. If an open biopsy were to be considered, ideally the same surgeon performing the tumor excision should execute the biopsy as risk of tumor spread is substantially higher.[21–23] Excisional biopsy can also be considered for superficial tumors <3cm, as this may be most conventional.[21,22] Differences in preferred biopsy technique between subspecialties may therefore possibly be explained by specialty bias. Fine needle aspirations are discouraged in MPNSTs as they have a high risk for uncertain diagnoses because of small specimen sizes.[21–23,27]

Surgical treatment in MPNST

Complete surgical excision with wide margins is the routine treatment of choice.[4,10,21,22] Nonetheless, even when obtaining R0 margins, MPNSTs can recur.[2–4,15,16] Some authors even propose that fresh frozen coupes are necessary intraoperatively.[2,3,28] There is a possibility that as MPNSTs have their perineural origin, skip lesions may be present along the nerve of origin.[28] Respondents to this survey also felt that resecting a longer course of the nerve may therefore be beneficial, encouraging future studies to evaluate this in depth. And while R1 resections are associated with a higher likelihood of recurrence, several large MPNST series have not shown that R1 resections are associated with worse survival compared to R0 resections.[4,6,10] This indicates a potential role for operating with closer margins in order to preserve function without altering a patient's prognosis.[29] For instance tumors in the brachial plexus may be adequately treated with epineural dissection and nerve reconstructions avoiding the need for a forequarter amputation.[30] Contrarily, 42% of respondents to this survey would never perform less extensive resections even if free surgical margins were not

presumed feasible. Function preservation was also not considered preoperatively by almost 30% of surgeons. However, considering it in an early stage of treatment may be beneficial, as long-term disabilities may be minimized since localized MPNSTs do have a median survival of 5-8 years.[5,10] Combining knowledge of reconstructive possibilities by reconstructive and nerve surgeons as an addition to oncological resection margins may improve the delicate balance between oncological and functional outcomes. Such a multidisciplinary approach by these surgical specialties may also optimize the preoperative surgical planning for the extent of the resection to preserve functional anatomy using planned positive margins, or going wider and resecting functional structures beyond the reconstruction tools of the plastic surgeons. Currently, functional reconstructions are uncommonly performed in STS patients, especially those requiring nerve reconstruction, even though outcomes can be very satisfactory.[31]

Multimodal treatment in MPNST

To date, no study has yet demonstrated that MPNSTs should be treated differently than other high-grade STS.[13,18] As such, MPNST treatment guidelines grossly follow general STS guidelines.[21,23] However, even in large dedicated sarcoma centers, the use of chemotherapy and radiotherapy differs significantly.[18] Radiotherapy was considered by most respondents in tumors sizes >10cm and positive surgical margins. This is concordance with findings in another survey on multimodal treatment in STS and STS guidelines.[21,32] Although surgical oncologists clearly preferred neoadjuvant administration of radiotherapy, others did not. Neoadjuvant administration did prove in one trial to require lower dosage of radiation, which eventually resulted in lower long-term morbidity at the price of increased postoperative complications.[33,34] However, neoadjuvant radiotherapy may complicate possible nerve reconstruction and fibrous tissue will always have to be removed to create a vascularized wound bed for nerve regeneration.[35] As such, the differences in opinion on preferred timing may also be related to specialty bias. Indications for the use of chemotherapy in localized MPNSTs and STS in general is conflicting as reflected by responses to this survey. Thus far, trials and meta-analyses have not been able to provide definitive conclusions on the beneficial effect of perioperative chemotherapy in STS as observed effects are relatively small.[36–39] Preliminary results from a recent randomized trial did however show a positive effect for localized high-risk (high-grade, large, and deep-seated) extremity STS on both overall survival and disease-free survival.[13] For MPNSTs, chemotherapy regimens should ideally involve an anthracycline-based regimen, such as doxorubicin, in combination with ifosfamide.[13,14,40,41] Preferred timing of chemotherapy administration has not been studied thoroughly, but several hypotheses exist favoring neoadjuvant therapy translated from research in breast cancer. This includes earlier initiation of systemic therapy, possible downstaging of the tumor, and eliminating micro-metastases before exposure to wound-healing cytokines triggered by operation.[41–43] However, these theories have not yet been proven in STS. Unfortunately, studies show that MPNSTs are relatively chemoresistant, possibly more so in NF1 patients.[41,43] Some smaller studies

suggest MPNST can respond well to chemotherapy, but exact populations that may respond are to be elucidated.[44,45] More clinical studies are warranted to find tumor-tailored non-cytotoxic treatments, alas, so far none have been proven effective in MPNSTs.[46] As the debate on exact role for multimodal therapy in localized disease is still evolving, advantages and disadvantages are to be discussed with patients after general discussion in a multidisciplinary tumor board. Several STS calculators have been proposed useful for decision-making.[47,48] Again, by including both oncological and reconstructive surgeons when planning patient treatment for localized disease an ideal strategy can be obtained for the timing of multimodal therapy as opposed to oncological resection and possible functional reconstruction.

Strengths and limitations

Limitations to this study are partially inherent to the survey methodology. Respondent bias should always be taken into account as only interested surgeons will fill out the survey. Furthermore, selection bias may be present as we restricted our survey distribution to a certain list of surgical societies, thereby excluding physicians that are not members of these societies. This study is however strengthened by the combination of respondents with experience in both sarcoma and peripheral nerve surgery. As patients will present themselves to several surgical subspecialties it is important that knowledge and experience are exchanged, more so when practice variation is present. Partially, as several elements of MPNST treatment have not been proven by high-level evidence, of which some will likely never be because of their low incidence. Future studies should be encouraged in combining data from several subspecialties and to further explore the ideal combination of surgical treatment and function preservation and the role of multimodal treatment. Multidisciplinary approaches are essential for optimal treatment of MPNSTs, possibly including collaboration of surgical oncologists, nerve surgeons, and reconstructive surgeons. In turn, consensus guidelines among all specialties treating MPNSTs can and should be made.

Conclusion

While a consensus among surgical oncologists is more apparent in preoperative diagnostics, this differs between surgical subspecialties. Some disagreement exists as well within subspecialties on less extensive resections in selected cases for function preservation. While surgeons agree on some indications for radiotherapy, preferred sequence of radiotherapy differed between surgical subspecialties and within subspecialties other than oncologic surgery. Chemotherapy seems less popular in localized disease and indications for its use lack consensus among surgeons. Differences between surgical subspecialties are likely caused by specialty bias and combining knowledge between surgical subspecialties may further ameliorate patient outcomes.

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Supplementary File 1 Survey Outline

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- … Free text

General introduction

Thank you for participating in this questionnaire about the treatment of malignant peripheral nerve sheath tumors. Please keep in mind that the questions regard your personal opinion on optimal treatment of localized disease.

1) Select your surgical subspecialty

- o Oncologic Surgery
- o Neurosurgery
- o Plastic Surgery
- o Orthopedics (other than oncologic surgery)
- o General Surgery (other than oncologic surgery)
- o ENT
- o Maxillofacial
- o Thoracic Surgery

2) Select your country of practice

- o Dropdown list of all countries

3) How many years ago did you finish your surgical training? Please provide your answer in full years

…

4) Are you subspecialized in peripheral nerve surgery?

- o Yes
- o No

5) Are you a fellowship trained: Multiple answers can be selected

- ▪ Peripheral nerve surgeon
- ▪ Sarcoma surgeon
- ▪ Other or none

6) On average, how many MPNST cases do you operate annually?

- o 0-1
- o 2-3
- o 3-5
- o >5

7) Select the tumor locations you operate. Multiple answers can be selected.

- Intracranial
- Extracranial head & neck
- (Para-) Spinal
- Superficial Thoracic
- Intrathoracic
- Abdominal
- Retroperitoneal
- Pelvic
- Extremities (excluding plexus)
- Brachial Plexus

8) Do you attempt to distinguish MPNSTs from its benign counterparts AND other sarcomas preoperatively?

- o Generally not, but we do use radiology and/or biopsy
- o With the use of radiology
- o With the use of biopsy
- o Using both biopsy and radiology

9) What type of imaging do you generally use preoperatively? Multiple answers can be selected.

- MRI
- CT-thorax
- FDG-PET
- Other

10) If there is a suspicion for an MPNST, what type of biopsy do <u>you</u> prefer using?

- o Open biopsy
- o Core needle biopsy
- o Fine needle aspiration
- o Stereotactic biopsy
- o Ultrasound-guided biopsy
- o Other
- o Generally no biopsy is performed: ...
- o Do not know

11) When deciding the use of radiotherapy, which of the following patient or tumor characteristics would prompt <u>you</u> to use radiation?

a) Primary tumor size 5-10 cm
b) Primary tumor size >10 cm
c) Age <50 years

d) Microscopic margin
e) Macroscopic margin
f) In principle, we always use radiotherapy

12) What is <u>your</u> preferred sequence of radiotherapy when used?

o Neoadjuvant
o Adjuvant
o No preference
o We never use radiation in localized disease

13) When deciding the use of systemic chemotherapy in localized disease, which of the following patient or tumor characteristics would prompt <u>you</u> to use systemic chemotherapy?

a) Primary tumor size 5-10 cm
b) Primary tumor size >10 cm
c) Age <50 years
d) Microscopic margin
e) Macroscopic margin
f) In principle, we always use chemotherapy

14) What is <u>your</u> preferred sequence of chemotherapy in localized MPNSTs when used?

o Neoadjuvant
o Adjuvant
o No preference
o We never use systemic chemotherapy in localized disease

15) What is the most common non-oncologic postoperative complication after MPNST surgery?

o Neuropathic pain, dysesthesia, allodynia, or cold intolerance
o Motor disability
o Sensory deficiency
o A combination of neuropathic pain and neurologic deficit
o None of the above

16) In your clinic, how often does a patient present with a functional motor deficit <u>post</u>operatively?

... %

17) In your clinic, how often does a patient present with neuropathic pain <u>post</u>operatively?

... %

18) Do you always consider preservation of function preoperatively? If 'sometimes', please explain briefly.

- o Yes
- o No, oncologic resection is always more important
- o Sometimes: ...

19) Given that oncological resection of some MPNSTs can cause large functional deficits, are there cases that you resect less of the tumor in order to preserve functionality?

- o Yes, sometimes
- o Yes, but only when free margins are not presumed possible
- o No, never

20) Do you operate MPNSTs together with a peripheral nerve surgeon?

- o Yes
- o No
- o Sometimes

21) Do you use intraoperative nerve conduction testing when operating MPNSTs?

- o Yes
- o No
- o Sometimes

22) Intraoperatively, do you always search for the nerve from which the MPNST originated? If 'no', please explain briefly.

- o Yes
- o No: ...
- o Sometimes

23) What is your preferred treatment of the transected nerve? If 'other', please explain briefly.

- o Nothing
- o Bury in bone/muscle/vein
- o Closure end with adhesive or epineural graft
- o Neurorrhaphy
- o Targeted Muscle Reinnervation
- o Other: ...

24) Do you perform functional reconstruction (i.e. muscle/nerve/tendon reconstructions) if a motor deficit is anticipated?

- o Never
- o Generally not
- o Sometimes
- o Always

25) Do you consider functional reconstruction (i.e. nerve reconstruction or innervated skin flap) if a sensory deficit is anticipated?

- o Never
- o Generally not
- o Sometimes
- o Always

26) What is <u>your</u> preferred timing of functional reconstruction after initial surgery?

- o Direct regardless of radiotherapy
- o Direct if no postoperative radiotherapy will administered, otherwise after radiotherapy
- o Delay of 3 months
- o Delay of 6-12 months
- o I do not consider MPNST patients eligible for functional reconstruction

27) What functional reconstructions do <u>you</u> consider as a possibility? Multiple answers can be selected.

- ▪ None
- ▪ Nerve reconstruction
- ▪ Nerve transfer
- ▪ Tendon transfer
- ▪ Free functional muscle transfer
- ▪ Do not know

28) In case ANY form of functional deficit is present (i.e. loss of sensibility or any motor function loss), select factors that would prevent <u>you</u> from considering functional reconstruction in a patient. Multiple answers can be selected.

- ▪ The general low survival of MPNSTs
- ▪ A non-extremity MPNST
- ▪ Use of radiotherapy
- ▪ Slow nerve regeneration
- ▪ Slow rehabilitation of function
- ▪ The nerve(s) from which an MPNST originated are 'sick' and cannot be used
- ▪ Other (provide answers in text field below)
- ▪ None

29) What should be the median survival of a patient, in your opinion, before considering functional reconstruction? Please provide your answer in full years.

...

30) The following situation is present: An MPNST has been resected with clear margins. MPNSTs grow 'perineurally', commonly recur, and metastasize frequently, do you believe that this may be due to microscopic satellite lesions along the nerve and by resecting the originating nerve as proximal and/or distally as possible could have beneficial effect?

- o Yes
- o No

If you have any questions regarding this survey or interest in collaboration for further research in MPNSTs, please leave your email address in the following text field.

...

6

A Bayesian Approach for Diagnostic Accuracy of Malignant Peripheral Nerve Sheath Tumors: a Systematic Review and Meta-analysis

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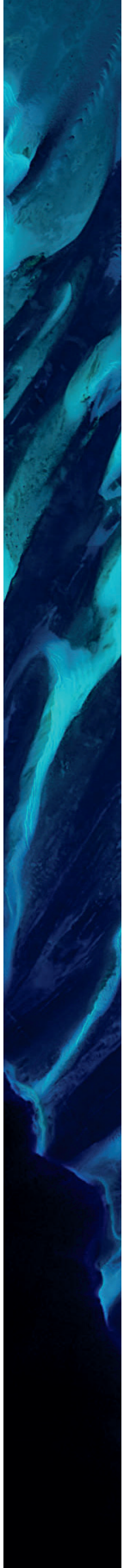
Submitted



Abstract

Background Malignant peripheral nerve sheath tumors (MPNST) carry a dismal prognosis and require early detection and complete resection. However, MPNSTs are prone to sampling errors and biopsies or resections are cumbersome and possibly damaging in benign PNST (BPNST). This study aimed to systematically review and quantify diagnostic accuracy of non-invasive tests for distinguishing MPNST from BPNST.

Methods Studies on accuracy of MRI, FDG-PET, and liquid biopsies were identified in PubMed and Embase from 2000-2019. Pooled accuracies were calculated using Bayesian bivariate meta-analyses. Individual level-patient data was analyzed for ideal maximum standardized uptake volume (SUVmax) threshold on FDG-PET.

Results Forty-three studies were selected for qualitative synthesis including data on 1875 patients and 2939 lesions. Thirty-five studies were included for meta-analyses. For MRI, absence of target sign showed highest sensitivity (0.99, 95% CI: 0.94-1.00); ill-defined margins (0.94, 95% CI: 0.88-0.98) and perilesional edema (0.95, 95% CI: 0.83-1.00) showed highest specificity. For FDG-PET, SUVmax and tumor-to-liver ratio show similar accuracy; sensitivity 0.94, 95% CI: 0.91-0.97 and 0.93, 95% CI: 0.87-0.97 respectively, specificity 0.81, 95% CI: 0.76-0.87 and 0.79, 95% CI: 0.70-0.86 respectively. SUVmax ≥3.5 yielded the best accuracy with a sensitivity of 0.99 (95% CI: 0.93-1.00) and specificity of 0.75 (95% CI: 0.56-0.90).

Conclusion Biopsies may be omitted in the presence of a target sign and the absence of ill-defined margins or perilesional edema. Because of diverse radiological characteristics of MPNST, biopsies will still commonly be required. In NF1, FDG-PET scans may further reduce biopsies. Ideal SUVmax threshold is ≥3.5.

Introduction

Peripheral nerve sheath tumors are relatively common and include both benign and malignant tumors. Schwannomas are the most common benign nerve sheath tumors (BPNSTs) and neurofibromas make up the largest proportion of remaining BPNSTs.[1,2] Nerve sheath tumors may arise sporadically or in association with neurofibromatoses. Malignant peripheral nerve sheath tumors (MPNSTs) may, in contrast to schwannomas, arise from neurofibromas and are rare and aggressive soft tissue sarcomas (STS), accounting for 2-3% of all STS.[3,4] Although MPNSTs are very rare in the common population, neurofibromatosis type 1 (NF1) patients have an 8-13% lifetime risk of developing an MPNST being the leading cause of mortality in these patients.[5,6] Prognosis of MPNSTs is poor with median survival ranging between 5-6 years, demanding aggressive treatment.[7,8] Adequate and timely recognition is paramount as surgical resection is key in improving survival.[7–9] However, the resection of MPNSTs commonly results in high postoperative morbidity and motor deficits.[10] This is in contrast to BPNST treatment that only requires resection in case lesions are symptomatic and which can be removed by intracapsular resections, minimizing neurologic damage.[11,12]

Unfortunately, BPNSTs and MPNSTs are difficult to distinguish based on presenting symptoms.[13,14] Computed tomography and ultrasound play a limited role in the diagnostic work-up and are mainly used to guide biopsies. Magnetic resonance imaging (MRI) should be used to further characterize lesions, but several studies argue that MRI's alone are insufficiently reliable to detect MPNSTs.[15,16] Biopsies are therefore commonly used, but standard use may be needlessly cumbersome and because of their origin in nerve tissue biopsies are often painful and may lead to persisting nerve damage.[17] Additionally, MPNSTs commonly arise within neurofibromas and harbor significant intratumoral heterogeneity making them prone to sampling errors possibly more so than other sarcomas.[18,19] Lastly, not all lesion sites are approachable for biopsy.[20] In NF1 patients the use of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET-CT) has gained popularity as several researches have suggested a high sensitivity of detecting MPNSTs using maximum standardized uptake values (SUVmax) as a quantitative metabolic imaging marker. However, ideal threshold values remain unknown and suggested thresholds may yield high false positive rates leading to unnecessary biopsies or even surgeries.[21,22] It is thus far difficult to find a balance in NF1 patients between prevention and overdiagnosis.

Over the past decades biomarkers have established their key role in diagnosis and treatment of numerous cancers, including prostate cancer,[23] breast cancer,[24] and lung cancer.[25] Non-invasive liquid biopsies are therefore of interest as well in the diagnosis malignant transformation in nerve sheath tumors. Percutaneous biopsies are ideally avoided, but given current uncertainties of accurately distinguishing MPNSTs and BPNSTs with non-invasive diagnostic tools, this study aimed to find diagnostic

accuracies of MRI, FDG-PET, and liquid biopsies by means of a systematic review and meta-analyses. These findings may result in characterization of lesions that obviate the need for biopsies.

Methods

Literature search

A systematic search was performed in both PubMed and Embase databases according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines, in order to identify all potentially relevant articles between January 2000 and November 2019. The search string was built with the help of a professional librarian using search terms related to "MRI", "PET", "liquid biopsy", and "MPNST". The exact search syntaxes for PubMed and Embase are shown in **Supplementary Table 1**. Studies were included when both extracranial MPNSTs and BPNSTs were evaluated and described their differences using MRI, FDG-PET, and/or liquid biopsy. Exclusion criteria were lack of full text, case reports, conference abstracts, and reviews. The initial review was conducted by two independent authors (E.M. and R.G.). Disagreements were solved through discussion, in which two additional authors were involved (D.H. and L.G.). By cross-referencing included articles, additional studies not initially included in our search were added.

Data extraction

Study, patient, and diagnostic test characteristics were extracted from included studies by two independent authors (R.G. and E.M.). Values of true positives (TP), false negatives (FN), false positives (FP), and true negatives (TN) were extracted per study for all mentioned diagnostic tests. Whenever this was not directly available, the rate of MPNST and provided sensitivity and specificity were used to recalculate TP, FN, FP, and TN. A true positive corresponded to an MPNST, a true negative to a BPNST. A true negative was concluded whenever the lesion was resected, there had been a biopsy with adequate follow-up or in NF1 patients the lesion was suspected to be benign and there had been adequate follow-up to exclude potential malignant transformation. Additionally, individual SUVmax values were collected when available. When the available data was insufficient for recalculation or individual SUVmax were missing, the corresponding authors of the study were requested for additional data. A reminder email was sent up to three times.

Statistical analysis

Using TP, FN, FP, and TN, sensitivity, specificity, and likelihood ratios were calculated for all available diagnostic tests. Sensitivity and specificity were plotted in forest plots with 95% credibility intervals (95% CI). Accuracy was based on determining the presence of an MPNST. Bayesian bivariate meta-analyses were performed on imaging

characteristics included in at least three independent studies using the package 'meta4diag' in R.[26] In case of overlapping data between studies, data from the largest and most appropriate study was chosen for inclusion in quantitative synthesis. Penalized complexity priors were used for prior distributions.[27] Bayesian bivariate meta-analyses allow between study heterogeneity and differences in threshold parameters even for smaller sized samples of studies. Summary data were presented using summary receiver-operating characteristic (SROC) plots. The models generate an SROC curve with summary operating points, including 95% confidence regions and 95% prediction regions. Precision of the summary operating point can be assessed by the 95% confidence region which shows the pooled variability of sensitivity and specificity. Heterogeneity was assessed visually. Sources of heterogeneity were searched through subgroup analyses categorizing both FDG-PET and MRI studies in: large number of lesions (≥50 lesions), large proportion of MPNST (>33%), symptomatic lesions included only, and histologically proven lesions included only (either by biopsy or resection). MRI studies were additionally categorized for inclusion of NF1 patients only or mixed cases. Heterogeneity in sensitivity and specificity were assessed separately. Using the individual patient data of SUVmax values Bayesian bivariate meta-analyses of diagnostic accuracy were performed for thresholds at 3.0, 3.5, 4.0, and 4.5. The best threshold was obtained by evaluating significant differences in sensitivity first, after which lowest sensitivity thresholds were excluded and highest specificity was evaluated. For all comparisons made, significant differences were concluded whenever the lower bound of the 95% credibility interval (CI) of the highest accuracy did not include the mean of the lower accuracy. For application purposes the likelihood ratios may be interpreted as follows. A positive likelihood ratio (pLR) of ≥10 or a negative likelihood ratio of <0.1 correspond to a strong certainty to rule an MPNST in or out respectively.[28] A pLR of 5-10 or an nLR of 0.1-0.2 correspond to a moderate certainty to rule an MPNST in our out. We anticipated only a few studies on liquid biopsies and functional MRI sequences which would exclude them from meta-analyses, thus characteristics found in these studies would be assessed qualitatively. All statistical analyses were performed using R version 3.6.0 (R Core Team, 2019).

Quality assessment

The quality of included studies was appraised by two independent authors (R.G. and E.M.) using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (**Supplementary File 1**). Disagreements were solved through discussion. For patient selection, case control studies, exclusion of patients with difficult diagnosis, or inclusion of histologically proven lesions only were deemed at high risk of bias. For index testing studies were assessed at high risk of bias when radiologists and nuclear medicine physicians were not blinded for pathology results or when new thresholds were used in results which were previously not determined in their method section. The reference standard was at high risk of bias when the pathologist was not blinded for results of the index test or if the lesion was found a BPNST without histological confirmation

and a follow-up of less than 6 months. Risk of bias regarding flow and timing was only present if studies changed their reference standard during study period. Applicability concerns were raised whenever a study was at high risk of bias.

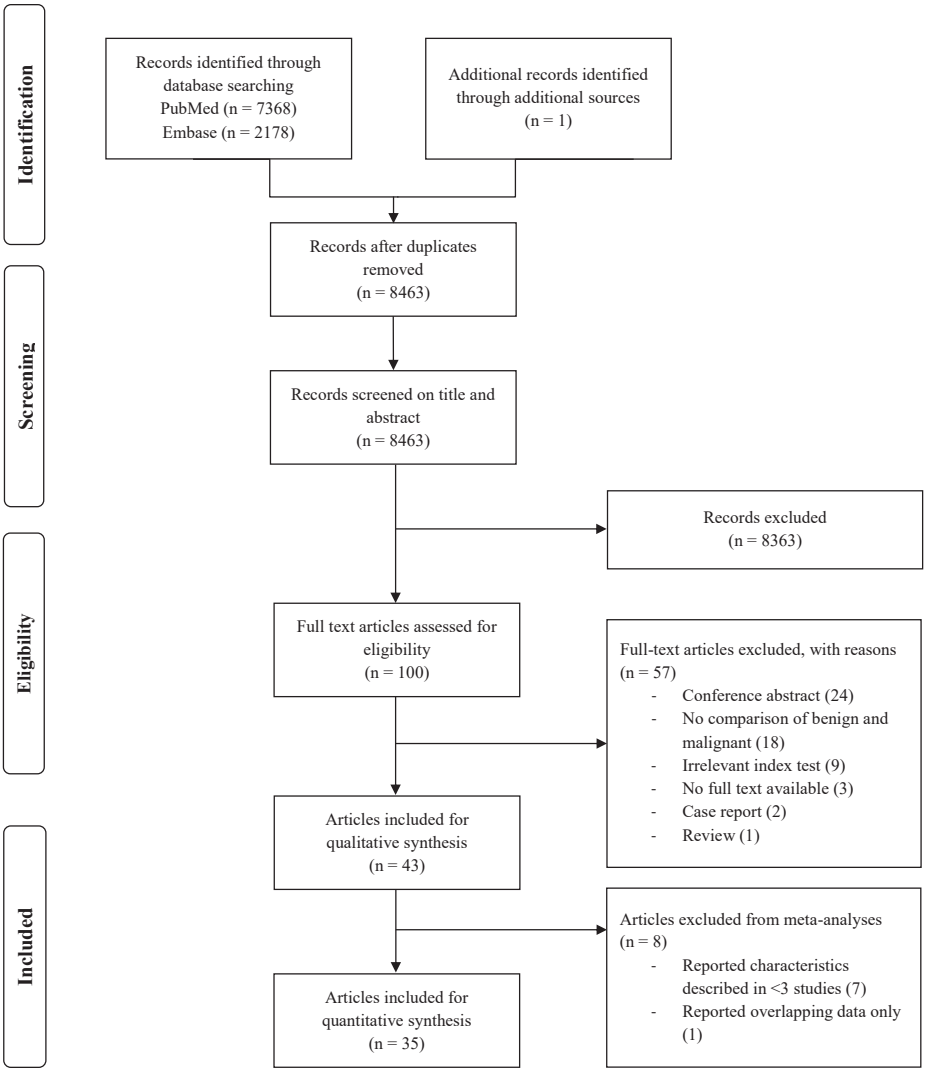


Figure 1 Flowchart depicting study selection

Results

After removal of duplicates, a total of 8463 citations were identified in PubMed and Embase databases. One hundred potentially relevant articles were selected through title/abstract screening. After full-text screening 43 studies were selected for qualitative synthesis (**Figure 1**). These studies included data on 1875 patients and 2939 lesions. Amongst the included studies were 12 studies on MRI characteristics, 21 studies on FDG-PET characteristics, 7 studies on both MRI and FDG-PET, and 3 studies on liquid biopsies (**Table 1**). Twenty-eight studies included NF1 patients only. In the remaining studies the percentage of NF1 patients ranged from 12-65%. The proportion of MPNST compared to BPNST varied from 2:1 to 1:29. Thirty-five studies were included for quantitative synthesis. Diagnostic accuracies of characteristics not included in quantitative synthesis are shown in **Supplementary Table 2**.

Conventional MRI characteristics

Sixteen studies describing a total of 12 conventional MRI characteristics were included for quantitative synthesis.[16,21,36–41,22,29–35] These studies included a total of 1041 tumors in 925 patients (48% NF1). Eight studies included in meta-analyses were at high risk of bias, mainly due to the inclusion of histologically confirmed lesions only or the exclusion of patients who had received treatment prior to imaging (**Supplementary File 1**).[21,22,29,30,33,34,36,41]

Nine studies reported on ill-defined margins.[22,30,32,34–36,38–40] Pooled sensitivity and specificity were 0.52 (95% CI: 0.40-0.65) and 0.94 (95% CI: 0.88-0.98) respectively. Pooled pLR was 11.03 (3.83-31.62) and nLR was 0.51 (0.36-0.66). The forest plot and the 95% prediction region in the SROC plot (**Figure 2 & Supplementary Figure 1**) demonstrated moderate heterogeneity between studies. Sensitivity was higher in studies with a smaller total sample of lesions (**Supplementary Table 3**). Specificity was lower in studies with a higher proportion of MPNSTs, those that included symptomatic lesions only or histologically proven lesions only.

Five studies reported on perilesional edema.[22,29,38–40] Pooled sensitivity and specificity were 0.65 (95% CI: 0.38-0.87) and 0.95 (95% CI: 0.83-1.00) respectively. Pooled pLR was 3415.18 (3.15-5948.77) and nLR was 0.38 (0.12-0.69). There was moderate heterogeneity between studies. Sensitivity was higher in studies with a smaller proportion of MPNST and when only NF1 patients were included and was lower when only histologically proven lesions were included.

Table 1 Study characteristics of included studies.

Author, year	Study period	Mean age (range)	Np	NI	NF1	Tumor type				Non-invasive diagnostics				Biomarkers
										MRI		PET-CT		
						MPNST	*NF*	*S*	*NA*	*Conventional*	*Functional*	*Features*	*TTS*	
Ahlawat 2018	2010-2016	40 (8-68)	42	48	50%	15	11	11	11	T1/T2	DWI/ADC			
Ahlawat 2019	2010-2017	30 (8-53)	21	55	100%	19	*NA*	*NA*	36	T1/T2	DWI/ADC	SUVmax, size	60	
Azizi 2018	2003-2014	14 (3-23)	41	114	100%	16	*NA*	*NA*	98			SUVmax, T/L	60	
Bensaid 2007	2000-2006	31 (7-77)	38	49	100%	6	20	1	22			T/L	60	
Benz 2010	2005-2008	46 (21-82)	34	40	41%	17	9	14	0			SUVmax, size	60	
Bredella 2007	2000-2006	37 (17-73)	45	50	100%	16	8	*NA*	26			SUVmax, SUVmean, qual	60	
Broski 2016	2002-2014	38 (16-79)	38	43	61%	20	17	6	0	T1/T2		SUVmax, T/L, MTV, TLG, heterogeneity	60	
Cardona 2003	*NA*	45 (18-81)	13	25	38%	13	4	2	6			SUVmean, qual	60	
Chhabra 2011	1996-2010	50 (15-92)	56	56	21%	21	24	11	0	T1/T2				
Chirindel 2015	2003-2013	36 (8-77)	41	93	100%	24	*NA*	*NA*	69				60, 240	
Combemale 2014	2000-2012	31 (2-77)	113	145	100%	40	55	*NA*	50			SUVmax, T/L	60	
Cook 2017	*NA*	35 (9-86)	54	54	100%	24	*NA*	*NA*	30			SUVmax, SUVmean, SUVpeak, GLCM, NGTDM, delayed	90, 240	
Demehri 2014	2008-2013	38 (18-54)	29	31	45%	9	6	14	2	T1/T2	DWI/ADC, DCE			
Derlin 2013	2006-2011	30 (2-63)	31	99	100%	9	*NA*	*NA*	90	T1/T2		SUVmax, SUVmean, HIsuv	60	
Fayad 2014	2009-2012	42 (11-78)	20	24	50%	4	3	6	11	T1/T2	MRS		*NA*	
Ferner 2000	1996-1998	24 (12-62)	18	23	100%	7	5	*NA*	11			SUVmean	60	
Ferner 2008	1996-2005	31 (5-71)	105	116	100%	29	28	*NA*	59			SUVmax	60	
Furniss 2007	1995-2004	43 (3-87)	30	205	54%	32	100	73	0	*NA*	*NA*			
Hummel 2010	*NA*	21 (5-50)	32	22	100%	5	*NA*	*NA*	17					ADM, HGF
Johansson 2014	*NA*	36 (12-69)	124	*NA*	63%	*NA*	*NA*	*NA*	*NA*					sAXL
Karabatsou 2009	*NA*	38 (19-63)	9	9	100%	5	4	0	0			SUVmax	60	
Karsy 2016	2007-2015	41 (*NA*)	127	127	46%	24	82	17	4	T1/T2				
Lerman 2019	2005-2015	35 (15-73)	107	408	100%	39	67	*NA*	302			SUVmax, T/L, HIsuv, TLG, TMTV	60	
Li 2008	*NA*	47 (20-82)	26	26	*NA*	9	1	16	0	T1/T2				
Matsumine 2008	*NA*	43 (14-80)	37	37	100%	19	18	0	0	T1/T2				

Table 1 Continued.

Author, year	Study period	Mean age (range)	Np	Nl	NF1	Tumor type				Non-invasive diagnostics				Biomarkers
										MRI		PET-CT		
						MPNST	*NF*	*S*	*NA*	*Conventional*	*Functional*	*Features*	*TTS*	
Matsumoto 2015	*NA*	43 (2-71)	23	23	*NA*	8	0	15	0	T1/T2				
Mautner 2007	*NA*	25.5 (8-47)	4	4	100%	1	3	0	0			SUVmean	*NA*	
Meany 2013	*NA*	18 (10-45)	14	60	100%	2	8	*NA*	50			SUVmax	60	
Moharir 2010	2006-2008	9 (2-14)	11	16	100%	2	*NA*	*NA*	14			SUVmax	45	
Nose 2013	2006-2011	52 (15-88)	*NA*	22	*NA*	10	2	10	0			SUVmax	60	
Park 2013	*NA*	33 (14-63)	104	*NA*	100%	30	*NA*	*NA*	39					IGFBP1, RANTES
Razek 2018	*NA*	34 (9-64)	34	34	100%	11	6	17	0	T1/T2	DWI/ADC			
Reinert 2018	2012-2018	20 (2-44)	28	83	100%	8	*NA*	*NA*	75	T1/T2	DWI/ADC	SUVmax, T/L, SUVmean	60	
Salamon 2013	2006-2011	33 (2-69)	50	159	100%	19	*NA*	*NA*	140			SUVmax, SUVmean, HIsuv, size, heterogeneity	60	
Salamon 2014	2006-2011	33 (2-69)	49	147	100%	18	*NA*	*NA*	129			SUVmax, T/L, SUVmean, TTF, TTM	60	
Salamon 2015	2006-2014	37 (17-69)	36	*NA*	100%	19	*NA*	*NA*	*NA*			SUVmax, T/L, SUVmean, WB-TLG, WB-MTV, size	60	
Schwabe 2019	2007-2016	30 (9-62)	41	70	100%	36	*NA*	*NA*	34	T1/T2		SUVmax, T/L, SUVpeak	60	
Tsai 2012	2000-2011	15 (1-20)	18	26	100%	10	16	0	0			SUVmax	60	
Van der Gucht 2016	2006-2012	33 (*NA*)	49	149	100%	16	24	*NA*	109			SUVmax, T/L, HIsuv, TLG, TMTV	60	
Warbey 2009	2004-2008	31 (9-86)	62	85	100%	21	18	*NA*	46			SUVmax, delayed	90, 240	
Wasa 2010	1990-2007	42 (16-83)	61	61	56%	41	20	0	0	T1/T2				
Well 2018	2014-2017	34 (17-54)	26	67	100%	12	30	*NA*	25	T1/T2	DWI/ADC			
Yu 2016	2011-2015	53 (23-78)	34	34	12%	6	26	2	0	T1/T2				

ADC: apparent diffusion coefficient, ADM: adrenomedullin, BPNST: benign peripheral nerve sheath tumor, DCE: dynamic contrast enhancement, DWI: diffusion-weighted imaging, HGF: hepatocyte growth factor, HIsuv: SUV-based heterogeneity index obtained by dividing intratumoral SUVmax by SUVmean of that lesion, IGFBP1: insulin-like growth factor binding protein 1, MPNST: malignant peripheral nerve sheath tumor, MRI: magnetic resonance imaging, MRS: magnetic resonance spectroscopy, MTV: metabolic tumor volume, NA: not available, NF: neurofibroma, Nl: number of lesions, Np: number of patients, PET-CT: positron emission tomography – computed tomography, qual: qualitative PET-CT assessment, RANTES: regulated upon activation normal T-cell expressed and secreted, S: schwannoma, sAXL: soluble fraction from the extracellular domain of AXL, SUVmax: maximum standardized uptake volume, SUVmean: mean standardized uptake volume, T/L: tumor-to-liver ratio, TLG: total lesion glycolysis, TMTV: total metabolic tumor volume, TTF: tumor-to-fat ratio, TTM: tumor-to-muscle ratio, TTS: time to scan in minutes, T1: T1-weighted imaging, T2: T2-weighted imaging.

Seven studies reported on cystic degeneration or necrosis.[22,30,32,37–40] Pooled sensitivity and specificity were 0.48 (95% CI: 0.23-0.71) and 0.86 (95% CI: 0.61-0.98) respectively. Pooled pLR was 5.75 (1.27-23.69) and nLR was 0.61 (0.34-0.91). There was moderate heterogeneity between studies. Sensitivity was higher in studies with smaller sample of lesions, smaller proportion of MPNST, and when only histologically proven lesions were included. Specificity was higher among studies with larger sample of lesions and lower in studies including NF1 patients only or histologically proven lesions only.

Three studies reported on signal heterogeneity on T1 sequences.[31,32,35] Pooled sensitivity and specificity were 0.85 (95% CI: 0.56-1.00) and 0.48 (95% CI: 0.03-0.96) respectively. Pooled pLR was 9.23 (0.81-31.82) and nLR was 1.60 (0.01-5.42). There was substantial heterogeneity between studies. Sensitivity was lower in studies including NF1 patients only. Specificity was higher in studies including NF1 patients only and those with a higher proportion of MPNST.

Five studies reported on signal heterogeneity on T2 sequences.[29–32,38] Pooled sensitivity and specificity were 0.78 (95% CI: 0.64-0.90) and 0.52 (95% CI: 0.23-0.80) respectively. Pooled pLR was 1.94 (0.90-4.82) and nLR was 0.49 (0.15-1.37). There was substantial heterogeneity between studies. Sensitivity was lower in studies with a smaller sample of lesions and in those that included histologically proven lesions only.

Six studies reported on irregular or peripheral tumor enhancement after contrast administration.[16,29,32,34,39,40] Pooled sensitivity and specificity were 0.63 (95% CI: 0.50-0.76) and 0.81 (95% CI: 0.60-0.95) respectively. Pooled pLR was 4.81 (1.44-16.60) and nLR was 0.46 (0.28-0.72). There was moderate heterogeneity between studies. Sensitivity was lower in studies including histologically proven lesions only. Specificity was higher in studies with a smaller sample of lesions and higher prevalence of MPNST.

Five studies reported on intratumoral lobulation.[32,35,36,38,39] Pooled sensitivity and specificity were 0.57 (95% CI: 0.41-0.72) and 0.89 (95% CI: 0.83-0.93) respectively. Pooled pLR was 5.38 (2.87-9.31) and nLR was 0.49 (0.30-0.68). There was limited heterogeneity between studies. Heterogeneity in sensitivity may be caused by studies with higher total number of lesions and including NF1 patients only. No sources were found explaining heterogeneity in specificity.

Three studies reported on absence of split-fat sign.[30,34,39] The split-fat sign represents fat deposition around the lesion and is usually seen as a tapered rim of fat signal near the proximal and distal ends of the lesion. Pooled sensitivity and specificity were 0.76 (95% CI: 0.57-0.91) and 0.44 (95% CI: 0.16-0.78) respectively. Pooled pLR was 1.67 (0.82-4.56) and nLR was 0.68 (0.15-1.94). There was limited heterogeneity between studies. Sensitivity was higher in studies with smaller proportion of MPNSTs. Specificity was higher in studies including NF1 patients only.

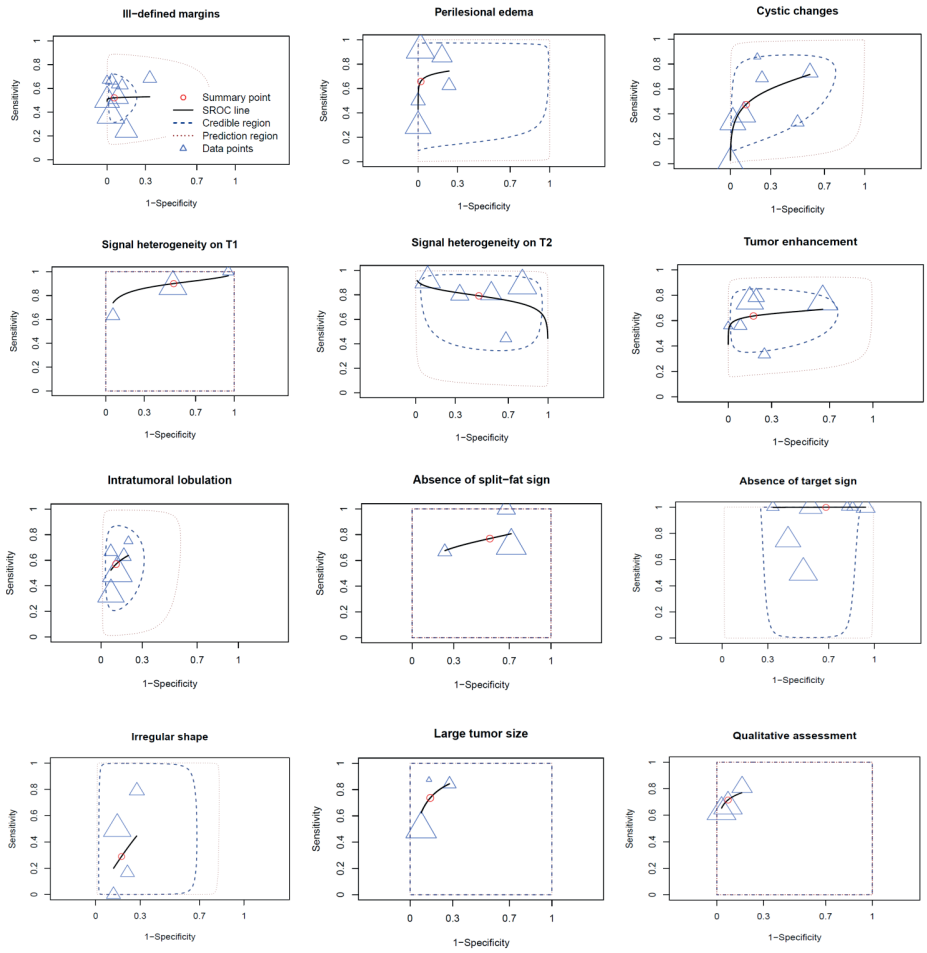


Figure 2 SROC's of MRI characteristics

Seven studies studied the use of absence of target sign, a classic sign in neurogenic tumors on T2-weighted imaging referring to a high signal intensity ring peripherally surrounding an area of low signal intensity centrally.[16,30,32,35,38–40] Pooled sensitivity and specificity were 0.99 (95% CI: 0.94-1.00) and 0.33 (95% CI: 0.15-0.54) respectively. Pooled pLR was 1.51 (1.13-2.25) and nLR was 0.04 (0.00-0.30). There was substantial heterogeneity between studies. Sensitivity was higher in studies with smaller amount of lesions, higher proportion of MPNSTs, including symptomatic lesions only, and histologically proven lesions only. Sensitivity was lower in those including NF1 patients only. Specificity was higher in studies including NF1 patients only.

Four studies reported on irregular shape.[31,35,38,39] Pooled sensitivity and specificity were 0.33 (95% CI: 0.04-0.73) and 0.82 (95% CI: 0.71-0.90) respectively. Pooled pLR was 2.03 (0.18-5.42) and nLR was 0.81 (0.26-1.22). There was substantial heterogeneity between studies. Sensitivity was higher in studies including a larger proportion of MPNST and those including NF1 patients only.

Three studies reported on tumor size.[21,33,36] Thresholds varied from 4.7-6.3cm. Pooled sensitivity and specificity were 0.72 (95% CI: 0.47-0.92) and 0.85 (95% CI: 0.69-0.94) respectively. Pooled pLR was 5.63 (2.05-13.65) and nLR was 0.34 (0.07-0.67). There was moderate heterogeneity between studies. Sensitivity was higher in studies with a higher proportion of MPNST. Specificity was higher in studies with smaller sample of lesions, lower proportion of MPNST, and those including histologically proven lesions only. Specificity was lower in studies including NF1 patients only.

Three studies reported on qualitative MRI assessment.[32,33,41] Pooled sensitivity and specificity were 0.71 (95% CI: 0.53-0.85) and 0.92 (95% CI: 0.81-0.98) respectively. Pooled pLR was 12.44 (2.13-39.05) and nLR was 0.32 (0.15-0.56). There was limited heterogeneity between studies, but no source of heterogeneity was found.

Functional MRI characteristics

Six studies reported on 16 functional MRI characteristics (**Supplementary Table 2**).[21,29,31,38,42,43] No characteristic was evaluated in more than 2 different populations. Mean apparent diffusion coefficient (ADCmean) was evaluated in two studies.[38,42] Sensitivity ranged from 0.91-0.92 and specificity from 0.91-0.98. pLR ranged from 10.46-50.42 and nLR from 0.09-0.10. Minimal ADC (ADCmin) was evaluated in two studies as well.[21,38] Sensitivity ranged from 0.89-0.98 and specificity from 0.93-0.94. pLR ranged from 14.15 to 14.43 and nLR from 0.03-0.12. One study used diffusion coefficient D and perfusion fraction f to investigate a number of characteristics.[38] Sensitivities ranged from 0.81-0.96 and specificity from 0.55-0.98. pLR ranged from 2.11-99.08 and nLR from 0.04-0.22. Dmin and fcenter yielded highest sensitivities (0.96), and dark and Dmargin highest specificity (0.99). One study reported on using the target sign on ADC and diffusion-weighted imaging (DWI).[29] Sensitivity ranged from 0.80-0.97 and specificity from 0.39-0.63. pLR ranged from 1.32-2.64 and nLR from 0.05-0.51. One study evaluated early arterial enhancement on dynamic contrast enhancement MRI.[31] Sensitivity was 0.50 and specificity 0.89, with a pLR of 4.50 and nLR of 0.56. Accuracy was highest when evaluating target sign on ADC mapping with higher specificity compared to static T1 weighted imaging. One study reported on trimethylamine (TMA) peak and TMA fraction.[43] Sensitivity was 0.90 for both and specificity was 0.50 for TMA peak and 0.62 for TMA fraction. pLR ranged from 1.8-2.35 and nLR from 0.16-0.20.

Table 2 Pooled diagnostic performance of Bayesian meta-analyses.

Characteristic	N	Median cut-off (range)	Pooled accuracies (95% CI)			
			Sensitivity	Specificity	Positive LR	Negative LR
Conventional MRI						
Ill-defined margins	9	*NA*	0.52 (0.40-0.65)	0.94 (0.88-0.98)	11.03 (3.83-31.62)	0.51 (0.36-0.66)
Perilesional edema	5	*NA*	0.65 (0.38-0.87)	0.95 (0.83-1.00)	3415.18 (3.15-5948.77)	0.38 (0.12-0.69)
Cystic changes	7	*NA*	0.48 (0.23-0.71)	0.86 (0.61-0.98)	5.75 (1.27-23.69)	0.61 (0.34-0.91)
Heterogeneity on T1	3	*NA*	0.85 (0.56-1.00)	0.48 (0.03-0.96)	9.23 (0.81-31.82)	1.60 (0.01-5.42)
Heterogeneity on T2	5	*NA*	0.78 (0.64-0.90)	0.52 (0.23-0.80)	1.94 (0.90-4.82)	0.49 (0.15-1.37)
Tumor enhancement	6	*NA*	0.63 (0.50-0.76)	0.81 (0.60-0.95)	4.81 (1.44-16.60)	0.46 (0.28-0.72)
Irregular shape	4	*NA*	0.33 (0.04-0.73)	0.82 (0.71-0.90)	2.03 (0.18-5.42)	0.81 (0.26-1.22)
Intratumoral lobulation	5	*NA*	0.57 (0.41-0.72)	0.89 (0.83-0.93)	5.38 (2.87-9.31)	0.49 (0.30-0.68)
Absence of target sign	7	*NA*	0.99 (0.94-1.00)	0.33 (0.15-0.54)	1.51 (1.13-2.25)	0.04 (0.00-0.30)
Absence of split-fat sign	3	*NA*	0.76 (0.57-0.91)	0.44 (0.16-0.78)	1.67 (0.82-4.56)	0.68 (0.15-1.94)
Tumor size	3	5.0 (4.7-6.25)	0.72 (0.47-0.92)	0.85 (0.69-0.94)	5.63 (2.05-13.65)	0.34 (0.07-0.67)
Qualitative assessment	3	*NA*	0.71 (0.53-0.85)	0.92 (0.81-0.98)	12.44 (2.13-39.05)	0.32 (0.15-0.56)
PET-CT						
SUVmax	13	3.96 (2.35-6.1)	0.94 (0.91-0.97)	0.81 (0.76-0.87)	5.22 (3.74-7.51)	0.07 (0.03-0.12)
Tumor-to-liver ratio	7	1.77 (1.38-3.0)	0.93 (0.87-0.97)	0.79 (0.70-0.86)	4.69 (2.89-7.41)	0.09 (0.03-0.18)
Qualitative assessment	5	*NA*	0.94 (0.88-0.98)	0.82 (0.71-0.91)	5.86 (3.00-11.24)	0.07 (0.02-0.16)
PET-CT individual patient-level data						
SUVmax	11	3.0	0.99 (0.94-1.00)	0.61 (0.40-0.80)	2.82 (1.59-5.64)	0.02 (0.00-0.13)
SUVmax	11	3.5	0.99 (0.93-1.00)	0.75 (0.56-0.90)	4.66 (2.12-11.39)	0.02 (0.00-0.13)
SUVmax	11	4.0	0.97 (0.86-1.00)	0.78 (0.62-0.91)	5.17 (2.44-11.76)	0.04 (0.00-0.21)
SUVmax	11	4.5	0.86 (0.63-0.98)	0.88 (0.77-0.97)	9.59 (3.24-30.96)	0.16 (0.01-0.46)

CI: credibility interval, LR: likelihood ratio, MRI: magnetic resonance imaging, N: number of studies, NA: not applicable, PET-CT: positron emission tomography – computed tomography, SUVmax: maximum standardized uptake volume.

FDG-PET characteristics

Twenty studies describing a total of 3 FDG-PET characteristics were included for quantitative synthesis.[15,16,48–57,20–22,37,44–47] These studies included a total of 1850 tumors in 924 patients. Most studies scanned 60 minutes after FDG injection, except for two studies that scanned at 45 and 90 minutes post-injection respectively. Seven studies included in meta-analyses were at high risk of bias for patient selection, mainly because they included histologically confirmed lesions only or patients who had received treatment prior to imaging were excluded (**Supplementary File 1**).[20–22,47,50,55,57] Two studies were at high risk of bias for the use of their reference standard which was a follow-up period of ≤6 months.[46,51] One study scored a high risk of bias for index test, because the nuclear medicine physician was not blinded to the pathology report.[58]

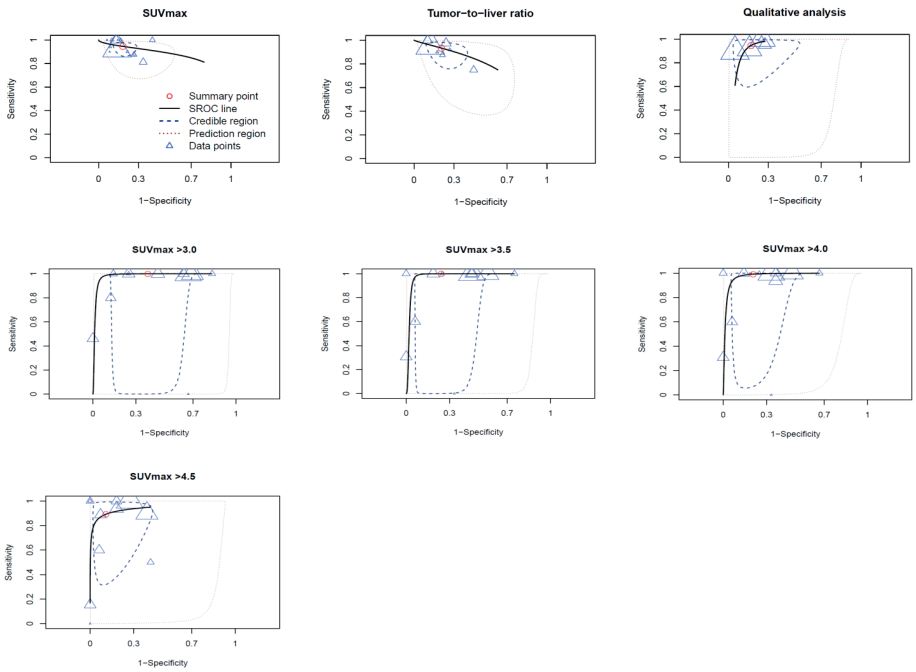


Figure 3 SROC's of PET characteristics

Twelve studies reported on SUVmax (**Table 2**).[16,20,49–51,21,22,37,44–48] Thresholds varied from 2.35-6.1. Pooled sensitivity and specificity were 0.94 (95% CI: 0.91-0.97) and 0.81 (95% CI: 0.76-0.87) respectively. Pooled pLR was 5.22 (3.74-7.51) and nLR was 0.07 (0.03-0.12). The forest plot and the 95% prediction region in the SROC plot demonstrated moderate heterogeneity between studies (**Figure 3 & Supplementary Figure 2**). Higher specificity was found in studies that included a higher proportion of MPNST (**Supplementary Table 3**).

Seven studies reported on the tumor SUVmax to liver SUVmean ratio (T/L-ratio).[16,22,37,44,46,52,53] Thresholds varied from 1.4-3.0. Pooled sensitivity and specificity were 0.93 (95% CI: 0.87-0.97) and 0.79 (95% CI: 0.70-0.86) respectively. Pooled pLR was 4.69 (2.89-7.41) and nLR was 0.09 (0.03-0.18). There was moderate heterogeneity between studies, but no source for heterogeneity was found.

Five studies reported on qualitative FDG-PET analysis.[15,54–57] Pooled sensitivity and specificity were 0.94 (95% CI: 0.88-0.98) and 0.82 (95% CI: 0.71-0.91) respectively. Pooled pLR was 5.86 (3.00-11.24) and nLR was 0.07 (0.02-0.16). There was moderate heterogeneity between studies. Higher sensitivity was found in studies including a smaller sample of lesions. Higher specificity was found in studies which included symptomatic lesions only.
Eleven studies reported individual patient-level data of SUVmax on 246 patients.[21,22,62,47,48,50,54,55,59–61] Highest sensitivities were found for thresholds at 3.0 and 3.5 (0.99) and highest specificity was found for a threshold at 4.5 (0.88, **Table 2**). Accuracy was not significantly different between thresholds of 3.0, 3.5, and 4.0. However, sensitivity at a threshold of 3.5 was non-significantly higher than 4.0 (0.99 vs. 0.97) and specificity was higher at 3.5 compared to 3.0 (0.75 vs. 0.61). There was substantial heterogeneity between studies (**Figure 3 & Supplementary Figure 2**). Sensitivity was higher in studies including a larger amount of lesions and a higher proportion of MPNST (**Supplementary Table 3**). Sensitivity was lower in studies that included symptomatic lesions only. Specificity was higher in studies including a smaller amount of lesions and symptomatic lesions only. Specificity was lower for studies including histologically proven lesions only.

Liquid biopsies
Three studies reported on liquid biopsies, identifying 4 potential circulating biomarkers. One study used microarray analysis to identify genes that encode putative secreted proteins in 22 patients with benign and/or malignant peripheral nerve sheath tumors.[63] They found elevated serum levels of adrenomedullin (ADM) as a potential biomarker for malignant transformation of PNST with significantly higher mean ADM concentrations in NF1 patients with MPNST compared to NF1 patients with plexiform neurofibromas only (0.24 vs. 0.18 ng/mL; p=0.03). The diagnostic accuracy was not provided. A second study found that soluble AXL (sAXL) serum levels were higher in NF1 patients with plexiform neurofibromas and MPNSTs compared to those with dermal neurofibromas only, sAXL could not differentiate MPNST from others.[64] A third study performed screening for 56 potential serum biomarkers in 104 NF1 patients (with and without MPNST) compared with 41 controls.[65] Insulin-growth factor binding protein 1 (IGFBP1) was elevated in MPNST patients and was able to discriminate them with a sensitivity of 0.90 and specificity of 0.50. Regulated upon Activation Normal T-cell Expressed and Secreted (RANTES) was also elevated and had a sensitivity of 0.90 and a specificity of 0.26 to discriminate MPNST patients.

Discussion

MRI characteristics could varyingly detect MPNST, but absence of a target sign was highly sensitive. Ill-defined margins and perilesional edema could adequately distinguish MPNSTs from BPNST. FDG-PET has the highest diagnostic accuracy for detecting MPNST in NF1 patients, with equal efficacy when using SUVmax or T/L ratio. Ideal threshold value of SUVmax seems to be ≥3.5. Functional MRI and liquid biopsies may be useful tools as well, but do require more research.

MRI in nerve sheath tumors

Both MPNSTs and BPNSTs can exhibit rather different characteristics on MRI, highlighted by findings in this study. Presence of a target sign was the only MRI characteristic that could rule out MPNST, because of its nLR of less than 0.1.[28] Based on this characteristic, biopsies could be obviated for tumors with target signs. However, two studies reported 6/94 MPNSTs in this meta-analyses with a target sign.[16,32] One may argue that in order to omit a biopsy, in addition to the presence of a target sign, perilesional edema and ill-defined margins should be absent as well. Moreover, many BPNSTs do not show a target sign; 59.9% (range: 43.3-94.3%) in this meta-analysis. Nevertheless, in the remaining 40.1%, a biopsy may possibly be omitted. Presence of perilesional edema and ill-defined margins can adequately detect MPNST as the pLRs are more than 10, but biopsies may still be needed because these features can be present in a minority of BPNST as well. Unfortunately, perilesional edema and ill-defined margins are only present in 29-92% and 25-68% of MPNSTs respectively. Other characteristics that only have a moderate ability to differentiate MPNST and BPNST should therefore also be considered, including cystic changes, heterogeneity on T1, intratumoral lobulation, and large tumor size. An ideal combination of moderately specific characteristics adjacent to ill-defined margins and perilesional edema is still lacking, but may further reduce the need for biopsies. This is partially reflected by the diagnostic accuracy of qualitative assessment of MRI's which could not outperform either sensitivity or specificity of single characteristics.[32,33,41] Likewise, studies that reported diagnostic algorithms combining features decreased in sensitivity, albeit a rise in specificity.[22,40] Hence, conventional MRI's are imperfect and further diagnostics including FDG-PET in NF1 and biopsies may still be necessary in many cases. Luckily, interobserver agreement of MRI characteristics are very good to excellent, making them reproducible for use.[29,31] Functional MRI sequences may provide additional value in MPNST as DWI and ADC mapping yielded higher accuracy of detecting malignancy than conventional MRI characteristics.[21,38] MPNSTs show increased cellularity which makes ADCmin values relevant. Its use has however only been tested in two distinct populations and warrants further investigation.

FDG-PET in NF1 patients

FDG-PET scans are increasingly being applied to detect malignancy in NF1 patients with varying frequency of use across centers. Many efforts have been made to find ideal

semiquantitative parameters that adequately detect MPNSTs as well as exclude benign neurofibromas. SUVmax is the most commonly used characteristic, but ideal thresholds vary across studies. The threshold of ≥3.5 has been proposed most commonly as the ideal threshold.[15,51,57] This has been debated as several authors claim the threshold should be higher for it to be useful. Nonetheless, the threshold of ≥3.5 yielded highest accuracies across 11 different populations, which strengthens the belief that this threshold should be used. Indeed the characteristic remains imperfect as it is only has a moderately good positive likelihood ratio (4.7), meaning biopsies still play an important role as neurofibromas may also exhibit SUVmax values of ≥3.5 in 34.6% of patients in this meta-analyses. Nevertheless, the remaining 65.4% with SUVmax values of <3.5 do not require biopsies if they do not present ill-defined margins or perilesional edema on MRI. Delayed scans have been proposed to increase the accuracy of detecting MPNSTs, but it has not yet repeatedly been proven.[45,51,56] Besides, this method requires more resources and exposes patients to additional radiation. SUV measurement may additionally vary across scanners due to differing reasons. The use of proportional SUV values of tumor to tissue may be more reproducible as it reduces measurement variations. Most commonly the T/L ratio is used, but ideal thresholds are still missing. The T/L ratio did provide equal diagnostic accuracy compared to SUVmax. To diminish variations across scanners and increase reproducibility of thresholds, the European Association of Nuclear Medicine Research Ltd (EARL) set up criteria to which scanners should adhere.[66] To our knowledge, none of the studies in this review reported on a population scanned with a PET scanner that adheres to these criteria. Qualitative assessment of FDG-PET scans is also not subjected to variation in measurements and although interobserver agreement is good within studies, standardized criteria are currently lacking. Besides the use of FDG-PET scans to identify malignant transformation, it may also facilitate CT-guided biopsies and increase accuracies.[67] MPNSTs arising from plexiform neurofibromas can show heterogeneous degrees of malignancy within one tumor and are notorious for sampling errors,[18,19] thus PET-CT guided biopsies may be beneficial. Several studies in this review have shown that PET-MRI may adequately be used in the NF1 population and is particularly interesting in these patients as it combines the accuracy of both diagnostic modalities.[16,22] Moreover, replacing the CT with an MRI scan diminishes radiation exposure, which may accumulate due to numerous follow-up scans necessary in NF1 populations.[68,69]

Strengths, limitations, and future perspectives

Limitations to this study include the relatively high proportion of studies included to be at high risk of bias, most commonly due to concerns regarding patient selection. There was heterogeneity among study populations which led to heterogeneity of diagnostic accuracy as evaluated by subgroup analyses. Studies could be too strict in patient selection when only histologically proven lesions are included, possibly representing a group of lesions that are considered high-risk of malignancy based on imaging. Contrarily, when non-symptomatic lesions are included the proportion of low-risk

lesions rises. Subgroup analyses in this study should however be interpreted with caution as many were performed on a small number of studies. Most studies were also retrospective of nature further diminishing quality of evidence. Despite these limitations using a Bayesian approach, the quantification of diagnostic accuracy and uncertainty of common MRI and FDG-PET characteristics were reliable even when total number of studies or patients was small and there was heterogeneity in thresholds.[26] Unfortunately many features of interest, such as delayed scanning in FDG-PET and functional MRI are thus far infrequently studied which excluded them from meta-analyses. Yet these features seem promising, possibly providing higher accuracies compared to features analyzed in meta-analyses. Based on the findings of this study, future research should investigate several knowledge gaps. First, the MRI characteristics found in this study should be validated in a large series of patients to distinguish a patient group at high-risk for malignant transformation which minimizes the need for further diagnostics in low-risk patients. Second, only symptomatic or growing lesions should undergo imaging. The value of cystic changes, heterogeneity on T1 and T2 weighted images, large tumor size, and intratumoral lobulation should be studied for additional value too. DWI and ADC imaging seem of interest as well and might be of particular interest in the sporadic patient population. Schwannoma's are the most common form of BPNST in sporadic patients and cannot be reliable distinguished on FDG-PET as schwannomas commonly have high levels of FDG uptake.[70] Also, schwannoma's with cystic changes are common (ancient schwannoma's) and may exhibit heterogeneous features.[31] MRI characteristics need to be assessed between sporadic and NF1 patients to explore possible variations in diagnostic accuracy which may necessitate different diagnostic guidelines. In NF1 the use of a SUVmax threshold of ≥3.5 should be replicated in a large database of patients who underwent scans that adhere to EARL criteria. Additionally, late scanning and other semiquantitative parameters should be evaluated in the same population to find one with higher specificity. Altogether, these findings may enable proper diagnostic algorithms to arise for evaluating MRI scans and using distinct threshold values of FDG-PET characteristics in NF1 populations. This way unnecessary imaging, biopsies, and harmful resections will diminish. In sporadic patients, suspect lesions should then undergo biopsy based on MRI findings. In NF1 patients, suspect lesions should be evaluated with additional FDG-PET imaging. Lesions with SUVmax >3.5 or high T/L ratio should have a PET-guided biopsy. Whenever biopsies of suspect lesions are negative one may consider nerve-sparing resection or a wait-and-scan approach. Furthermore, the use of radiomics and deep learning has not yet been studied in nerve sheath tumors, but may be useful when studies are performed correctly including sufficient MPNST images. It may even help stratifying low and high-grade MPNSTs.[71–73] The search for an ideal liquid biopsy should be stimulated as well since its use may diminish the need for FDG-PET scans and decrease radiation exposure in the NF population who is already prone to tumorigenesis.

Conclusion

Conventional MRI may rule out MPNSTs in the presence of a target sign and obviates the need for biopsies or additional FDG-PET scans. Presence of ill-defined margins or perilesional edema is highly suspect of malignant transformation and requires biopsies or FDG-PET scans in NF1 for further characterization even in the presence of a target sign. However, MRI characteristics are varyingly present in MPNSTs. Therefore, cystic changes, heterogeneity on T1 weighted images, intratumoral lobulation, and large tumor size should be taken into account as well. FDG-PET scans should be offered to NF1 patients with symptomatic and suspect lesions on MRI to further reduce the need for biopsies. SUVmax and T/L ratio have similar accuracies. Ideal threshold for SUVmax seems to be ≥3.5. Functional MRI sequences may be useful as well, but require more research for their exact implementation. Liquid biopsies have not yet proven higher diagnostic accuracy than available imaging techniques.

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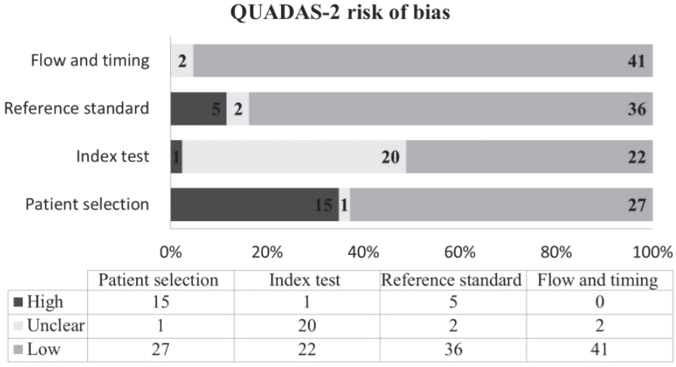
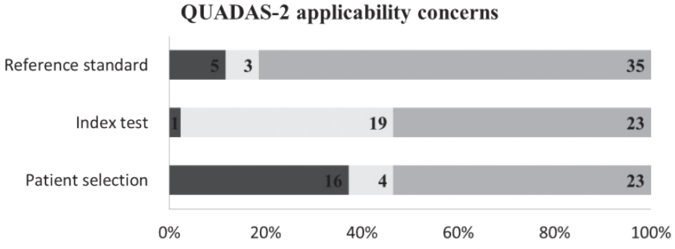
Supplementary File 1 QUADAS-2 tool for methodological assessment



	Patient selection	Index test	Reference standard	Flow and timing
High	15	1	5	0
Unclear	1	20	2	2
Low	27	22	36	41

Proportion of studies with high, unclear or low RISK of BIAS



	Patient selection	Index test	Reference standard
High	16	1	5
Unclear	4	19	3
Low	23	23	35

Proportion of studies with high, unclear or low
APPLICABILITY CONCERNS

Items	Sub-category questions	Explanation	Answers	%
Rob: patient selection	Was a consecutive or random sample of patients enrolled?	Consecutive or random sample Patient enrollment unclear or not described Non-random selection of patients	+ ? -	
	Was a case-control design avoided?	Case control design avoided Case controlled study	+ -	
	Did the study avoid inappropriate exclusions?	Exclusion due to lack of data of index test or reference test Exclusion criteria not described Excluding patients who had received radiotherapy, chemotherapy, percutaneous biopsy, were difficult to diagnose or including only patients with histologically confirmed (benign) lesions	+ ? -	

Items	Sub-category questions	Explanation	Answers	%
	Could the selection of patients have introduced bias?	One or more questions suggested "high risk" Two or more questions suggested "unclear" without any answers of high risk Question 1 + 2 suggested "low risk", question 3 suggested unclear or "low risk"	High risk Unclear Low risk	
Rob: index test	Were the index test results interpreted without knowledge of the results of the reference standard?	Radiologist or nuclear medicine physician blinded Unclear, not described Radiologist or nuclear medicine physician not blinded	+ ? -	
	If a threshold was used, was it pre-specified?	Use of threshold clearly described in study methods or based on ROC analysis New threshold used, not previously described in protocol or study methods	+ -	
	Could the conduct or interpretation of the index test have introduced bias?	One or more questions suggested "high risk" Question 1 suggested "unclear", question 2 suggested unclear or "low risk" Question 1 + 2 suggested "low risk"	High risk Unclear Low risk	
Rob: reference test	Is the reference standard likely to correctly classify the target condition?	Follow-up period > 6 months Follow-up period not described Follow-up period ≤ 6 months	+ ? -	
	Were the reference standard results interpreted without knowledge of the results of the index test?	Pathologist or researcher blinded Unclear, not described Pathologist or researcher not blinded	+ ? -	
	Could the reference standard, its conduct, or its interpretation have introduced bias?	One or more questions suggested "high risk" Both question 1 + 2 suggested "unclear" without any answers of high risk Questions 1 suggested "low risk", question 2 suggested unclear or "low risk"	High risk Unclear Low risk	
Rob: flow and timing	Was there an appropriate interval between index test(s) and reference standard?	MRI/PET-CT performed before excision of lesion or before/after follow-up MRI/PET-CT performed after histological confirmation	+ -	
	Did all patients receive a reference standard?	All patients receive reference standard Unclear, not described Including patients without reference standard	+ ? -	

Items	Sub-category questions	Explanation	Answers	%
	Did patients receive the same reference standard?	Patients receiving the same reference standard during the duration of the study	+	
		Unclear, not described	?	
		Pathology criteria changed during patient follow-up	-	
	Were all patients included in the analysis?	Clearly described follow-up protocol	+	
		Lack of clearly described follow-up protocol	-	
	Could the patient flow have introduced bias?	Loss to follow-up favoring subgroups	High risk	
		Unclearly described flowchart or follow-up of included patients	Unclear	
		Clearly described flowchart and follow-up of included patients	Low risk	
Ac: patient selection	Is there concern that the included patients do not match the review question?	Risk of bias for patient selection considered "high risk" or studies including patients with non-random sample of nerve sheath tumors, or studies only including patients with histologically confirmed diagnosis of bpnsts	High risk	
		Risk of bias for patient selection considered "unclear", or studies with an unclearly described selection procedure for inclusion of patients	Unclear	
		Risk of bias for patient selection considered "low risk" and providing a clear selection procedure with inclusion criteria of included patients	Low risk	
Ac: index test	Is there concern that the index test, its conduct, or interpretation differ from the review question?	Risk of bias for index test considered "high risk"	High risk	
		Risk of bias for index test considered "unclear"	Unclear	
		Risk of bias for index test considered "low risk"	Low risk	
Ac: reference standard	Is there concern that the target condition as defined by the reference standard does not match the review question?	Risk of bias for reference standard considered "high risk"	High risk	
		Risk of bias for reference standard considered "unclear", or no description of follow-up or biopsy procedure was provided	Unclear	
		Risk of bias for reference standard considered "low risk" and a clear description of follow-up or biopsy procedure was provided	Low risk	

Modified Quality Assessment of Diagnostic Accuracy Studies 2 tool. Questions used per category and explanatory note are provided. Abbreviations: Ac: applicability concerns, MRI: magnetic resonance imaging, PET-CT: positron emission tomography – computed tomography, Rob: risk of bias, ROC: receiver operating characteristic.

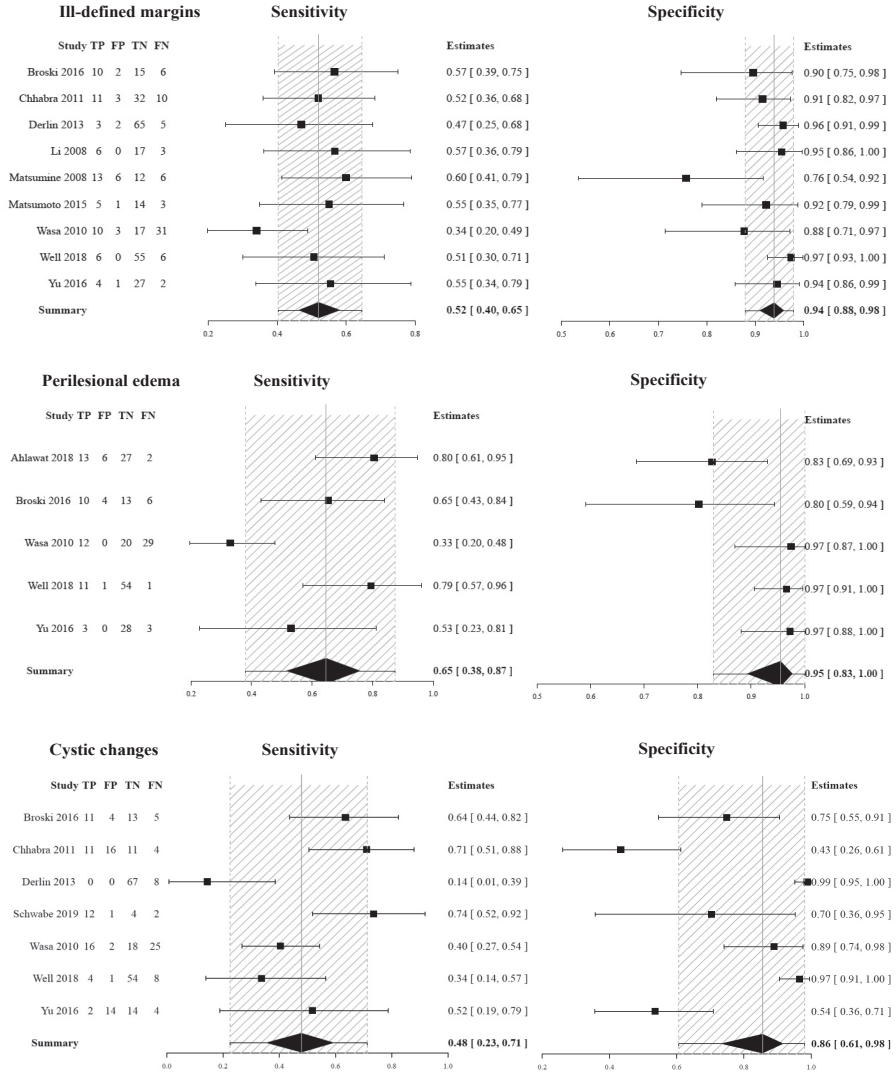
Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Ahlawat 2018	++-H	?+?	++L	++++L			
Ahlawat 2019	++-H	++L	+?L	++++L			
Azizi 2018	++?L	++L	+?L	++++L			
Bensaid 2007	++?L	++L	+?L	++++L			
Benz 2010	++-H	-+H	+?L	++++L			
Bredella 2007	++?L	++L	+?L	++++L			
Broski 2016	++-H	++L	+?L	++++L			
Cardona 2003	++-H	++L	+?L	++++L			
Chhabra 2011	++-H	?+?	+?L	++++L			
Chirindel 2015	++?L	?+?	+?L	++++L			
Combemale 2014	++?L	++L	+?L	++++L			
Cook 2017	++?L	?+?	+?L	++++L			
Demehri 2014	++?L	++L	+?L	++++L			
Derlin 2013	++?L	++L	+?L	++++L			
Fayad 2014	++-H	?+?	-?H	++++L			
Ferner 2000	++?L	++L	-?H	++++L			
Ferner 2008	++-H	++L	+?L	++++L			
Furniss 2007	++-H	?+?	+?L	++++L			
van der Gucht 2016	++?L	++L	+?L	++++L			
Hummel 2010	++?L	?+?	-?H	++++L			
Johansson 2014	?—H	?+?	???	???-?			
Karabatsou 2009	++?L	?+?	+?L	++++L			
Karsy 2016	?+-H	?+?	+?L	++++L			
Lerman 2019	+++L	++L	-?H	++++L			
Li 2008	++-H	?+?	+?L	++++L			
Matsumine 2008	++?L	++L	+?L	++++L			
Matsumoto 2015	++?L	?+?	+?L	++++L			
Mautner 2007	++?L	?+?	+?L	++++L			
Meany 2013	++?L	?+?	???	++++L			
Moharir 2010	++-H	?+?	+?L	++++L			
Nose 2013	++?L	?+?	+?L	++++L			
Park 2013	????	?+?	??L	???-?			
Razek 2018	++-H	++L	+?L	++++L			
Reinert 2018	+++L	++L	+?L	++++L			
Salamon 2013	+++L	++L	+?L	++++L			
Salamon 2014	+++L	++L	+?L	++++L			
Salamon 2015	+++L	?+?	+?L	++++L			
Schwabe 2019	++?L	++L	+?L	++++L			
Tsai 2012	++-H	++L	+?L	++++L			
Warbey 2009	++?L	++L	-?H	++++L			
Wasa 2009	++?L	?+?	+?L	++++L			
Well 2018	+++L	++L	+?L	++++L			
Yu 2016	++?L	?+?	+?L	++++L			

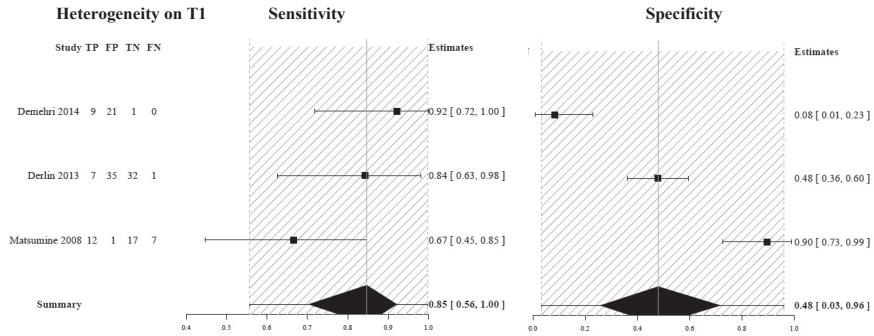
High risk: H, low risk: L, unclear risk: ?

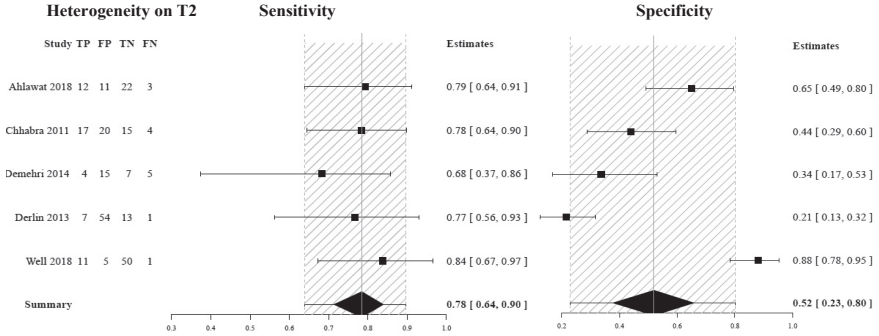
Quality assessment

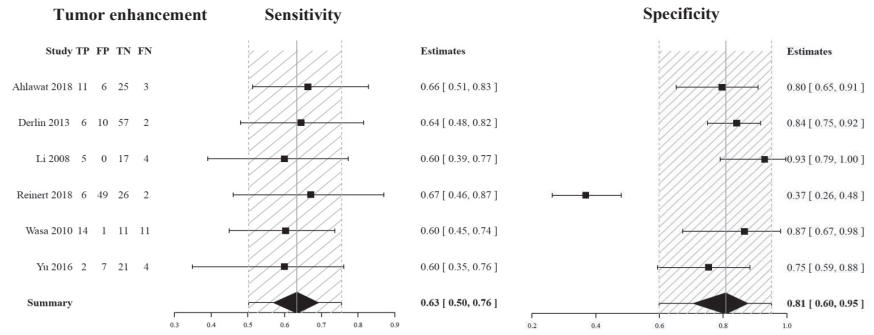
The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2 tool) is the current research standard for evaluation of studies validating diagnostic tests and was used to rate study quality of all diagnostic studies included in this review (Table X1). The results of the QUADAS-2 tool indicate risk of bias and applicability concerns for the following categories: patient selection, index test, reference standard and flow and timing (risk of bias only). This study used a modified QUADAS-2 tool using categorical questions adjusted to study design of the included studies (Table X2). The full QUADAS-2 tool can be found on the QUADAS website (www.quadas.org).

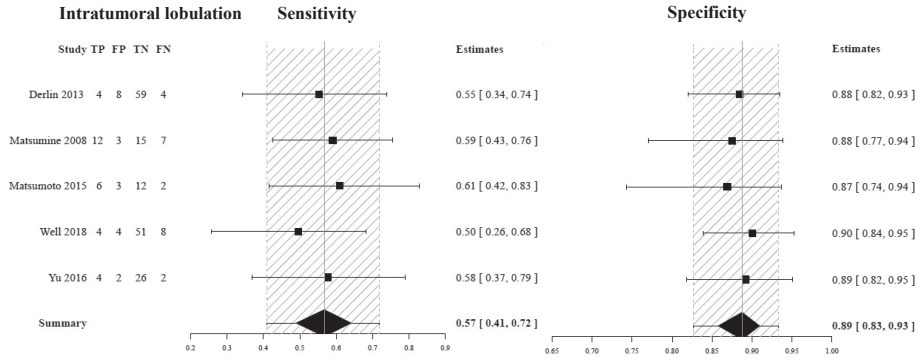
Supplementary Figure 1 Forest plots of MRI characteristics meta-analyses

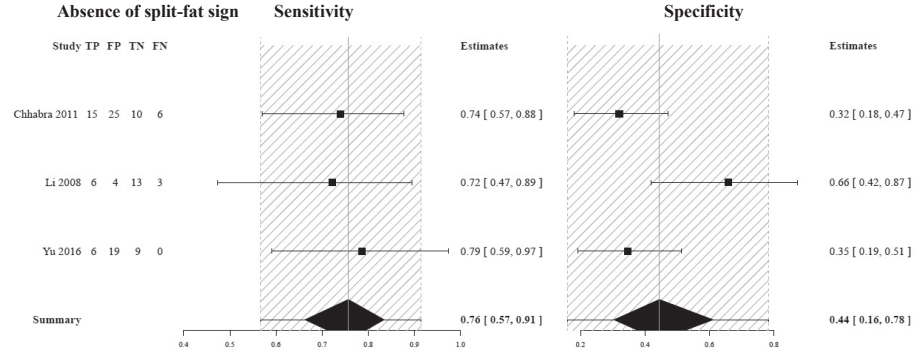


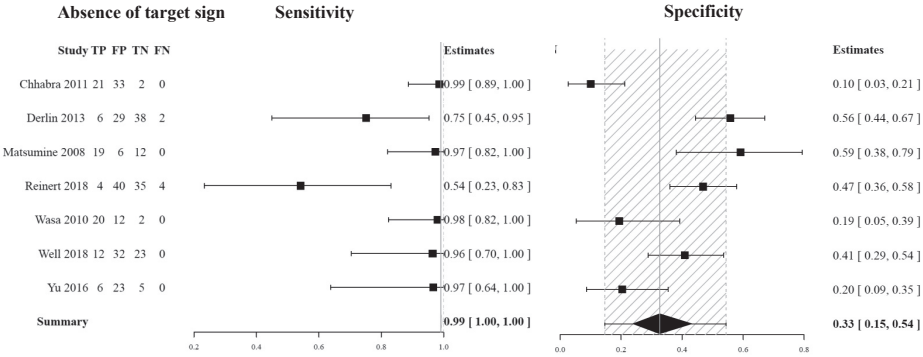

Heterogeneity on T1
Sensitivity
Specificity
Study TP FP TN FN
Estimates
Demehri 2014 9 21 1 0
0.92 [0.72, 1.00]
0.08 [0.01, 0.23]
Derlin 2013 7 35 32 1
0.84 [0.63, 0.98]
0.48 [0.36, 0.60]
Matsumine 2008 12 1 17 7
0.67 [0.45, 0.85]
0.90 [0.73, 0.99]
Summary
0.85 [0.56, 1.00]
0.48 [0.03, 0.96]
0.4 0.5 0.6 0.7 0.8 0.9 1.0
0.0 0.2 0.4 0.6 0.8 1.0

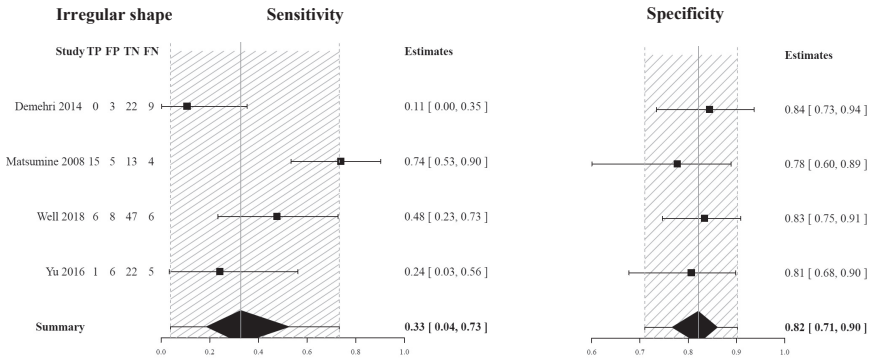

Heterogeneity on T2
Sensitivity
Specificity
Study TP FP TN FN
Estimates
Ahlawat 2018 12 11 22 3
0.79 [0.64, 0.91]
0.65 [0.49, 0.80]
Chhabra 2011 17 20 15 4
0.78 [0.64, 0.90]
0.44 [0.29, 0.60]
Demehri 2014 4 15 7 5
0.68 [0.37, 0.86]
0.34 [0.17, 0.53]
Derlin 2013 7 54 13 1
0.77 [0.56, 0.93]
0.21 [0.13, 0.32]
Well 2018 11 5 50 1
0.84 [0.67, 0.97]
0.88 [0.78, 0.95]
Summary
0.78 [0.64, 0.90]
0.52 [0.23, 0.80]
0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
0.2 0.4 0.6 0.8 1.0

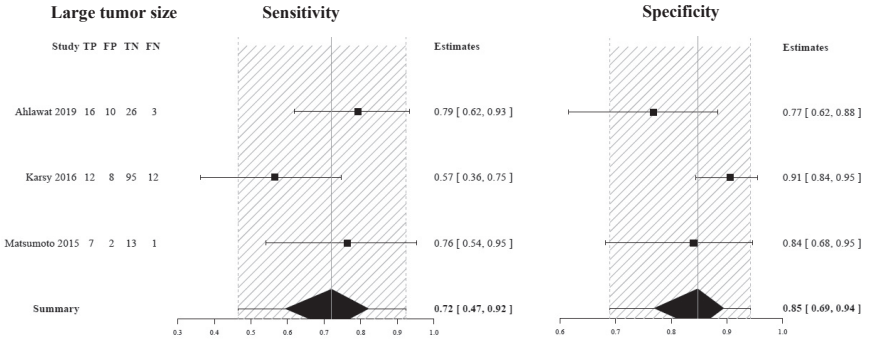

Tumor enhancement
Sensitivity
Specificity
Study TP FP TN FN
Estimates
Ahlawat 2018 11 6 25 3
0.66 [0.51, 0.83]
0.80 [0.65, 0.91]
Derlin 2013 6 10 57 2
0.64 [0.48, 0.82]
0.84 [0.75, 0.92]
Li 2008 5 0 17 4
0.60 [0.39, 0.77]
0.93 [0.79, 1.00]
Reinert 2018 6 49 26 2
0.67 [0.46, 0.87]
0.37 [0.26, 0.48]
Wasa 2010 14 1 11 11
0.60 [0.45, 0.74]
0.87 [0.67, 0.98]
Yu 2016 2 7 21 4
0.60 [0.35, 0.76]
0.75 [0.59, 0.88]
Summary
0.63 [0.50, 0.76]
0.81 [0.60, 0.95]
0.3 0.4 0.5 0.6 0.7 0.8 0.9
0.2 0.4 0.6 0.8 1.0

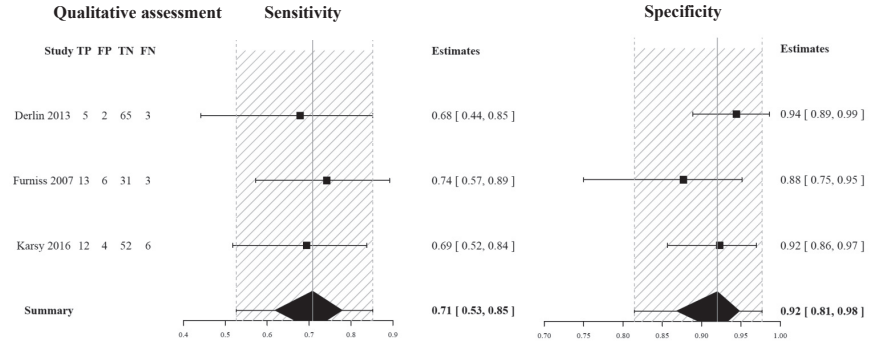

Intratumoral lobulation
Sensitivity
Specificity
Study TP FP TN FN
Estimates
Derlin 2013 4 8 59 4
0.55 [0.34, 0.74]
0.88 [0.82, 0.93]
Matsumine 2008 12 3 15 7
0.59 [0.43, 0.76]
0.88 [0.77, 0.94]
Matsumoto 2015 6 3 12 2
0.61 [0.42, 0.83]
0.87 [0.74, 0.94]
Well 2018 4 4 51 8
0.50 [0.26, 0.68]
0.90 [0.84, 0.95]
Yu 2016 4 2 26 2
0.58 [0.37, 0.79]
0.89 [0.82, 0.95]
Summary
0.57 [0.41, 0.72]
0.89 [0.83, 0.93]
0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9
0.65 0.70 0.75 0.80 0.85 0.90 0.95 1.00


Absence of split-fat sign
Sensitivity
Specificity
Study TP FP TN FN
Estimates
Chhabra 2011 15 25 10 6
0.74 [0.57, 0.88]
0.32 [0.18, 0.47]
Li 2008 6 4 13 3
0.72 [0.47, 0.89]
0.66 [0.42, 0.87]
Yu 2016 6 19 9 0
0.79 [0.59, 0.97]
0.35 [0.19, 0.51]
Summary
0.76 [0.57, 0.91]
0.44 [0.16, 0.78]
0.4 0.5 0.6 0.7 0.8 0.9 1.0
0.2 0.4 0.6 0.8

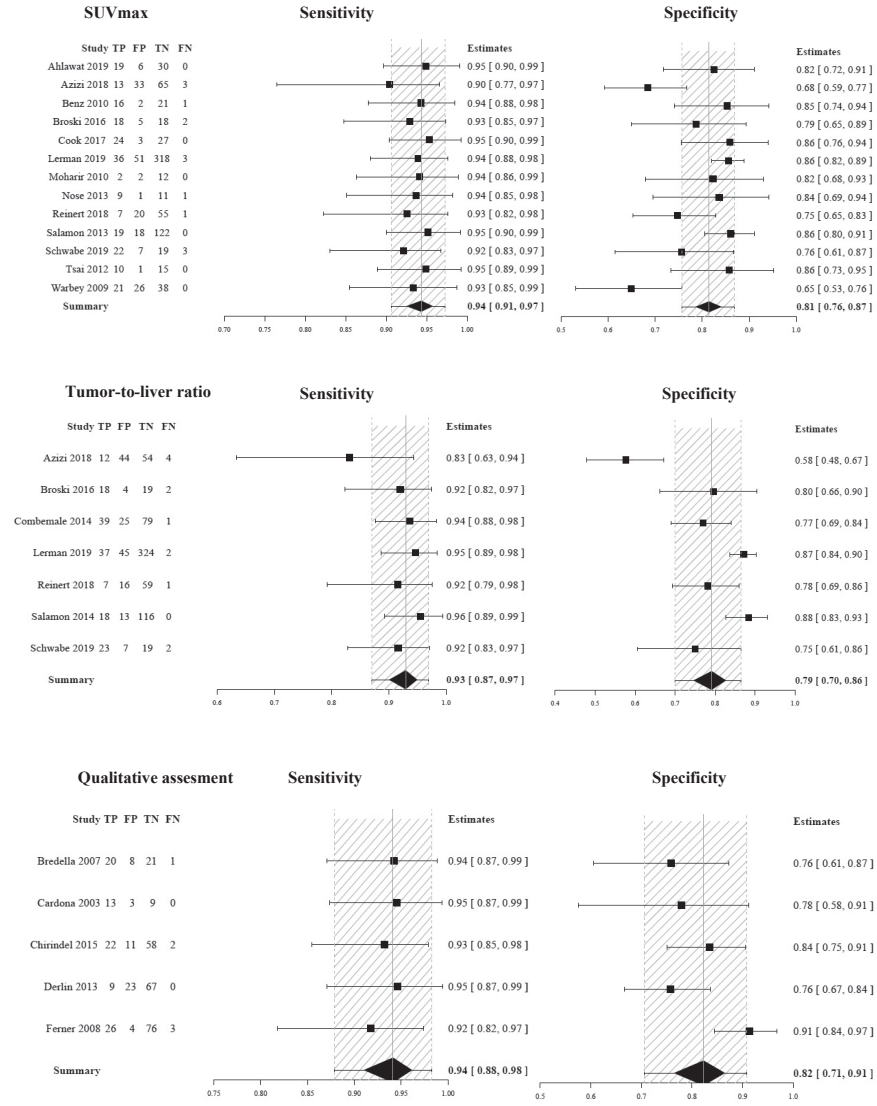

Absence of target sign
Sensitivity
Specificity
Study TP FP TN FN
Estimates
Chhabra 2011 21 33 2 0
0.99 [0.89, 1.00]
0.10 [0.03, 0.21]
Derlin 2013 6 29 38 2
0.75 [0.45, 0.95]
0.56 [0.44, 0.67]
Matsumine 2008 19 6 12 0
0.97 [0.82, 1.00]
0.59 [0.38, 0.79]
Reinert 2018 4 40 35 4
0.54 [0.23, 0.83]
0.47 [0.36, 0.58]
Wasa 2010 20 12 2 0
0.98 [0.82, 1.00]
0.19 [0.05, 0.39]
Well 2018 12 32 23 0
0.96 [0.70, 1.00]
0.41 [0.29, 0.54]
Yu 2016 6 23 5 0
0.97 [0.64, 1.00]
0.20 [0.09, 0.35]
Summary
0.99 [1.00, 1.00]
0.33 [0.15, 0.54]
0.2 0.4 0.6 0.8 1.0
0.0 0.2 0.4 0.6 0.8

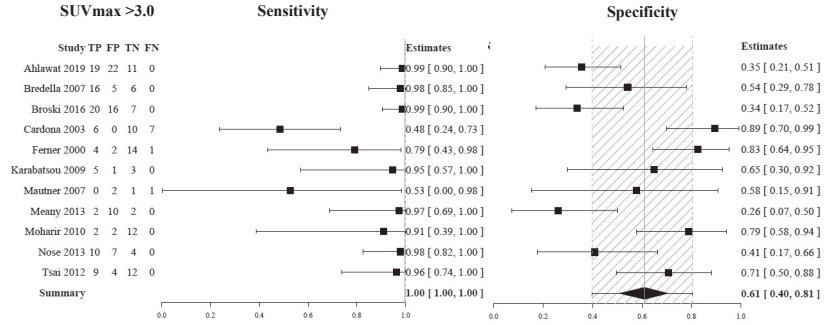

Irregular shape
Sensitivity
Specificity
Study TP FP TN FN
Estimates
Demehri 2014 0 3 22 9
0.11 [0.00, 0.35]
0.84 [0.73, 0.94]
Matsumine 2008 15 5 13 4
0.74 [0.53, 0.90]
0.78 [0.60, 0.89]
Well 2018 6 8 47 6
0.48 [0.23, 0.73]
0.83 [0.75, 0.91]
Yu 2016 1 6 22 5
0.24 [0.03, 0.56]
0.81 [0.68, 0.90]
Summary
0.33 [0.04, 0.73]
0.82 [0.71, 0.90]
0.0 0.2 0.4 0.6 0.8 1.0
0.6 0.7 0.8 0.9 1.0

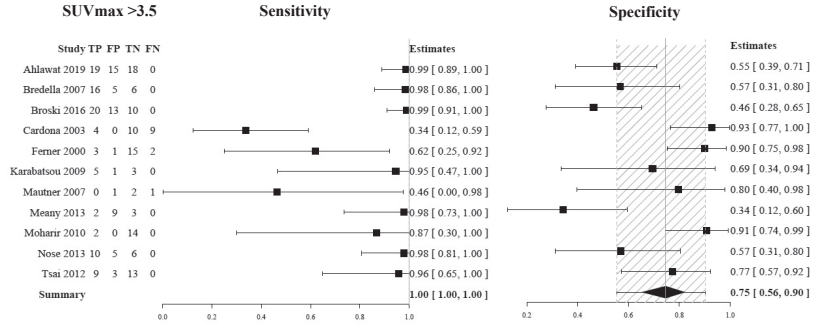

Large tumor size
Sensitivity
Specificity
Study TP FP TN FN
Estimates
Ahlawat 2019 16 10 26 3
0.79 [0.62, 0.93]
0.77 [0.62, 0.88]
Karsy 2016 12 8 95 12
0.57 [0.36, 0.75]
0.91 [0.84, 0.95]
Matsumoto 2015 7 2 13 1
0.76 [0.54, 0.95]
0.84 [0.68, 0.95]
Summary
0.72 [0.47, 0.92]
0.85 [0.69, 0.94]
0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
0.6 0.7 0.8 0.9 1.0

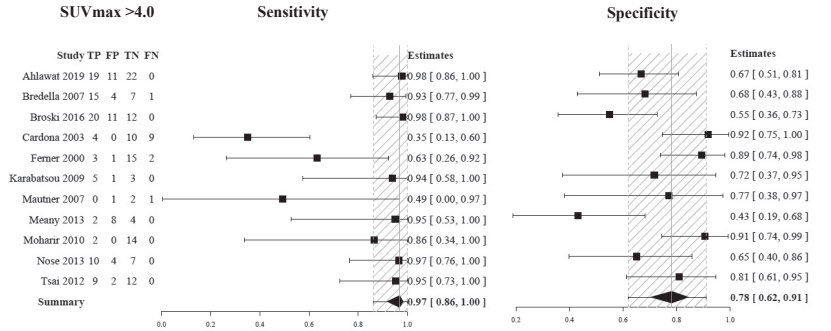

Qualitative assessment
Sensitivity
Specificity
Study TP FP TN FN
Estimates
Derlin 2013 5 2 65 3
0.68 [0.44, 0.85]
0.94 [0.89, 0.99]
Furniss 2007 13 6 31 3
0.74 [0.57, 0.89]
0.88 [0.75, 0.95]
Karsy 2016 12 4 52 6
0.69 [0.52, 0.84]
0.92 [0.86, 0.97]
Summary
0.71 [0.53, 0.85]
0.92 [0.81, 0.98]
0.4 0.5 0.6 0.7 0.8 0.9
0.70 0.75 0.80 0.85 0.90 0.95 1.00

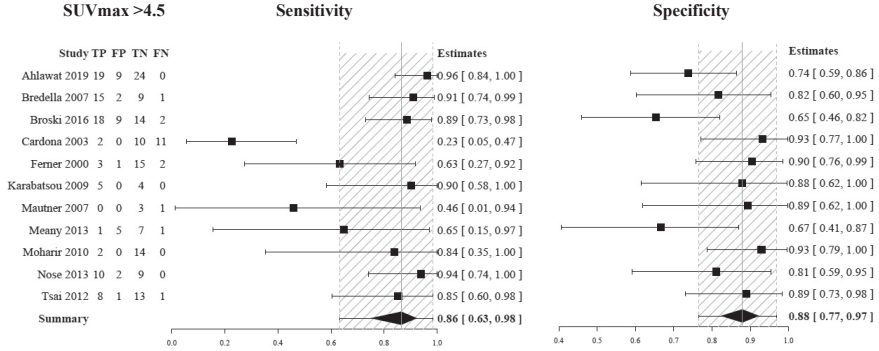
Supplementary Figure 2 Forest plots of PET meta-analyses




SUVmax >3.0
Sensitivity
Specificity
Study TP FP TN FN
Estimates
Ahlawat 2019 19 22 11 0
0.99 [0.90, 1.00]
0.35 [0.21, 0.51]
Bredella 2007 16 5 6 0
0.98 [0.85, 1.00]
0.54 [0.29, 0.78]
Broski 2016 20 16 7 0
0.99 [0.90, 1.00]
0.34 [0.17, 0.52]
Cardona 2003 6 0 10 7
0.48 [0.24, 0.73]
0.89 [0.70, 0.99]
Ferner 2000 4 2 14 1
0.79 [0.43, 0.98]
0.83 [0.64, 0.95]
Karabatsou 2009 5 1 3 0
0.95 [0.57, 1.00]
0.65 [0.30, 0.92]
Mautner 2007 0 2 1 1
0.53 [0.00, 0.98]
0.58 [0.15, 0.91]
Meany 2013 2 10 2 0
0.97 [0.69, 1.00]
0.26 [0.07, 0.50]
Moharir 2010 2 2 12 0
0.91 [0.39, 1.00]
0.79 [0.58, 0.94]
Nose 2013 10 7 4 0
0.98 [0.82, 1.00]
0.41 [0.17, 0.66]
Tsai 2012 9 4 12 0
0.96 [0.74, 1.00]
0.71 [0.50, 0.88]
Summary
1.00 [1.00, 1.00]
0.61 [0.40, 0.81]
0.0 0.2 0.4 0.6 0.8 1.0
0.0 0.2 0.4 0.6 0.8 1.0


SUVmax >3.5
Sensitivity
Specificity
Study TP FP TN FN
Estimates
Ahlawat 2019 19 15 18 0
0.99 [0.89, 1.00]
0.55 [0.39, 0.71]
Bredella 2007 16 5 6 0
0.98 [0.86, 1.00]
0.57 [0.31, 0.80]
Broski 2016 20 13 10 0
0.99 [0.91, 1.00]
0.46 [0.28, 0.65]
Cardona 2003 4 0 10 9
0.34 [0.12, 0.59]
0.93 [0.77, 1.00]
Ferner 2000 3 1 15 2
0.62 [0.25, 0.92]
0.90 [0.75, 0.98]
Karabatsou 2009 5 1 3 0
0.95 [0.47, 1.00]
0.69 [0.34, 0.94]
Mautner 2007 0 1 2 1
0.46 [0.00, 0.98]
0.80 [0.40, 0.98]
Meany 2013 2 9 3 0
0.98 [0.73, 1.00]
0.34 [0.12, 0.60]
Moharir 2010 2 0 14 0
0.87 [0.30, 1.00]
0.91 [0.74, 0.99]
Nose 2013 10 5 6 0
0.98 [0.81, 1.00]
0.57 [0.31, 0.80]
Tsai 2012 9 3 13 0
0.96 [0.65, 1.00]
0.77 [0.57, 0.92]
Summary
1.00 [1.00, 1.00]
0.75 [0.56, 0.90]
0.0 0.2 0.4 0.6 0.8 1.0
0.2 0.4 0.6 0.8 1.0


SUVmax >4.0
Sensitivity
Specificity
Study TP FP TN FN
Estimates
Ahlawat 2019 19 11 22 0
0.98 [0.86, 1.00]
0.67 [0.51, 0.81]
Bredella 2007 15 4 7 1
0.93 [0.77, 0.99]
0.68 [0.43, 0.88]
Broski 2016 20 11 12 0
0.98 [0.87, 1.00]
0.55 [0.36, 0.73]
Cardona 2003 4 0 10 9
0.35 [0.13, 0.60]
0.92 [0.75, 1.00]
Ferner 2000 3 1 15 2
0.63 [0.26, 0.92]
0.89 [0.74, 0.98]
Karabatsou 2009 5 1 3 0
0.94 [0.58, 1.00]
0.72 [0.37, 0.95]
Mautner 2007 0 1 2 1
0.49 [0.00, 0.97]
0.77 [0.38, 0.97]
Meany 2013 2 8 4 0
0.95 [0.53, 1.00]
0.43 [0.19, 0.68]
Moharir 2010 2 0 14 0
0.86 [0.34, 1.00]
0.91 [0.74, 0.99]
Nose 2013 10 4 7 0
0.97 [0.76, 1.00]
0.65 [0.40, 0.86]
Tsai 2012 9 2 12 0
0.95 [0.73, 1.00]
0.81 [0.61, 0.95]
Summary
0.97 [0.86, 1.00]
0.78 [0.62, 0.91]
0.0 0.2 0.4 0.6 0.8 1.0
0.2 0.4 0.6 0.8 1.0


SUVmax >4.5
Sensitivity
Specificity
Study TP FP TN FN
Estimates
Ahlawat 2019 19 9 24 0
0.96 [0.84, 1.00]
0.74 [0.59, 0.86]
Bredella 2007 15 2 9 1
0.91 [0.74, 0.99]
0.82 [0.60, 0.95]
Broski 2016 18 9 14 2
0.89 [0.73, 0.98]
0.65 [0.46, 0.82]
Cardona 2003 2 0 10 11
0.23 [0.05, 0.47]
0.93 [0.77, 1.00]
Ferner 2000 3 1 15 2
0.63 [0.27, 0.92]
0.90 [0.76, 0.99]
Karabatsou 2009 5 0 4 0
0.90 [0.58, 1.00]
0.88 [0.62, 1.00]
Mautner 2007 0 0 3 1
0.46 [0.01, 0.94]
0.89 [0.62, 1.00]
Meany 2013 1 5 7 1
0.65 [0.15, 0.97]
0.67 [0.41, 0.87]
Moharir 2010 2 0 14 0
0.84 [0.35, 1.00]
0.93 [0.79, 1.00]
Nose 2013 10 2 9 0
0.94 [0.74, 1.00]
0.81 [0.59, 0.95]
Tsai 2012 8 1 13 1
0.85 [0.60, 0.98]
0.89 [0.73, 0.98]
Summary
0.86 [0.63, 0.98]
0.88 [0.77, 0.97]
0.0 0.2 0.4 0.6 0.8 1.0
0.4 0.5 0.6 0.7 0.8 0.9 1.0

Supplementary Table 1 Search syntaxes for PubMed and Embase databases

PubMed search: 13-Nov-2019	((Neurofibromatosis[Title/Abstract] OR NF1[Title/Abstract] OR "Neurofibromatosis 1"[MeSH]) AND (Biomarker[Title/Abstract] OR radiolog*[Title/Abstract] OR imaging[Title/Abstract] OR diagnostic*[Title/Abstract] OR tomography[Title/Abstract] OR MRI[Title/Abstract] OR PET[Title/Abstract] OR "Diagnostic Techniques and Procedures"[MeSH] OR Biomarkers[MeSH]) AND (MPNST*[Title/Abstract] OR malignant peripheral nerve sheath tum*[Title/Abstract] OR malignant neurilemmoma[Title/Abstract] OR malignant schwannoma[Title/Abstract] OR neurofibrosarcoma[Title/Abstract] OR Neurilemmoma[MeSH])) AND "2000/01/01"[PDat] : "2019/11/13"[PDat]
Embase search: 13-Nov-2019	(('Neurofibromatosis':ab,ti OR 'NF1':ab,ti OR 'Neurofibromatosis type 1'/exp) AND ('Biomarker':ab,ti OR 'radiolog*':ab,ti OR 'imaging':ab,ti OR 'diagnostic*':ab,ti OR 'tomography':ab,ti OR 'MRI':ab,ti OR 'PET':ab,ti OR 'diagnostic procedure'/exp OR 'biological marker'/exp) AND ('MPNST*':ab,ti OR 'malignant peripheral nerve sheath tum*':ab,ti OR 'malignant neurilemmoma':ab,ti OR 'malignant schwannoma':ab,ti OR 'neurofibrosarcoma':ab,ti OR 'malignant neurilemoma'/exp)) AND [2000-2019]/py

Supplementary Table 2 Diagnostic accuracy non-meta-analysis

Study	N	Characteristic	Cut-off	Accuracies (95% CI)			
				Sensitivity	Specificity	pLR	nLR
			Qualitative MRI				
Chhabra 2011	56	Calcification	*NA*	0.13 (0.03-0.40)	0.94 (0.63-0.99)	2.25 (0.10-49.04)	0.93 (0.71-1.21)
Broski 2016	38	1 feature	*NA*	0.81 (0.57-0.93)	0.65 (0.41-0.83)	2.30 (1.16-4.57)	0.29 (0.10-0.85)
Broski 2016	38	2 features	*NA*	0.75 (0.51-0.90)	0.88 (0.66-0.97)	6.38 (1.68-24.16)	0.28 (0.12-0.67)
Broski 2016	38	3 features	*NA*	0.44 (0.24-0.67)	0.97 (0.78-1.00)	15.88 (0.98-257.27)	0.58 (0.37-0.88)
Matsumine 2008	37	Depth	*NA*	0.98 (0.80-1.00)	0.13 (0.04-0.35)	1.12 (0.93-1.36)	0.19 (0.01-3.71)
Wasa 2010	61			0.89 (0.77-0.96)	0.21 (0.09-0.43)	1.14 (0.89-1.45)	0.50 (0.15-1.66)
Demehri 2014	29	Joint extension	*NA*	0.05 (0.01-0.35)	0.98 (0.82-1.00)	2.3 (0.05-107.97)	0.97 (0.83-1.13)
Demehri 2014	29	Eccentricity to nerve	*NA*	0.45 (0.20-0.73)	0.46 (0.27-0.65)	0.83 (0.38- 1.81)	1.21 (0.59-2.47)
Li 2008	26			0.95 (0.66-1.00)	0.86 (0.64-0.96)	6.84 (2.15-21.80)	0.06 (0.00-0.87)
Demehri 2014	29	Vascular encasement	*NA*	0.15 (0.04-0.46)	0.98 (0.82-1.00)	6.9 (0.31-155.22)	0.87 (0.67-1.14)
Demehri 2014	29	Cortical invasion	*NA*	0.15 (0.04-0.46)	0.98 (0.82-1.00	6.9 (0.31-155.22)	0.87 (0.67-1.14)
			Functional MRI				
Well 2018	26	ADCdark	*NA*	0.92 (0.65-0.99)	0.98 (0.90-1.00)	50.42 (7.18-354.20)	0.09 (0.01-0.55)
Razek 2018	34	ADCmean	*NA*	0.91 (0.62-0.98)	0.91 (0.73-0.98)	10.46 (2.75- 39.82)	0.10 (0.02-0.65)
Well 2018	26			0.92 (0.65-0.99)	0.98 (0.90-1.00)	50.42 (7.18-354.20)	0.09 (0.01-0.55)
Ahlawat 2019	21	ADCmin	$<1*10^{-3}$	0.98 (0.80-1.00)	0.93 (0.81-0.98)	14.43 (4.35-47.86)	0.03 (0.00-0.42)
Well 2018	26			0.89 (0.62-0.97)	0.94 (0.84-0.98)	14.15 (5.04- 39.77)	0.12 (0.03-0.56)
Well 2018	26	dark	*NA*	0.81 (0.54-0.94)	0.99 (0.92-1.00)	90.46 (5.66- 1446.71)	0.19 (0.06-0.59)
Well 2018	26	Dmargin	*NA*	0.89 (0.62-0.97)	0.99 (0.92-1.00)	99.08 (6.23- 1575.42)	0.12 (0.03-0.53)
Well 2018	26	Dmean	*NA*	0.92 (0.65-0.99)	0.98 (0.90-1.00)	50.42 (7.18- 354.20)	0.09 (0.01-0.55)
Well 2018	26	Dmin	*NA*	0.96 (0.72-1.00)	0.96 (0.87-0.99)	21.54 (6.38- 72.70)	0.04 (0.00-0.61)
Well 2018	26	fcenter	*NA*	0.96 (0.72-1.00)	0.55 (0.42-0.67)	2.11 (1.55-2.87)	0.07 (0.01-1.08)
Well 2018	26	fmargin	*NA*	0.83 (0.55-0.95)	0.75 (0.62-0.84)	3.27 (1.95-5.50)	0.22 (0.06-0.8)
Demehri 2014	31	Early arterial enhancement	*NA*	0.50 (0.22-0.79)	0.89 (0.67-0.97)	4.50 (1.03-19.75)	0.56 (0.28-1.15)
Ahlawat 2018	42	Target sign on ADC mapping	*NA*	0.97 (0.76-1.00)	0.63 (0.47-0.77)	2.64 (1.68-4.13)	0.05 (0.00-0.77)

Supplementary Table 2 Continued.

Study	N	Characteristic	Cut-off	Accuracies (95% CI)			
				Sensitivity	Specificity	pLR	nLR
Ahlawat 2018	42	Target sign DWI b-value 50	*NA*	0.80 (0.55-0.93)	0.39 (0.25-0.56)	1.32 (0.91-1.92)	0.51 (0.17-1.52)
Ahlawat 2018	42	Target sign DWI b-value 400	*NA*	0.93 (0.70-0.99)	0.55 (0.38-0.70)	2.05 (1.38-3.06)	0.12 (0.02-0.83)
Ahlawat 2018	42	Target sign DWI b-value 800	*NA*	0.93 (0.70-0.99)	0.49 (0.33-0.65)	1.81 (1.27-2.59)	0.14 (0.02-0.94)
Fayad 2014	16	TMA peak	*NA*	0.90 (0.46-0.99)	0.50 (0.29-0.72)	1.80 (1.03-3.15)	0.20 (0.01-2.89)
Fayad 2014	16	TMA fraction	>50%	0.90 (0.46-0.99)	0.62 (0.39-0.81)	2.35 (1.20-4.61)	0.16 (0.01-2.31)
				^{18}F-FDG PET			
Cook 2017	54	SUVpeak	*NA*	0.90 (0.73-0.97)	0.98 (0.86-1.00)	55.80 (3.56- 875.02)	0.10 (0.03-0.33)
Schwabe 2019	41		4.5	0.94 (0.78-0.99)	0.69 (0.50-0.83)	2.99 (1.70-5.26)	0.08 (0.02-0.41)
Cook 2017	54	SUVpeak 4h	*NA*	0.94 (0.78-0.99)	0.98 (0.86-1.00)	58.28 (3.72-912.70)	0.06 (0.01-0.29)
Cook 2017	54	SUVmax 4h	*NA*	0.98 (0.83-1.00)	0.92 (0.77-0.98)	12.15 (3.70-39.94)	0.02 (0.00-0.34)
Warbey 2009	62		3.5	0.93 (0.75-0.98)	0.87 (0.77-0.93)	7.13 (3.77-13.47)	0.08 (0.02-0.37)
Cardona 2003	13	SUVmean	1.8	0.96 (0.73-1.00)	0.81 (0.54-0.94)	5.01 (1.64-15.35)	0.04 (0.00-0.68)
Cook 2017	54		*NA*	0.90 (0.73-0.97)	0.95 (0.82-0.99)	18.60 (3.88-89.10)	0.11 (0.03-0.34)
Cook 2017	54	SUVmean 4h	*NA*	0.96 (0.80-0.99)	0.93 (0.79-0.98)	14.38 (3.76- 54.98)	0.05 (0.01-0.31)
Chirindel 2015	41	SULmax	3.2	0.92 (0.74-0.98)	0.87 (0.77-0.93)	7.03 (3.78-13.08)	0.10 (0.03-0.36)
Chirindel 2015	41	SULmax 4h	4.1	0.96 (0.80-0.99)	0.88 (0.79-0.94)	8.27 (4.29-15.94)	0.05 (0.01-0.32)
Lerman 2019	127	HISUV	1.63	0.84 (0.70-0.92)	0.53 (0.48-0.58)	1.80 (1.51-2.14)	0.30 (0.15-0.62)
Salamon 2013	50		1.4	0.98 (0.80-1.00)	0.79 (0.72-0.85)	4.66 (3.36-6.47)	0.03 (0.00-0.49)
Salamon 2014	49	Tumor-to-muscle ratio	2.8	0.97 (0.79-1.00)	0.39 (0.31-0.47)	1.59 (1.36-1.86)	0.07 (0.00-1.05)
Salamon 2014	49	Tumor-to-fat ratio	7.7	0.97 (0.79-1.00)	0.50 (0.42-0.59)	1.96 (1.63-2.37)	0.05 (0.00-0.81)
Broski 2016	38	FDG heterogeneity	*NA*	0.83 (0.63-0.94)	0.44 (0.26-0.63)	1.48 (0.99-2.21)	0.38 (0.13-1.10)
Salamon 2013	50		*NA*	0.98 (0.80-1.00)	0.83 (0.76-0.88)	5.61 (3.89-8.10)	0.03 (0.00-0.47)
Chirindel 2015	41	Qualitative analysis 4h	*NA*	0.92 (0.74-0.98)	0.81 (0.70-0.89)	4.87 (2.94-8.06)	0.10 (0.03-0.39)
Cook 2017	54	SD	*NA*	0.92 (0.74-0.98)	0.97 (0.83-0.99)	27.5 (3.99-189.61)	0.09 (0.02-0.33)
Cook 2017	54	SD 4h	*NA*	0.90 (0.73-0.97)	0.98 (0.86-1.00)	55.8 (3.56-875.02)	0.10 (0.03-0.33)

Supplementary Table 2 Continued.

Study	N	Characteristic	Cut-off	Accuracies (95% CI)			
				Sensitivity	Specificity	pLR	nLR
Chirindel 2015	41	SULmax/liver	2.7	0.92 (0.74-0.98)	0.94 (0.86-0.98)	15.81 (6.06 -41.25)	0.09 (0.02-0.33)
Chirindel 2015	41	SULmax/liver 4h	4.3	0.96 (0.80-0.99)	0.93 (0.84-0.97)	13.23 (5.66 -30.89)	0.05 (0.01-0.31)
Broski 2016	38	TLG/liverSUVmax	59.5	0.75 (0.53-0.89)	0.87 (0.68-0.96)	5.75 (1.94-17.02)	0.29 (0.13-0.62)
Broski 2016	38	TLG/liverSUVmean	73.6	0.80 (0.58-0.92)	0.87 (0.68-0.96)	6.13 (2.09-18.02)	0.23 (0.09-0.56)
Broski 2016	38	MTV	42.5	0.80 (0.58-0.92)	0.78 (0.58-0.90)	3.68 (1.64-8.24)	0.26 (0.10-0.63)
Van der Gucht 2016	49		88	0.94 (0.72-0.99)	0.79 (0.62-0.89)	4.42 (2.26-8.63)	0.08 (0.01-0.53)
Lerman 2019	107	TMTV	53.5	0.85 (0.70-0.93)	0.68 (0.63-0.73)	2.65 (2.17-3.23)	0.23 (0.11-0.47)
Salamon 2015	36	WB-TMTV	19680	0.95 (0.75-0.99)	0.80 (0.68-0.88)	4.74 (2.76-8.12)	0.07 (0.01-0.45)
Broski 2016	38	TLG	208	0.70 (0.48-0.86)	0.91 (0.73-0.98)	8.05 (2.08-31.21)	0.33 (0.17-0.65)
Lerman 2019	107		172	0.85 (0.70-0.93)	0.76 (0.71-0.80)	3.51 (2.80-4.39)	0.20 (0.10-0.42)
Salamon 2015	36	WB-TLG	82627	0.95 (0.75-0.99)	0.84 (0.72-0.91)	5.79 (3.16-10.62)	0.06 (0.01-0.43)
Cook 2017	54	FOE	*NA*	0.86 (0.68-0.95)	0.98 (0.86-1.00)	53.32 (3.40-837.33)	0.14 (0.05-0.38)
Cook 2017	54	FOE 4h	*NA*	0.9 (0.73-0.97)	0.98 (0.86-1.00)	55.8 (3.56-875.02)	0.10 (0.03-0.33)
Cook 2017	54	FOU	*NA*	0.86 (0.68-0.95)	0.98 (0.86-1.00)	53.32 (3.40-837.33)	0.14 (0.05-0.38)
Cook 2017	54	FOU 4h	*NA*	0.92 (0.74-0.98)	0.97 (0.83-0.99)	27.5 (3.99-189.61)	0.09 (0.02-0.33)
Cook 2017	54	GLCMcon	*NA*	0.33 (0.18-0.53)	0.8 (0.63-0.91)	1.667 (0.67- 4.15)	0.83 (0.60-1.17)
Cook 2017	54	GLCMcon 4h	*NA*	0.58 (0.39-0.76)	0.83 (0.66-0.93)	3.5 (1.47-8.34)	0.50 (0.30-0.82)
Cook 2017	54	GLCMen	*NA*	0.58 (0.39-0.76)	0.87 (0.70-0.95)	4.38 (1.65-11.58)	0.48 (0.29-0.79)
Cook 2017	54	GLCMen 4h	*NA*	0.58 (0.39-0.76)	0.73 (0.56-0.86)	2.188 (1.11-4.33)	0.57 (0.34-0.96)
Cook 2017	54	GLCMhomo	*NA*	0.25 (0.12-0.45)	0.97 (0.83-0.99)	7.5 (0.97-58.13)	0.78 (0.61-0.99)
Cook 2017	54	GLCMhomo 4h	*NA*	0.50 (0.31-0.69)	0.67 (0.49-0.81)	1.5 (0.79-2.86)	0.75 (0.47-1.20)
Cook 2017	54	GLCMun	*NA*	0.54 (0.35-0.72)	0.30 (0.17-0.48)	0.77 (0.5-1.20)	1.53 (0.76-3.07)
Cook 2017	54	GLCMun 4h	*NA*	0.83 (0.64-0.93)	0.33 (0.19-0.51)	1.25 (0.92-1.70)	0.50 (0.18-1.40)
Cook 2017	54	NGTDMbus	*NA*	0.79 (0.60-0.91)	0.70 (0.52-0.83)	2.64 (1.47-4.73)	0.30 (0.13-0.67)
Cook 2017	54	NGTDMbus 4h	*NA*	0.67 (0.47-0.82)	0.67 (0.49-0.81)	2.00 (1.12 -3.57)	0.50 (0.27-0.93)

Supplementary Table 2 Continued.

Study	N	Characteristic	Cut-off	Accuracies (95% CI)			
				Sensitivity	Specificity	pLR	nLR
Cook 2017	54	NGTDMco	*NA*	0.83 (0.64-0.93)	0.83 (0.66-0.93)	5.00 (2.20-11.35)	0.20 (0.08-0.50)
Cook 2017	54	NGTDMco 4h	*NA*	0.79 (0.60-0.91)	0.87 (0.70-0.95)	5.94 (2.33-15.13)	0.24 (0.11-0.53)
Cook 2017	54	NGTDMcomp	*NA*	0.79 (0.60-0.91)	0.70 (0.52-0.83)	2.64 (1.47-4.73)	0.30 (0.13-0.67)
Cook 2017	54	NGTDMcomp 4h	*NA*	0.79 (0.60-0.91)	0.70 (0.52-0.83)	2.64 (1.47-4.73)	0.30 (0.13-0.67)
Cook 2017	54	NGTDMcontr	*NA*	0.83 (0.64-0.93)	0.47 (0.30-0.64)	1.56 (1.07-2.28)	0.36 (0.14-0.95)
Cook 2017	54	NGTDMcontr 4h	*NA*	0.50 (0.31-0.69)	0.67 (0.49-0.81)	1.5 (0.79-2.86)	0.75 (0.47-1.20)
Cook 2017	54	SUVmax/NGTDMcontr	*NA*	0.92 (0.74-0.98)	0.93 (0.79-0.98)	13.75 (3.59-52.74)	0.09 (0.02-0.34)
Cook 2017	54	SUVmax/NGTDMcontr 4h	*NA*	0.83 (0.64-0.93)	0.90 (0.74-0.97)	8.33 (2.81-24.74)	0.19 (0.08-0.46)

ADC: apparent diffusion coefficient, ADCmean: mean ADC of tumors, ADCmin: minimum ADC of tumors, CE T1-W : target sign on static post contrast sequence; CI: confidence interval, D: diffusion coefficient, f: perfusion fraction, FOE: first-order entropy, FOU: first-order uniformity, GLCMcon: grey-level co-occurrence matrices contrast, GLCMen: grey-level co-occurrence matrices entropy, GLCMhomo: grey-level co-occurrence matrices homogeneity, GLCMun: grey-level co-occurrence matrices uniformity, HISUV: SUV-based heterogeneity index obtained by dividing intratumoral SUVmax by SUVmean of that lesion, MRI: magnetic resonance imaging, MRI 1 feature: perilesional edema or cystic degeneration/necrosis or irregular margins, MRI 2 features: two of the following features: perilesional edema, cystic degeneration/necrosis, and irregular margins, MRI 3 features: perilesional edema and cystic degeneration/necrosis and irregular margins, N: number of patients, NA: not applicable, NGTDMbus: neighbourhood grey-tone difference matrices busyness,
NGTDMco: neighbourhood grey-tone difference matrices coarseness, NGTDMcomp: neighbourhood grey-tone difference matrices complexity, NGTDMcontr: neighbourhood grey-tone difference matrices contrast, nLR: negative likelihood ratio, PET-CT: positron emission tomography – computed tomography, pLR: positive likelihood ratio, SD: standard deviation of heterogeneity, Sens: sensitivity, Spec: specificity, SULmax: maximum standardized uptake value derived for lean body, SULmax/liver: lesion uptake adjusted to mean liver activity, SUV: standardized uptake volume, SUVmax: maximum standardized uptake volume, SUVmean: mean standardized uptake volume, SUVpeak: peak standardized uptake volume, TMA fraction: quantitative trimethylamine fraction, TMA peak: qualitative presence of trimethylamine peak, TMTV: total metabolic tumor volume, WB-TMTV: whole-body total metabolic tumor volume.

Supplementary Table 3 Subgroup analyses of meta-analyses

Characteristic	Subgroup		N	Pooled accuracies (95% CI)	
				Sensitivity	Specificity
		MRI			
Ill-defined margins	Total number of lesions	<50	5	0.66 (0.52-0.78)	0.91 (0.79-0.98)
		≥50	4	0.38 (0.27-0.52)	0.95 (0.87-0.99)
	Prevalence MPNST	≤33%	3	0.50 (0.27-0.73)	0.98 (0.94-1.00)
		>33%	6	0.53 (0.39-0.69)	0.88 (0.80-0.95)
	NF1 patients only	Yes	3	0.54 (0.32-0.75)	0.94 (0.80-0.99)
		No	6	0.51 (0.36-0.68)	0.93 (0.83-0.99)
	Symptomatic lesions only	Yes	2	0.67 (0.48-0.83)	0.86 (0.46-1.00)
		No	4	0.51 (0.36-0.66)	0.97 (0.87-1.00)
	Histologically proven only	Yes	7	0.54 (0.41-0.69)	0.90 (0.82-0.96)
		No	2	0.45 (0.20-0.71)	0.98 (0.94-1.00)
Perilesional edema	Total number of lesions	<50	3	0.67 (0.26-0.94)	0.88 (0.57-1.00)
		≥50	2	0.60 (0.18-0.95)	0.99 (0.95-1.00)
	Prevalence MPNST	≤33%	3	0.80 (0.55-0.94)	0.95 (0.80-1.00)
		>33%	2	0.44 (0.18-0.76)	0.98 (0.83-1.00)
	NF1 patients only	Yes	1	0.89 (0.56-0.99)	0.97 (0.80-0.99)
		No	4	0.55 (0.36-0.75)	0.92 (0.82-0.99)
	Symptomatic lesions only	Yes	0	*NA*	*NA*
		No	2	*NA*	*NA*
	Histologically proven only	Yes	3	0.43 (0.25-0.65)	1.00 (1.00-1.00)
		No	2	0.88 (0.69-0.97)	0.83 (0.08-1.00)
Cystic changes	Total number of lesions	<50	4	0.69 (0.48-0.85)	0.58 (0.36-0.81)
		≥50	3	0.28 (0.09-0.47)	0.98 (0.93-1.00)
	Prevalence MPNST	≤33%	4	0.65 (0.41-0.86)	0.71 (0.25-0.97)
		>33%	3	0.22 (0.04-0.48)	0.93 (0.70-1.00)
	NF1 patients only	Yes	4	0.56 (0.22-0.86)	0.65 (0.30-0.91)
		No	3	0.38 (0.06-0.76)	0.97 (0.89-1.00)
	Symptomatic lesions only	Yes	0	*NA*	*NA*
		No	4	*NA*	*NA*
	Histologically proven only	Yes	5	0.62 (0.38-0.82)	0.66 (0.44-0.86)
		No	2	0.18 (0.02-0.47)	0.99 (0.95-1.00)
Heterogeneity on T1	Total number of lesions	<50	2	0.78 (0.58-0.96)	0.48 (0.02-0.97)
		≥50	1	0.83 (0.46-0.99)	0.49 (0.01-0.99)
	Prevalence MPNST	≤33%	2	0.92 (0.72-0.99)	0.26 (0.03-0.59)
		>33%	1	0.63 (0.38-0.83)	0.91 (0.53-1.00)
	NF1 patients only	Yes	2	0.70 (0.53-0.84)	0.70 (0.38-0.95)
		No	1	1.00 (1.00-1.00)	0.08 (0.02-0.39)
	Symptomatic lesions only	Yes	1	0.70 (0.53-0.84)	0.70 (0.38-0.95)
		No	2	1.00 (1.00-1.00)	0.08 (0.00-0.39)
	Histologically proven only	Yes	2	0.78 (0.58-0.96)	0.48 (0.02-0.97)
		No	1	0.84 (0.46-0.99)	0.49 (0.01-0.99)

Supplementary Table 3 Continued.

Characteristic	Subgroup		N	Pooled accuracies (95% CI)	
				Sensitivity	Specificity
Heterogeneity on T2	Total number of lesions	<50	2	0.65 (0.38-0.86)	0.49 (0.08-0.91)
		≥50	3	0.85 (0.70-0.95)	0.54 (0.15-0.89)
	Prevalence MPNST	≤33%	4	0.77 (0.62-0.88)	0.54 (0.24-0.82)
		>33%	1	0.80 (0.57-0.94)	0.44 (0.05-0.91)
	NF1 patients only	Yes	2	0.89 (0.68-0.98)	0.58 (0.12-0.94)
		No	3	0.72 (0.52-0.87)	0.47 (0.11-0.86)
	Symptomatic lesions only	Yes	0	*NA*	*NA*
		No	4	*NA*	*NA*
	Histologically proven only	Yes	1	0.45 (0.18-0.75)	0.36 (0.02-0.89)
		No	3	0.85 (0.71-0.94)	0.61 (0.24-0.90)
Tumor enhancement	Total number of lesions	<50	4	0.59 (0.43-0.73)	0.88 (0.67-0.98)
		≥50	2	0.74 (0.49-0.91)	0.61 (0.18-0.93)
	Prevalence MPNST	≤33%	4	0.69 (0.52-0.83)	0.70 (0.43-0.89)
		>33%	2	0.56 (0.36-0.74)	0.96 (0.79-1.00)
	NF1 patients only	Yes	2	0.74 (0.49-0.91)	0.61 (0.18-0.93)
		No	4	0.59 (0.43-0.73)	0.88 (0.67-0.98)
	Symptomatic lesions only	Yes	1	0.55 (0.27-0.81)	0.67 (0.52-1.00)
		No	3	0.63 (0.44-0.80)	0.66 (0.41-0.86)
	Histologically proven only	Yes	3	0.52 (0.34-0.68)	0.90 (0.68-0.99)
		No	3	0.76 (0.58-0.89)	0.67 (0.29-0.93)
Intratumoral lobulation	Total number of lesions	<50	3	0.67 (0.48-0.82)	0.86 (0.75-0.94)
		≥50	2	0.40 (0.20-0.64)	0.90 (0.82-0.95)
	Prevalence MPNST	≤33%	3	0.47 (0.28-0.68)	0.91 (0.84-0.95)
		>33%	2	0.67 (0.45-0.84)	0.81 (0.65-0.92)
	NF1 patients only	Yes	3	0.50 (0.31-0.69)	0.89 (0.81-0.94)
		No	2	0.70 (0.43-0.90)	0.87 (0.73-0.90)
	Symptomatic lesions only	Yes	1	0.63 (0.39-0.83)	0.82 (0.60-0.95)
		No	3	0.47 (0.29-0.66)	0.91 (0.85-0.95)
	Histologically proven only	Yes	3	0.67 (0.50-0.81)	0.87 (0.76-0.93)
		No	2	0.41 (0.22-0.62)	0.90 (0.83-0.95)
Absence of split-fat sign	Total number of lesions	<50	2	0.79 (0.55-0.94)	0.52 (0.29-0.77)
		≥50	1	0.70 (0.46-0.88)	0.30 (0.08-0.62)
	Prevalence MPNST	≤33%	1	1.00 (1.00-1.00)	0.33 (0.16-0.54)
		>33%	2	0.69 (0.53-0.83)	0.46 (0.31-0.64)
	NF1 patients only	Yes	1	0.65 (0.33-0.89)	0.75 (0.51-0.91)
		No	2	0.78 (0.59-0.91)	0.30 (0.19-0.44)
	Symptomatic lesions only	Yes	1	0.65 (0.33-0.89)	0.75 (0.51-0.91)
		No	2	0.78 (0.59-0.91)	0.30 (0.19-0.44)
	Histologically proven only	Yes	3	*NA*	*NA*
		No	0	*NA*	*NA*

Supplementary Table 3 Continued.

Characteristic	Subgroup		N	Pooled accuracies (95% CI)	
				Sensitivity	Specificity
Absence of target sign	Total number of lesions	<50	3	1.00 (1.00-1.00)	0.31 (0.11-0.59)
		≥50	4	0.88 (0.70-0.98)	0.35 (0.16-0.58)
	Prevalence MPNST	≤33%	4	0.84 (0.65-0.96)	0.41 (0.20-0.63)
		>33%	3	1.00 (1.00-1.00)	0.24 (0.08-0.49)
	NF1 patients only	Yes	4	0.87 (0.73-0.95)	0.51 (0.42-0.59)
		No	3	1.00 (1.00-1.00)	0.12 (0.06-0.21)
	Symptomatic lesions only	Yes	1	1.00 (1.00-1.00)	0.65 (0.28-0.92)
		No	5	0.90 (0.77-0.97)	0.32 (0.18-0.48)
	Histologically proven only	Yes	4	1.00 (1.00-1.00)	0.22 (0.09-0.40)
		No	3	0.78 (0.55-0.94)	0.48 (0.27-0.71)
Irregular shape	Total number of lesions	<50	3	0.34 (0.10-0.62)	0.80 (0.69-0.88)
		≥50	1	0.50 (0.12-0.88)	0.85 (0.72-0.93)
	Prevalence MPNST	≤33%	3	0.25 (0.10-0.44)	0.84 (0.76-0.90)
		>33%	1	0.77 (0.51-0.93)	0.71 (0.49-0.88)
	NF1 patients only	Yes	2	0.65 (0.25-0.92)	0.80 (0.58-0.93)
		No	2	0.08 (0.00-0.36)	0.83 (0.63-0.95)
	Symptomatic lesions only	Yes	1	0.76 (0.51-0.93)	0.71 (0.48-0.88)
		No	3	0.25 (0.10-0.44)	0.84 (0.76-0.90)
	Histologically proven only	Yes	3	0.34 (0.10-0.62)	0.80 (0.69-0.88)
		No	1	0.50 (0.12-0.88)	0.85 (0.72-0.93)
Tumor size	Total number of lesions	<50	2	0.61 (0.42-0.80)	0.91 (0.83-0.96)
		≥50	1	0.82 (0.59-0.95)	0.72 (0.53-0.86)
	Prevalence MPNST	≤33%	1	0.50 (0.29-0.71)	0.92 (0.84-0.97)
		>33%	2	0.84 (0.68-0.94)	0.77 (0.63-0.88)
	NF1 patients only	Yes	1	0.83 (0.59-0.95)	0.72 (0.53-0.86)
		No	2	0.61 (0.42-0.80)	0.91 (0.83-0.96)
	Symptomatic lesions only	Yes	0	*NA*	*NA*
		No	2	*NA*	*NA*
	Histologically proven only	Yes	2	0.61 (0.42-0.80)	0.91 (0.83-0.96)
		No	1	0.83 (0.59-0.95)	0.72 (0.53-0.86)
Qualitative assessment	Total number of lesions	<50	0	*NA*	*NA*
		≥50	3	*NA*	*NA*
	Prevalence MPNST	≤33%	3	*NA*	*NA*
		>33%	0	*NA*	*NA*
	NF1 patients only	Yes	0	*NA*	*NA*
		No	3	*NA*	*NA*
	Symptomatic lesions only	Yes	0	*NA*	*NA*
		No	2	*NA*	*NA*
	Histologically proven only	Yes	2	0.73 (0.56-0.86)	0.89 (0.80-0.95)
		No	1	0.61 (0.29-0.87)	0.96 (0.89-0.99)

Supplementary Table 3 Continued.

Characteristic	Subgroup		N	Pooled accuracies (95% CI)	
				Sensitivity	Specificity
		PET			
SUVmax	Total number of lesions	<50	5	0.93 (0.84-0.98)	0.88 (0.79-0.94)
		≥50	8	0.95 (0.90-0.98)	0.79 (0.71-0.85)
	Prevalence MPNST	≤33%	6	0.93 (0.87-0.98)	0.77 (0.68-0.85)
		>33%	7	0.95 (0..90-0.98)	0.86 (0.78-0.92)
	Symptomatic lesions only	Yes	4	1.00 (1.00-1.00)	0.81 (0.68-0.92)
		No	5	0.94 (0.84-0.99)	0.80 (0.68-0.89)
	Histologically proven only	Yes	4	0.90 (0.81-0.96)	0.87 (0.71-0.92)
		No	9	0.96 (0.92-0.99)	0.81 (0.74-0.87)
Tumor-to-liver ratio	Total number of lesions	<50	1	0.88 (0.66-0.98)	0.81 (0.54-0.95)
		≥50	6	0.93 (0.88-0.97)	0.79 (0.70-0.86)
	Prevalence MPNST	≤33%	5	0.93 (0.86-0.98)	0.79 (0.68-0.88)
		>33%	2	0.90 (0.73-0.98)	0.77 (0.55-0.92)
	Symptomatic lesions only	Yes	0	*NA*	*NA*
		No	4	*NA*	*NA*
	Histologically proven only	Yes	2	0.90 (0.78-0.97)	0.77 (0.58-0.91)
		No	5	0.93 (0.87-0.97)	0.79 (0.70-0.87)
Qualitative assessment	Total number of lesions	<50	1	1.00 (1.00-1.00)	0.73 (0.38-0.94)
		≥50	4	0.93 (0.86-0.97)	0.83 (0.73-0.91)
	Prevalence MPNST	≤33%	3	0.92 (0.83-0.98)	0.85 (0.72-0.94)
		>33%	2	0.96 (0.84-1.00)	0.72 (0.45-0.91)
	Symptomatic lesions only	Yes	2	0.93 (0.80-0.99)	0.90 (0.78-0.97)
		No	3	0.94 (0.84-0.99)	0.77 (0.65-0.87)
	Histologically proven only	Yes	0	*NA*	*NA*
		No	5	*NA*	*NA*
		PET-CT individual patient-level data			
SUVmax >3.5	Total number of lesions	<50	10	0.91 (0.80-0.98)	0.74 (0.60-0.86)
		≥50	1	1.00 (1.00-1.00)	0.55 (0.17-0.89)
	Prevalence MPNST	≤33%	4	0.76 (0.30-0.98)	0.79 (0.54-0.95)
		>33%	7	0.97 (0.90-1.00)	0.69 (0.49-0.86)
	Symptomatic lesions only	Yes	4	0.72 (0.41-0.94)	0.93 (0.84-0.98)
		No	6	0.98 (0.90-1.00)	0.52 (0.38-0.65)
	Histologically proven only	Yes	4	0.95 (0.77-1.00)	0.59 (0.31-0.84)
		No	7	0.93 (0.78-1.00)	0.78 (0.62-0.91)

CI: credible interval, MPNST: malignant peripheral nerve sheath tumor, MRI: magnetic resonance imaging, N: number of studies, NA: not applicable, NF1: neurofibromatosis type 1, PET-CT: positron emission tomography – computed tomography, SUVmax: maximum standardized uptake volume

7

Non-cytotoxic Systemic Treatment in Malignant Peripheral Nerve Sheath Tumors (MPNST): a Systematic Review from Bench to Bedside

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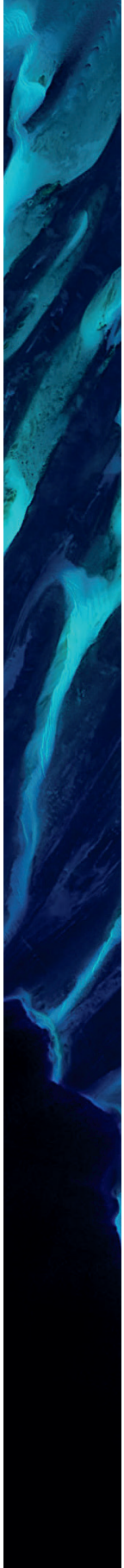

Abstract

Background Malignant peripheral nerve sheath tumors (MPNSTs) are aggressive soft tissue sarcomas. Once metastasized, prognosis is poor despite regular treatment with conventional cytotoxic drugs. This study reviews the preclinical and clinical results of non-cytotoxic systemic therapy in MPNST.

Methods A systematic search was performed in PubMed and Embase databases according to the PRISMA guidelines. Search terms related to 'MPNST', 'targeted therapy', 'immunotherapy', and 'viral therapy' were used. Only *in vivo* studies and clinical trials were included. Clinicaltrials.gov was also searched for any ongoing trials including MPNST patients. Qualitative synthesis was performed on all studies stratifying per target: membrane, cytoplasmic, nuclear, immunotherapy and oncolytic viruses, and other. *In vivo* studies were assessed for treatment effect on tumor growth (low/intermediate/high), survival, and metastases. Clinical trials were assessed on response rate, progression-free survival, and overall survival.

Results After full-text screening, 60 *in vivo* studies and 19 clinical trials were included. A total of 13 trials are ongoing and unpublished. The included trials displayed relatively poor response rates thus far, with patients achieving stable disease at best. Inhibiting cytoplasmic targets most commonly yielded high treatment effect, predominantly after mTOR inhibition. Oncolytic viruses and angiogenesis inhibition also demonstrate intermediate to high effect. Therapies including a combination of drugs were most effective in controlling tumor growth. Several ongoing trials investigate potentially promising pathways, while others have yet to be established.

Conclusion Targeting the PI3K/Akt/mTOR pathway seems most promising in the treatment of MPNSTs. Oncolytic viruses and angiogenesis inhibition represent emerging therapies that require further study. Combinations of targeted therapies are most likely key to maximize treatment effect.

Introduction

Malignant peripheral nerve sheath tumors (MPNSTs) are rare, but aggressive soft tissue sarcomas (STS) with high rates of recurrence and metastasis.[1–3] Almost half of all cases are related to neurofibromatosis type I (NF1), while others occur sporadically or after radiation exposure.[1,4] The *NF1* gene is commonly affected in MPNSTs causing the loss of neurofibromin, a Ras inhibiting enzyme.[5] Ras activation results in the downstream activation of Ras pathways, leading to upregulation of mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K).[6] However, loss of neurofibromin alone is not enough to cause an MPNST.[7] Research over the last three decades has implicated multiple factors in the pathogenesis of MPNSTs, including loss of function in *TP53*, *CDKN2A*, *SUZ12*, and *PTEN* genes, as well as amplification of epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), and MET.[8–12] Despite our increased understanding of the complex biology underlying MPNSTs, prognosis has remained poor, with 5-year survival rates ranging from 30-60% in patients who have undergone curative surgery of their tumor, and even lower rates in those with advanced and metastatic disease.[1–3,13]

Surgery with wide negative margins remains the mainstay treatment for MPNST.[1,3] Radiotherapy is commonly used either postoperatively or in a neoadjuvant setting as it improves local control, but does not affect overall survival.[1,14,15] In a study investigating neoadjuvant chemotherapy, histotype-guided treatment of four STS types, including MPNST (this cohort was treated with etoposide-ifosfamide), has not shown any benefit compared to standard anthracycline based chemotherapy.[16] Therefore, there has thus far been no rationale for treating MPNST differently from other STS. Neoadjuvant chemotherapy could be considered for high-grade, large, and deep MPNST,[16,17] and may allow initially inoperable patients to become operable.[2,18] However, over 10% of MPNST patients present with unresectable or metastatic disease.[2,3,19] Additionally, 40-60% of patients receiving treatment with curative intent will develop metastatic disease.[19–21]

For the whole group of STS, first line palliative chemotherapy consists of an anthracycline (doxorubicin or epirubicin) containing schedule. This might be combined doxorubicin and ifosfamide or doxorubicin monotherapy. Overall, a clinical response rate of approximately 21% has been reported for MPNST treated with combined doxorubicin and ifosfamide.[18] Adding ifosfamide to doxorubicin has improved progression-free survival (PFS), but not overall survival (OS), and comes at the cost of increased toxicity.[22]

The high rates of advanced and metastatic disease and poor response to standard chemotherapy highlight the need for novel therapies in the treatment of MPNST. Targeted therapy and immunotherapy has brought new options to many other cancer types, but is not yet established in STS in general or MPNST specifically. Especially target specific, non-cytotoxic treatments are of interest as they may specifically

target tumors and have limited systemic side-effects. As insights in the differences between STS subtypes are growing, more specific testing to allow for identification and subsequent personalization of treatment is necessary; however, given that MPNST represent a rare sarcoma subtype, such personalization has thus far been challenging. To better understand emerging treatment options, we pooled the available literature and performed a systematic review of non-cytotoxic systemic therapies in MPNST, aiming to guide future research efforts by identifying the most relevant targets and combinations.

Methods

Literature search

A systematic search was performed in both PubMed and Embase databases according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, in order to identify all potentially relevant articles published from 2000-2018. The search string was built with the help of a professional librarian using search terms related to 'MPNST' and non-cytotoxic treatments. The exact search syntaxes for PubMed and Embase are provided in Supplemental Table S1. Preclinical studies were included if they studied non-cytotoxic drugs on MPNSTs *in vivo*. Clinical studies were included if they presented results of non-cytotoxic systemic therapy specifically in MPNST patients. Articles were excluded if they were retrospective or single case studies, reviews, presented non-specific MPNST data, included data on cytotoxic drugs or drugs that were only tested *in vitro*, or did not provide data on tumor growth, survival, or metastases. Clinicaltrials.gov was also searched with synonyms of 'MPNST' to obtain all ongoing non-cytotoxic drug trials enrolling MPNST patients. Cross-referencing of included papers and registered trials was performed, which identified six additional papers. These studies did not include a synonym of MPNST in either their title or abstract. The initial review was carried out by two independent authors (EM, NL). Disagreements were solved through discussion, in which one additional senior author was involved (ID).

Data extraction and synthesis

Data extracted from preclinical studies included: animal model used, most effective treatment regimen studied, tissues investigated, and treatment effect on tumor growth, survival, and metastasis. The treatment effect on tumor growth was evaluated according to the mean relative tumor volume (RTV) comparing the latest mean volume measurement of the control group (C) to the mean volume of the treatment group (T) at that time point:[23,24] T/C ≤15% represented high effect (black); T/C ≤45% but >15% represented intermediate effect (dark gray); and T/C >45% represented low effect (light gray, **Table 1**). Tumor growth was either assessed by tumor volume, weight, or area. Drugs were categorized as membrane targets, cytoplasmic targets, nuclear targets,

immunotherapy and oncolytic viruses, or other targets. Data extracted from clinical trials included: study design, number of patients, age of population, treatment regimen, and treatment effect on response rate, PFS, and OS. Study phase, country, intervention, anticipated accrual, and end date were extracted from registered unpublished trials. Qualitative synthesis was performed summarizing data from preclinical and clinical studies according to target pathway, immunotherapy and oncolytic viruses, and a rest group.

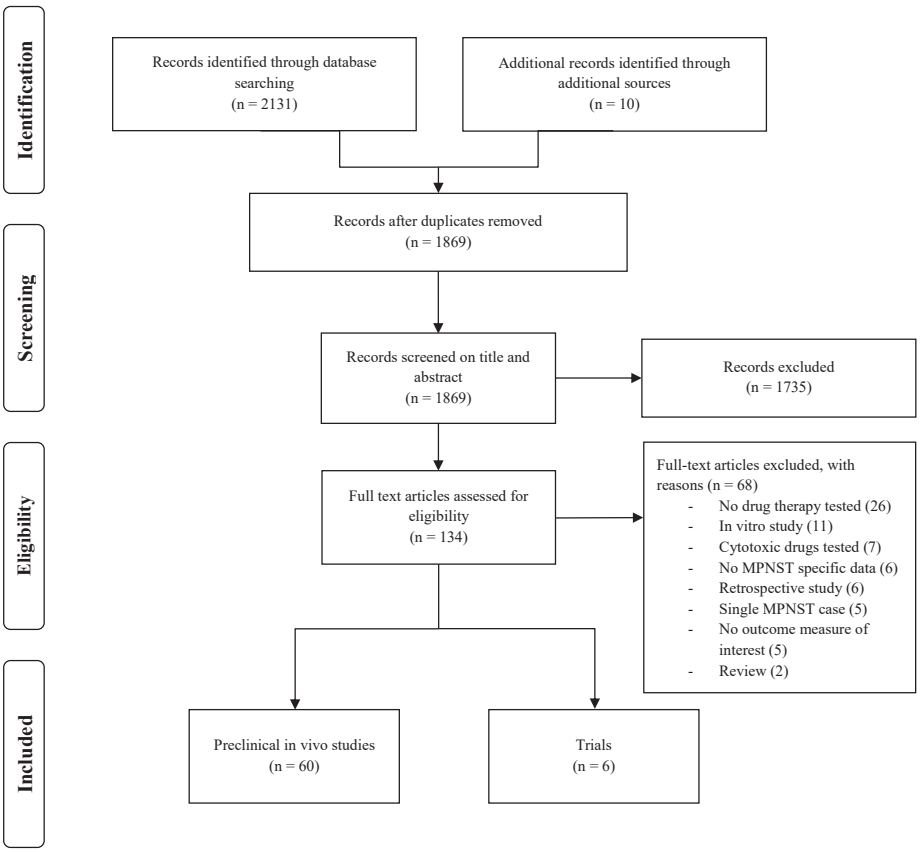

Figure 1 Flowchart depicting study selection

Results

Following removal of duplicates, a total of 1938 articles and registered trials were identified in PubMed and Embase databases. Title/abstract screening resulted in selection of 203 potentially relevant articles, of which sixty-six were selected for qualitative synthesis after full-text screening (**Figure 1**). A total of sixty preclinical *in*

vivo studies were found that used numerous genetically engineered mouse models (GEMM), (non)-cultured NF1 and sporadic patient xenografts, allografts from GEMMs, and one zebrafish model (**Table 1**). Nineteen trials were identified, of which six have already been published (**Table 2**), and thirteen are ongoing (**Table 3**). Figure 2 presents the most important target pathways identified in MPNSTs.

Membrane targets – in vivo

Eight studies investigated membrane targets *in vivo* (**Table 1**). Six used receptor tyrosine kinase (RTK) targeted treatments with intermediate to high effect on tumor growth.[25–30] The addition of verteporfin (TAZ/YAP inhibitor) to sorafenib yielded intermediate effects on tumor growth in an allograft model, while monotherapy of either drugs had significantly worse effects.[28] The chemokine receptor CXCR4 stimulates cell cycle progression through PI3K and β-catenin signalling. In one *in vivo* study, inhibition of CXCR4 showed intermediate effect on tumor growth and increased survival of mice.[29] Two *in vivo* studies investigated the effect of estrogen receptor blockade; one found a low effect on tumor growth,[31] and another showed that the addition of a calmodulin inhibitor enhanced the effect on tumor growth.[32]

Membrane targets – trials

Four published clinical trials investigating the effect of an RTK inhibitor, of which one[33] specifically examined MPNST patients (**Table 2**), were identified. None of the trials found an appreciable clinical response in MPNST patients, with only 0-20% of the patients achieving stable disease.[33–36] Four additional trials were still ongoing at the time this review was written, one of which will only include MPNST patients. This study will evaluate the efficacy

of the multikinase inhibitor pexidartinib in combination with mTOR inhibitor sirolimus (NCT02584647, **Table 3**). Multiple other trials were identified that will enroll patients with soft tissue sarcomas (NCT02584309, NCT02180867) and CD56 expressing tumors (NCT02452554) targeting additional membrane targets. One of these trials will investigate the effect of doxorubicin and ifosfamide with the addition of pazopanib, currently the only registered RTK inhibitor for STS, in a neoadjuvant setting including patients with resectable soft tissue sarcomas (NCT02180867).

Table 1 Preclinical in vivo studies.

Author, year	Model	Regimen	Pathway	Tissue	NF1[a]	Outcome		
						Growth[b]	Survival[c]	Metastasis[d]
			Membrane targets					
Johansson, 2008	XM	Erlotinib + sirolimus	EGFR, mTOR	STS26T	S		*NA*	*NA*
Byer, 2011	OXM	Tamoxifen	ER	ST88-14	NF1		*NA*	*NA*
Torres, 2011	XM	Cabozantinib	Multikinase (incl. MET, VEGFR2)	STS26T	S		*NA*	
				MPNST724	S		*NA*	*NA*
Mo, 2013	AA, GEMM	AMD3100	CXCR4	sMPNST	*NA*		*NA*	*NA*
				NPcis	*NA*	*NA*		*NA*
Ohishi, 2013	XM	Imatinib	Multikinase (incl. c-Kit)	HS-Sch-2	S		*NA*	*NA*
				FMS-1	NF1		*NA*	*NA*
				NMS-2PC	NF1		*NA*	*NA*
Brosius, 2014	OXM	Tamoxifen + trifluoperazine	ER, calmodulin	ST88-14	NF1		*NA*	*NA*
				STS26T	S		*NA*	*NA*
Patwardhan, 2014	XM	Pexidartinib + sirolimus	Multikinase (incl. c-Kit), mTOR	MPNST	*NA*		*NA*	*NA*
Castellsague, 2015	OXM	Sorafenib + doxorubicin/ sirolimus	Multikinase (incl. VEGFR), mTOR	NF1-001	NF1		*NA*	*NA*
				NF1-002	NF1		*NA*	*NA*
				SP-001	S		*NA*	*NA*
				SP-002	S		*NA*	*NA*
				S462	NF1		*NA*	*NA*
Lock, 2016	GEMM	Cabozantinib + PD0325901	Multikinase (incl. MET, VEGFR2), MEK	NPcis	*NA*		*NA*	*NA*
Ki, 2017	ZFM	Sunitinib	Multikinase (incl. VEGFR)	*NF1a*$^{+/-}$; *NF1b*$^{-/-}$;*p53*$^{m/m}$	*NA*		*NA*	*NA*
Wu, 2018	AA	Sorafenib + verteporfin	Multikinase (incl. VEGFR), TAZ/YAP	*Lats1/2*$^{-/-}$	*NA*		*NA*	*NA*

Table 1 Continued.

Author, year	Model	Regimen	Pathway	Tissue	NF1[a]	Outcome		
						Growth[b]	Survival[c]	Metastasis[d]
			Cytoplasmic targets					
Hirokawa, 2006	XM	Sichuan	PAK1	S462	NF1		*NA*	*NA*
Johannessen, 2008	GEMM	Sirolimus	mTOR	NPcis	*NA*		*NA*	*NA*
Demestre, 2009	XM	Bio 30 + CAPE	PAK1	S462	NF1		*NA*	
Lee, 2009	XM	OSU03012	PDK1	HMS-97	S		*NA*	*NA*
Qi, 2009	XM	Saposin C protein	Lysosomes	STS26T	S		*NA*	*NA*
Banerjee, 2010	XM	Cucurbaticin-1	STAT3	ST88-14	NF1		*NA*	*NA*
Bhola, 2010	XM	Sirolimus	mTOR	*NA*	NF1		*NA*	*NA*
De Raedt, 2011	GEMM	Sirolimus + IPI-504	mTOR, Hsp90	NPcis	*NA*			*NA*
Ghadimi, 2012	XM	Voxtalisib + chloroquine	PI3K, mTOR, autophagy	MPNST724	S		*NA*	*NA*
				STS26T	S		*NA*	
Dodd, 2013	GEMM	PD0325901	MEK	*NF1*$^{fl/fl}$; *Ink4a/Arf*$^{fl/fl}$	*NA*		*NA*	*NA*
Jessen, 2013	XM	PD0325901	MEK	S462TY	NF1			*NA*
Brundage, 2014	XM	Everolimus	mTOR	S462TY	NF1		*NA*	*NA*
De Raedt, 2014	GEMM	PD0325901 + JQ1	MEK, BET	NPcis; *SUZ12*$^{-/-}$	*NA*		*NA*	*NA*
				NPcis	*NA*		*NA*	*NA*
Malone, 2014	GEMM	Sirolimus + PD0325901	mTOR, MEK	NPcis	*NA*		*NA*	*NA*
Watson, 2014	GEMM	Everolimus + PD0325901	mTOR, MEK	*NF1*$^{fl/fl}$; *Pten*$^{fl/fl}$	*NA*	*NA*		*NA*
				Pten$^{fl/fl}$; *EGFR*	*NA*	*NA*		*NA*
Wu, 2014	XM	FLLL32	JAK2/STAT3	S462TY	NF1		*NA*	*NA*
Yamashita, 2014	XM	Everolimus + bortezomib	mTOR, proteasome	NF90.8	NF1		*NA*	*NA*
Slotkin, 2015	XM	Sapanisertib + sirolimus	mTOR	MPNST	*NA*		*NA*	*NA*
Kendall, 2016	XM	PD0325901	MEK	S462TY	NF1			*NA*
Sweeney, 2016	AA	PD0325901 + PTT	MEK	M2	*NA*			*NA*

Table 1 Continued.

Author, year	Model	Regimen	Pathway	Tissue	NF1[a]	Outcome		
						Growth[b]	Survival[c]	Metastasis[d]
Malone, 2017	GEMM	Sapanisertib + panobinostat	mTOR, HDAC	NPcis	*NA*		*NA*	*NA*
Semenova, 2017	XM	Frax1036 +/- PD0325901	PAK1, MEK	S462TY	NF1		*NA*	*NA*
				STS26T	S		*NA*	
Nuclear targets								
Hirokawa, 2005	XM	Depsipeptide	HDAC	S805	NF1		*NA*	*NA*
Lopez, 2011	XM	Abexinostat + chloroquine	HDAC, autophagy	MPNST642	NF1		*NA*	*NA*
				MPNST724	S		*NA*	*NA*
				STS26T	S		*NA*	
Patel, 2012	XM	Alisertib	AURKA	S462TY	NF1			*NA*
Mohan, 2013	XM	Alisertib	AURKA	NF1-MPNST	NF1		*NA*	*NA*
				SP-MPNST	S		*NA*	*NA*
Patel, 2014	AA	JQ1	BET	sMPNST	*NA*		*NA*	*NA*
Lopez, 2015	AA	PCI-48012	HDAC8	MPNST6IEPVI	*NA*		*NA*	*NA*
Nair, 2015	XM	TAK-960	PLK1	MPNST	*NA*		*NA*	*NA*
Perez, 2015	XM	Palbociclib	CDK4/6	S14	*NA*			*NA*
Zhang, 2015	XM	DZNep	EZH2	MPNST724	S		*NA*	*NA*
Kivlin, 2016	XM	Olaparib	PARP	STS26T	S			*NA*
				MPNST724	S		*NA*	*NA*
Nair, 2017	XM	Selinexor + carfilzomib	XPO1, proteasome	MPNST	*NA*		*NA*	*NA*
Payne, 2018	OXM	Alisertib	AURKA	STS26T	S	*NA*		*NA*
Immunotherapy and oncolytic viruses								
Liu, 2006	AA	G47Δ-PF4	oHSV	M2	*NA*			*NA*
Liu, 2006	AA	G47Δ-dnFGFR	oHSV	M2	*NA*		*NA*	*NA*
Mahller, 2007	XM	hrR3	oHSV	STS26T	S			*NA*
Mahller, 2008	XM	rQT3	oHSV	STS26T	S		*NA*	*NA*
				S462TY	NF1			*NA*
Maldonado, 2010	XM	oHSV-MDK-34.5	oHSV	STS26T	S			*NA*

Table 1 Continued.

Author, year	Model	Regimen	Pathway	Tissue	NF1[a]	Outcome		
						Growth[b]	Survival[c]	Metastasis[d]
Antoszczyk, 2014	OXM, AA	G47Δ-IL12/PF4	oHSV	S462	S			*NA*
				M2	*NA*			*NA*
				M3	*NA*			*NA*
Deyle, 2015	XM	MV-NIS	oMV	ST88-14	NF1			*NA*
				S462TY	NF1			*NA*
Currier, 2017	XM	HSV1716 + alisertib	oHSV, AURKA	S462TY	NF1			*NA*
			Other					
Mashour, 2005	AA	DHA	Apoptosis	32-5-30	*NA*			*NA*
Ghadimi, 2012	XM	Sepantromium bromide	Survivin	MPNST724	S		*NA*	*NA*
				STS26T	S		*NA*	
Wang, 2012	XM	Triptolide	Apoptosis	STS26T	S		*NA*	*NA*
Demestre, 2013	XM	PEDF	Multi-antitumor	S462	NF1		*NA*	*NA*
Patel, 2015	XM	C75	FAS	STS26T	S		*NA*	*NA*
Zewdu, 2016	XM	Verticillin A	Apoptosis	MPNST724	S		*NA*	*NA*
Ikuta, 2017	XM	MU	Hyaluronan synthesis	sNF96.2	NF1		*NA*	*NA*
Semenova, 2017	XM	Nifedipine	Ca^{2+}-channel	S462TY	NF1		*NA*	*NA*

[a]: NF1 patient cells or sporadic patient cells, [b]: either volume, weight, or area, low activity (light gray), intermediate activity (dark gray), high activity (black), [c]: increased survival (black) [d]: less metastases (black)

AA: auto- and/or allograft mouse model, AURKA: aurora kinase A, BET: bromo- and extra-terminal domain, CAPE: caffeic acid phenethyl ester, CDK: cyclin-dependent kinase, CXCR4: CXC-chemokine receptor 4, DHA: docosahexaenoic acid, DZNep: 3-deazaneplanocin A, EGFR: epidermal growth factor receptor, ER: estrogen receptor, EZH2: enhancer of zeste homolog 2, FAS: fatty acid synthase, GEMM: genetically modified mouse model, HDAC: histone deacetylase, Hsp90: heat shock protein 90, JAK2: Janus kinase 2, MEK: mitogen-activated protein kinase kinase, MPNST: malignant peripheral nerve sheath tumor, mTOR: mammalian target of rapamycin, MU: 4-methylumbelliferone, NA: not applicable/available, NF1: neurofibromatosis type 1, NPcis: mutation of NF1 and p53 gene on both alleles, oHSV: oncolytic herpes simplex virus, oMV: oncolytic measles virus, OXM: orthotopic xenograft mouse model, PARP: poly (ADP-ribose) polymerase, PEDF: pigment epithelium-derived factor, PDK1: phosphoinositide-dependent kinase-1, PDX: patient-derived xenograft, PI3K: phosphoinositide 3-kinase, PLK1: polo-like kinase 1, PTT: phototermal therapy, S: sporadic, STAT3: signal transducer and activator of transcription 3, XM: xenograft mouse model, XPO1: exportin 1, ZFM: genetically engineered zebrafish model

Cytoplasmic targets – in vivo

Cytoplasmic targets were investigated in 25 *in vivo* studies (**Table 1**). Most studies (n = 22) focused on a target within the MAPK or the PI3K/Akt/mTOR pathway. In those targeting the PI3K/Akt/mTOR pathway, a high effect on tumor growth (14/17 cell lines) and survival was observed (3/3 cell lines). Targeting mTOR in combination with membrane targets,[37–39] other cytoplasmic targets,[40–42] or an epigenetic target[43] showed high effect on tumor growth (8/8 cell lines) and survival (3/3 cell lines). One study found a higher effect of pexidartinib compared to imatinib as an addition to mTOR inhibition.[38] The addition of sorafenib (targets include VEGFR, PDGFR, and Raf) to an mTOR inhibitor showed the best effect on tumor size in NF1-mutated xenografts, while the addition of doxorubicin showed best effects in sporadic patient xenografts.[39] The addition of a proteasome inhibitor to mTOR inhibition was only effective if radiotherapy was administered as well.[44] The addition of a mitogen-activated protein kinase (MEK) inhibitor to mTOR inhibition did not prolong survival in a murine model, but did decrease toxicity compared to single agent usage.[42] MEK inhibition itself did not show high effects on tumor growth;[45–48] however in combination with other target inhibitors the effect on tumor growth improved (5/5 cell lines).[8,30,49] The addition of silmasertib, an epigenetic modulator of CK2, did not have a superior effect over MEK-inhibiting monotherapy.[47] PAK1 influences the MAPK pathway by activating MEK and ERK. In multiple studies, inhibition of PAK1 resulted in intermediate to high effects on tumor growth as a single drug.[49–51] One study showed that the addition of a MEK inhibitor to a PAK1 inhibitor increased its effect in both NF1 and sporadic cell lines.[49] Although EGFR inhibitors in MPNST have shown poor results in clinical studies, downstream inhibition of Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) showed intermediate to high effect *in vivo*.[52,53]

Cytoplasmic targets – trials

One trial evaluating the effect of mTOR inhibition in combination with bevacizumab, a VEGF inhibitor, demonstrated stable disease in 3/25 patients.[54] A total of three trials that were ongoing at the time of this review were investigating the role of an mTOR inhibitor in combination with a MEK inhibitor (NCT03433183), pazopanib (NCT02601209), or heat shock protein 90 (Hsp90) inhibitor (NCT02008877, **Table 3**). The latter trial was completed, although its results were not yet published.

Nuclear targets – in vivo

The effect of nuclear target inhibitors was investigated in twelve studies, identifying this class of drugs to have intermediate to high effects on tumor growth (**Table 1**). Multiple studies found a high effect on survival (4/4 cell lines) or tumor growth (5/15 cell lines) via *in vivo* inhibition of several epigenetic pathways.[55–63] Aurora kinase A (AURKA) is one of these epigenetic regulators, which regulates centrosome maturation and chromosome separation. Alisertib, an AURKA inhibitor was found to have a higher effect on tumor growth and survival compared to a combination of doxorubicin and ifosfamide *in vivo*.[63]

CDK4/6 and EZH2 act via influence on the cell cycle; *in vivo* studies showed that their inhibition has intermediate effect on tumor growth.[64,65] XPO1 is the main nuclear export protein and transports proteins such as survivin. One *in vivo* study found intermediate effect of XPO1 inhibition combined with proteasome inhibitor carfilzomib.[66]

Table 2 Published clinical trials.

Author, year	Study Design	N	Age	Drug	Pathway	Outcome		
						RR	PFS	OS
Membrane targets								
Albritton, 2006	Phase II unresectable or metastatic MPNST	20	≥18	Erlotinib	EGFR	1 SD, 19 PD	2 months	4 months
Chugh, 2009	Phase II metastatic or recurrent sarcomas	5	≥10	Imatinib	Multikinase (incl. c-Kit)	1 SD, 4 PD	*NA*	*NA*
Maki, 2009	Phase II metastatic or recurrent sarcomas	12	≥18	Sorafenib	Multikinase (incl. VEGFR)	3 SD, 9 PD	1.7 months	4.9 months
Schuetze, 2016	Phase II high-grade, advanced sarcomas	14	≥13	Dasatinib	Multikinase (incl. BCR/ABL)	14 PD	2-month: 14% 4-month: 7%	*NA*
Cytoplasmic targets								
Widemann, 2016	Phase II recurrent or metastatic MPNST	25	≥18	Everolimus + Bevacizumab	mTOR, VEGF	3 SD, 22 PD	*NA*	*NA*
Nuclear targets								
Dickson, 2016	Phase II advanced or metastatic sarcomas	10	≥18	Alisertib	AURKA	No response (SD and PD)	13 weeks, 12-week: 60%	69 weeks

AURKA: aurora kinase A, CI: confidence interval, CR: complete remission, EGFR: endothelial growth factor receptor, mTOR: mammalian target of rapamycin, N: total MPNST patients included, NA: not available, OS: overall survival, PD: progressive disease, PFS: progression free survival, RR: response rate, SD: stable disease, VEGF: vascular endothelial growth factor, VEGFR: vascular endothelial growth factor

Table 3 Ongoing clinical trials.

NCT number	Country	Phase	Tumor type	N	Age	Drug	Pathway	Completion date
			Membrane targets					
NCT02584647	US	I II	STS MPNST	49	≥18	Pexidartinib + sirolimus	Multikinase, mTOR	10-2021
NCT02452554	US	II	CD56 expressing tumors (MPNST)	114	1-30	Lorvotuzumab mertansine	CD56	03-2020
NCT02584309	US	II	STS (MPNST)	73	≥18	Doxorubicin + olaratumab	Anthracycline, PDGFRα	10-2023
NCT02180867	US	II/III*	STS (MPNST)	340	≥2	Doxorubicin + ifosfomide +/-pazopanib	Multikinase, anthracycline, alkylans	12-2018
			Cytoplasmic targets					
NCT03433183	US	II	MPNST	21	≥18	Vistusertib + selumetinib	mTOR, MEK	09-2021
NCT02008877	US	I/II	MPNST	20	≥16	Sirolimus + ganetespib	mTOR, Hsp90	07-2018
NCT02601209	US	I II	STS STS (MPNST)	137	≥18	Sapanisertib +/- pazopanib	mTOR, multikinase	09-2020
			Nuclear targets					
NCT02986919	US	II	MPNST	24	≥18	CPI-0610	BET	03-2020
NCT03009201	US	IB	STS (MPNST)	36	≥12	Ribociclib + doxorubicin	CDK4/6, anthracycline	12-2020
			Immunotherapy and oncolytic virus					
NCT02691026	Norway	II	MPNST	18	≥18	Pembrolizumab	PD1	12-2025
NCT02834013	US	II	Rare tumors (MPNST)	707	≥18	Nivolumab + ipilimumab	PD1, CTLA4	08-2020
NCT02700230	US	I	MPNST	30	≥18	MV-NIS	oMV	06-2021
NCT00931931	US	I	Non-CNS solid tumors (MPNST)	18	7-30	HSV1716	oHSV	03-2018

*: neoadjuvant in resectable disease
BET: bromo- and extra-terminal domain, CDK: cyclin-dependent kinase, CNS: central nervous system, Hsp90: heat shock protein 90, M: months, MEK: mitogen-activated protein kinase kinase, MPNST: malignant peripheral nerve sheath tumor, mTOR: mammalian target of rapamycin, N: accrual of patients, oHSV: oncolytic herpes simplex virus, oMV: oncolytic measles virus, PD1: programmed cell death protein 1, PDGFRα: platelet-derived growth factor receptor alpha, STS: soft tissue sarcoma, US: United States

Nuclear targets – trials

Although in a preclinical setting alisertib showed positive results, a trial that included ten MPNST patients found no tumor response (**Table 2**).[67] Median PFS was thirteen weeks, with a median OS of sixty-nine weeks. A trial that was ongoing at time of publication was investigating the effect of a bromo- and extra-terminal domain (BET) inhibitor in advanced or metastatic MPNST patients (NCT02986919, **Table 3**).An ongoing phase Ib trial enrolling patients with MPNSTs, among other soft tissue sarcomas, is investigating the effect of ribociclib, a CDK4/6 inhibitor, combined with doxorubicin (NCT03009201).

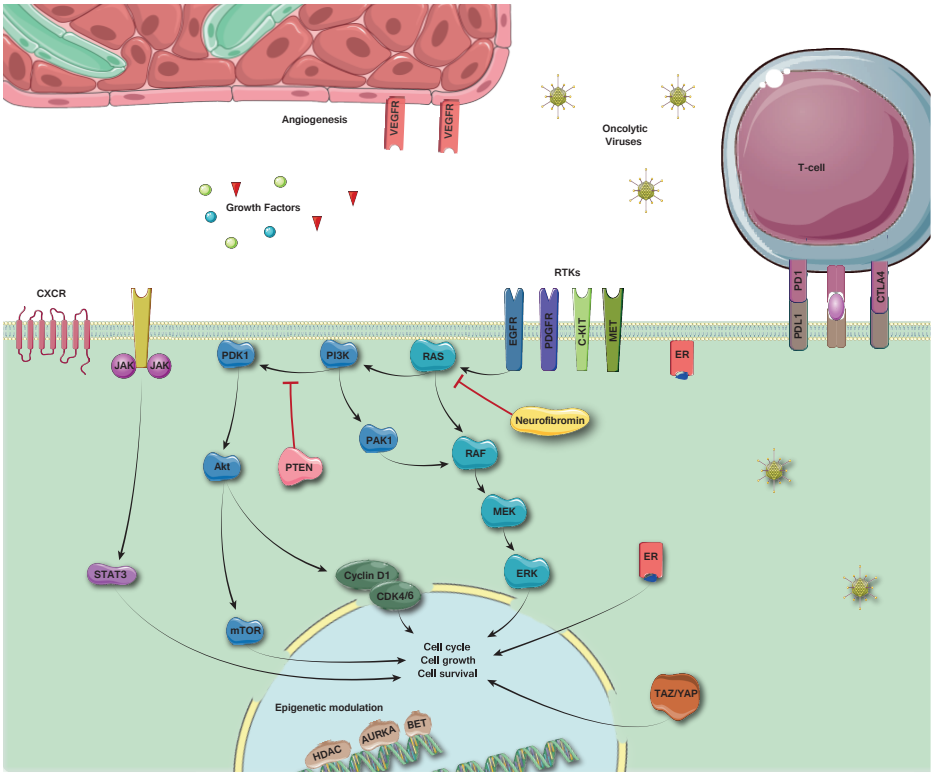

Figure 2 Cellular pathways in MPNST. AURKA: aurora kinase A; BET: bromo- and extra-terminal domain; CDK: cyclin-dependent kinase; CTLA4: cytotoxic T-lymphocyte associated protein 4; CXCR: CXC-chemokine receptor; EGFR: epidermal growth factor receptor; ER: estrogen receptor; ERK: extracellular signal-regulated kinases; HDAC: histone deacetylase; JAK: Janus kinase; MEK: mitogen-activated protein kinase kinase; mTOR: mammalian target of rapamycin; PD1: programmed cell death protein 1; PDGFR: platelet-derived growth factor receptor; PDK1: phosphoinositide-dependent kinase-1; PDL1: programmed death-ligand 1; PI3K: phosphoinositide 3-kinase; PTEN: phosphatase and tensin homolog; STAT3: signal transducer and activator of transcription 3; VEGFR: vascular endothelial growth factor receptor

Immunotherapy and oncolytic viruses – in vivo

Next to tumor cell specific targeting, immunotherapy may also play a role in MPNST treatment. With an evolving role in other cancer types, no *in vivo* studies have thus far been published investigating immunotherapy regimens specifically in MPNST. Oncolytic viruses are thought to affect tumors in several ways, one of which involves the upregulation of the immune system. Eight studies investigated the effect of oncolytic viruses in MPNST *in vivo* (**Table 1**). Seven studies used an oncolytic herpes simplex virus (oHSV) with mostly intermediate to high effect (10/12 cell lines) on tumor growth.[68–74] One study used an oncolytic measles virus (oMV) and showed high efficacy in one xenograft model, but low effect in another.[75] Almost all studies looked at survival and showed a statistically significant benefit for treatment with oncolytic viruses

compared to a placebo control group. The addition of erlotinib, an EGFR inhibitor, did not significantly improve the efficacy compared to oHSV monotherapy *in vivo*.[70] However, additional AURKA inhibition was found to have a synergistic effect on both tumor growth and survival.[74]

Immunotherapy and oncolytic viruses –trials

Two ongoing trials are investigating the role of PD1 checkpoint inhibitors (**Table 3**): one looks at PD1 inhibitors alone and includes MPNST patients only (NCT02691026), while the other study combines the PD1 inhibitor nivolumab with CTLA-4 inhibitor ipilimumab and includes patients with rare tumors, one of which is MPNST (NCT02834013). No clinical trial has yet evaluated the effect of oncolytic viruses in MPNSTs. Two trials are registered of which one will use an oMV in MPNST patients only (NCT02700230) and the other, which is complete and whose results are pending, investigated the effect of an oHSV in non-central nervous system (CNS) solid tumors including MPNSTs (NCT00931931, **Table 3**).

Other targets – in vivo

Eight studies investigated other types of drugs, targeting different pathways including fatty acid synthase (FAS),[76] pigment epithelium-derived factor (PEDF),[77] calcium channels,[78] survivin,[79] hyaluronan synthesis,[80] and other apoptosis-inducing pathways (**Table 1**).[81–83] Most studies found an intermediate effect on tumor growth (6/9 cell lines), and only verticillin A and PEDF were found to have a high effect on tumor growth.[77,83] Docosahexaenoic acid (DHA) showed an intermediate effect on tumor growth, but increased survival significantly.[81] None of these drugs has yet been established in a trial setting that includes MPNST patients.

Discussion

MPNST still remains a highly aggressive sarcoma subtype with poor outcome despite regular cytotoxic treatment. Novel strategies to target metastatic MPNST and improve its outcomes, both in terms of survival as well as quality of life, are needed. In locally advanced disease, neoadjuvant treatment that can downsize the primary tumor and allow for subsequent surgical resection is also of value. In this review, we sought to describe new approaches to treat advanced MPNST. Multiple membrane, cytoplasmic, and nuclear actors are potential targets in the therapy of MPNST, of which mTOR inhibition is most commonly investigated *in vivo* and has frequently resulted in high responses on tumor growth (81.3% of cell lines) and survival (100% of cell lines).

Targeted therapies

In vivo, RTK inhibitors that include VEGFR inhibition have also shown intermediate to high responses. However, monotherapy with an RTK inhibitor has not shown tumor

regression clinically in MPNSTs except for a modest prolongation of median progression free survival in case of pazopanib treatment in all types STS.[84] Apart from two *in vivo* studies using cabozantinib, no other study has yet investigated the effect of MET inhibition, although it is a known contributor to malignancy in MPNSTs. RTK inhibitors targeting both the VEGF pathway as well as other pathways, or combinations with other treatment types might therefore be of interest. Unfortunately, although MPNSTs are Ras-driven tumors, no drug has yet been found to successfully target Ras. Ras inhibitors are difficult to create due to a lack of well-defined druggable pockets and cavities on its surface.[85] Targeting upregulated downstream targets of Ras is nevertheless possible. Besides upregulation of the PI3K/Akt/mTOR pathway, upregulation of the MAPK pathway in NF1 tumors has been described several times.[6] In this review we described the potential of mTOR inhibitors, which might be increased by the current development of more specific inhibitors of elements of the mTOR pathway. Although single agent MEK inhibition has not resulted in tumor suppression,[45–47] combinations with mTOR inhibitors might prove potent in terms of anti-tumorigenic effects, but at the cost of increased toxicity.[30,41] The, translationally controlled tumor protein (TCTP), a downstream effector of both the MAPK and mTOR, can be successfully inhibited leading to cell death in NF1-associated tumors.[86] and was found to increase mTOR activity when upregulated, indicating a positive feedback loop. *In vivo* studies on MPNST models are, however, still warranted. Other targets of interest identified in this review are PAK1 inhibitors,[49–51] as well as PI3K inhibitors. ERK inhibitors are being developed as well, which may have less toxicity, but their effect on MPNST cells is still unknown.[87]

Immunotherapy

While checkpoint inhibitors are gaining interest in other types of tumors, they have yet to be extensively studied in STS. Two ongoing trials will hopefully elucidate the role of these types of drugs in MPNST (NCT02691026, NCT02834013). Oncolytic viruses are showing efficacy without severe toxicity in various cancers including MPNSTs.[88,89] Moreover, as demonstrated for other tumors, an additional pathway inhibitor may give a synergistic effect when combined with oncolytic viruses.[74] Overall, while therapies with oncolytic viruses appear promising in MPNST, more *in vivo* studies are needed to better understand their role as well at the role for any treatment combinations.

Progress in systemic treatment

The lack of progress in the treatment of MPNST is multi-factorial. First, adequate preclinical models representing both NF1-associated MPNSTs as well as sporadic MPNSTs are lacking. The causal mechanisms behind NF1-associated MPNST may differ from those in sporadic MPNST, resulting in different sensitivity for treatment. This is supported by the fact that in conventional chemotherapy, NF1 patients are known to have a lower response rate.[2,17,90] However, only few *in vivo* studies show a difference in response on tumor growth between NF1 and sporadic patient-derived models, while others show no difference. Thus, clinical translation of these differences might

be difficult and should ultimately be assessed in clinical trials. Second, the preclinical data have to be robust before performing a clinical trial. For example, Albritton et al. based their trial on evidence found from one *in vitro* study.[91] It is reasonable to consider *in vitro* studies by themselves as weaker evidence compared to *in vivo* studies, and it is therefore unsurprising that such studies might not effectively translate to the clinical setting.[92] Third, most studies include all types of STS since it is challenging to perform a trial in a disease as rare as MPNST. In this review, four out of the six identified studies were performed in all types of soft tissue sarcomas, for which preclinical evidence was not necessarily found in MPNSTs specifically. The investigators should however be applauded for their efforts in performing histotype subanalyses, although likely underpowered, as certain histological subtypes might well be more sensitive to a particular drug therapy than others. Finally, as suggested by the present review that is based on *in vivo* evidence, a combination of different drugs is likely to be more potent in MPNST patients compared to monotherapy. However, many of the published trials only investigated single targeted therapy.

Strengths and limitations

Unfortunately, quantitative comparison between different studies investigating different treatments *in vivo* was not fully feasible. To date, no tool has been established that shows high reliability of translating preclinical outcomes into clinical evidence, limiting the ability to make direct comparisons between preclinical studies. Despite the challenges in drawing quantitative comparisons across studies, assessing treatment effect by stratifying outcomes into low, intermediate, and high effect has been successfully done previously.[23] Overall, despite these limitations, to our knowledge, the current article represents the largest review to date to pool the available literature on in vivo therapies for MPSNT. By assessing various animal models and treatment regimens through a descriptive systematic review, we aimed to facilitate treatment-related decisions in patients with MPNST.[93] For now, such animal studies serve as the cornerstone to the advancement of therapeutics for MPNST in humans and are therefore necessary to carefully review and assess prior to initiation of human trials.[92] Identification of multiple potential MPNST drugs in this review underscore fundamental principles that will guide optimization of treatment regimens in the future. For example, novel therapies should focus on improving survival while simultaneously limiting toxicity and maintaining quality of life. The utility of ultimately discovering a systemic treatment specifically targeting MPNSTs may drastically alter the course of the MPNST management, allowing for preoperative tumor reduction and potentially minimizing the need for higher doses of radiation as well as more intensive surgeries.

Conclusion

Non-cytotoxic systemic treatments have not yet demonstrated clinical efficacy for MPNST, but most promising are approaches targeting the PI3K/Akt/mTOR and VEGFR pathways, as well as utilization of oncolytic viruses. A combination of therapies will most likely be key to maximizing treatment effects. With several clinical trials now, at least in part, recruiting MPNST patients, new insights into therapeutic options for MPNST will likely result.

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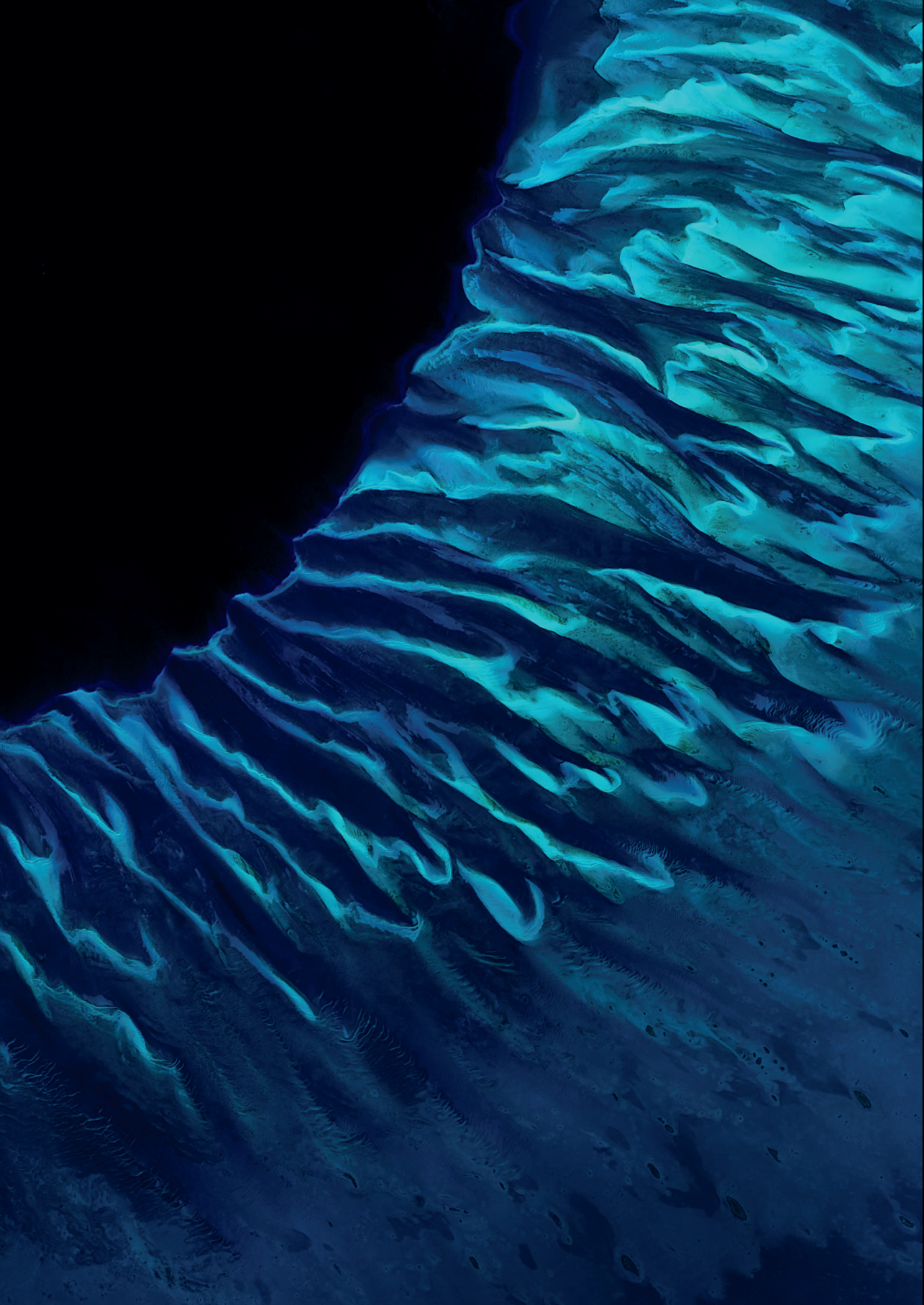
Supplemental Table 1 Search syntaxes for PubMed and Embase databases

Pubmed search: 03-2018	((MPNST*[Title/Abstract] OR malignant peripheral nerve sheath tum*[Title/Abstract] OR malignant neurilemmoma*[Title/Abstract]) OR malignant schwannoma*[Title/Abstract] OR Neurilemmoma[MeSH Terms] AND (pre-clinical[Title/Abstract] OR preclinical[Title/Abstract] OR vivo[Title/Abstract] OR animal experimentation[MeSH Terms] OR drug evaluation, preclinical[MeSH Terms] OR chemotherap*[Title/Abstract] OR drug therap*[Title/Abstract] OR systemic therap*[Title/Abstract] OR molecular therap*[Title/Abstract] OR immunotherap*[Title/Abstract] OR immune therap*[Title/Abstract] OR systemic treatment[Title/Abstract] OR target therap*[Title/Abstract] OR targeted therap*[Title/Abstract] OR virus[Title/Abstract] OR viral[Title/Abstract] OR drug therapy[MeSH Terms])) Filters: Publication date from 2000/01/01 to 2018/12/31
Embase search: 03-2018	('mpnst*':ab,ti OR 'malignant peripheral nerve sheath tum*':ab,ti OR 'malignant neurilemmoma*':ab,ti OR 'malignant schwannoma*':ab,ti OR 'malignant neurilemoma'/exp) AND ('chemotherap*':ab,ti OR 'drug therap*':ab,ti OR 'systemic therap*':ab,ti OR 'molecular therap*':ab,ti OR 'immunotherap*':ab,ti OR 'immune therap*':ab,ti OR 'systemic treatment':ab,ti OR 'target therap*':ab,ti OR 'targeted therap*':ab,ti OR 'virus':ab,ti OR 'viral':ab,ti OR 'drug therapy'/exp OR 'pre-clinical':ab,ti OR 'preclinical':ab,ti OR 'vivo':ab,ti OR 'in vivo study'/exp) AND [article]/lim AND [2000-2018]/py AND [Embase]/lim



PART II

Functional Outcomes and Possibilities for Treatment in MPNST

8

Resuscitating Extremities after Soft Tissue Sarcoma Resections: Are Functional Reconstructions an Overlooked Option in Limb Salvage? A Systematic Review

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Dullaart MJ
van de Sande MAJ
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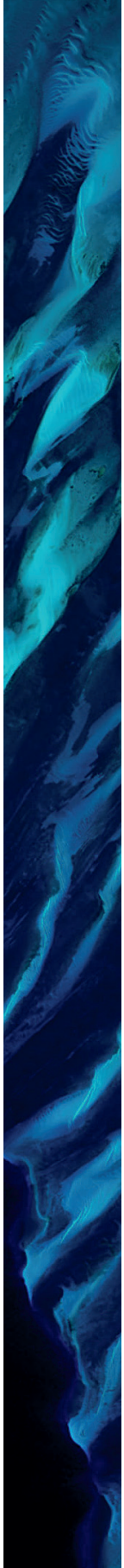
European Journal of Surgical Oncology. 2019 Oct, 45(10): 1762-9.



Abstract

Background Although resection of extremity soft tissue sarcomas can occasionally lead to large disabilities, literature regarding the necessity and outcome of functional reconstructions are scarce. The goal of this review is to assess outcomes and usage of functional reconstructions in light of multimodal treatment.

Methods A systematic search was performed in July 2018 in PubMed and Embase databases according to the PRISMA guidelines. Search terms related to 'soft tissue sarcoma' and 'functional reconstruction' were used. Case series evaluating outcomes of functional reconstructions after STS resection were included. Functional reconstructions were limited to free functioning muscle transfers, tendon reconstructions, and nerve reconstructions. Qualitative synthesis was performed on all studies. Tumor grade, multimodal treatment, reconstruction, outcomes, and complications were collected from individual patient data. Results were summarized by tumor site.

Results Fourteen studies were included after full-text screening. A total of 134 patients were described, of which the majority (74.9%) had functional reconstructions in the lower extremity. Radiotherapy and chemotherapy were administered in 60.3% and 49.4% respectively. Free functioning muscle transfers were used in 41.0% of all cases, tendon reconstructions in 58.2%, and nerve reconstructions in only 12.7%. A wide variety of outcome measures were used. Most patients regained good functionality, also after multimodal treatment. Unfavorable outcomes were often related to flap failure or allograft tendon rupture.

Conclusion Functional reconstructions in extremity STS are rarely described, but generally result in good functionality in spite of multimodal treatment. Early participation of reconstructive surgeons may help achieve ideal functional and oncological outcomes.

Introduction

With an annual incidence of approximately 4 cases per 100,000, soft-tissue sarcomas (STS) comprise 1% of adult cancers.[1] Around 15% and 35% of all STS arise in upper and lower extremities respectively.[2] Resection with clear margins remains key to improve survival and diminish local and distant recurrences.[3,4] While amputation was not uncommon in the past, limb-sparing surgery (LSS) has become standard of care as it improves functionality providing it does not decrease local control.[5,6] Radiotherapy is often part of limb-sparing treatment for local control and many centers are increasingly preferring preoperative to postoperative radiotherapy because it has lower long-term toxicities, albeit its higher postoperative complication rates.[7–12]

The rise of limb-salvage surgery has partly been due to a combination of improved local control using radiotherapy and an increase in reconstructive possibilities, but the main goal of plastic surgery has traditionally been soft tissue coverage.[13] Functional reconstructions, the replacement of lost functions due to complete muscle, tendon, or nerve resections, are gaining popularity in trauma cases but still little can be found in STS literature.[13–15] This is in contrast with the reconstruction of major arteries, and to a lesser extend veins, which are more common practice in centrally located sarcoma, especially in leiomyosarcoma where the tumor derives from a vein. Several reasons may underlie the latter. Firstly, in most cases where muscles are resected, the remaining muscles are able to hypertrophy after resection and partially replace the function of the resected muscle.[16] Secondly, about a quarter of STS grow superficially, obviating the need for large muscle resection.[17] Thirdly, the focus of treatment is obtaining adequate margins and improving oncological outcome, as well as preventing major complications or wound healing problems. Therefore, research has not focused on the potential role of functional reconstructions so far. Finally, the rather poor prognosis of some STS patients and limited knowledge of rehabilitation may withhold surgeons to consider such reconstructions. As a result functional reconstructions are often not implemented as common practice.[13,14,18] It should be noted that not only motor deficits are regarded as functional deficits; sensory loss may also be present after resection of sensory or mixed nerves.

Achieving clear margins in LSS may often be compromised by involvement of critical structures such as nerves, bones, or arteries.[19] Resection of aforementioned structures can result in large functional deficits.[19–24] Techniques as preoperative limb perfusion, preoperative radiotherapy, and epineural dissection are several ways that have shown to diminish the need for resection of such critical structures.[8,25–27] However, their resection is sometimes inevitable, especially when the tumors are encasing major structures or are deriving from major structures such as MPNSTs which may originate from large nerves. Frequently, such involvement is considered an indication for amputation because of its anticipated functional deficit.[19,28,29] However, since STS has a

relatively high incidence at a younger age, and treatment options are slowly improving, more STS patients will become long-term survivors,[30] resulting in an increased amount of patients with lifelong disabilities.

The purpose of this review is to summarize current literature on functional reconstructions used in extremity STS and assess their feasibility and outcomes in light of multimodal treatment. This may help sarcoma teams to improve selection of future candidates for such reconstructions before initial treatment.

Methods

Literature search

A systematic search was performed in both PubMed and Embase databases according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines, in order to identify all potentially relevant articles as of July 2018. The search string was built with the help of a professional librarian using search terms related to "soft tissue sarcoma" and "functional reconstruction". The exact search syntaxes for PubMed and Embase are shown in **Supplementary Table 1**. Studies were included that evaluated outcomes of functional reconstructions after soft tissue sarcoma resection. Only free functioning muscle transfers, tendon reconstruction using transfers or allografts, or any nerve reconstruction were considered a functional reconstruction. Replantation of tendons or muscles after tumor excision was not regarded as such. Exclusion criteria included lack of full text, outcomes not stratified for soft tissue sarcomas, case reports, no use of functional outcome measures, no human studies, and languages other than English, Dutch, French, or German. The initial review was conducted by two independent authors (E.M. and M.J.D.). Disagreements were solved through discussion, in which one additional author was involved (J.H.C.).

Data extraction and synthesis

All data was extracted at an individual patient level and included tumor grade (high/low), tumor site, treatment with radiotherapy or chemotherapy, reconstruction(s) performed, oncologic (survival, local recurrence, metastasis) and functional outcomes, and duration of follow-up. Patients with bone sarcomas or non-extremity sites were excluded from qualitative synthesis, as well as patients with incomplete outcome data. Patients were also excluded in case of soft tissue coverage only, or in case individual patient data in tables and article text did not clarify if functional reconstruction was performed. Results were summarized and stratified per anatomical site: shoulder, upper arm, forearm, hand/wrist, upper leg, and lower leg. In each study the mean of each functional outcome was calculated per muscle group.

Results

After removal of duplicates, a total of 2902 citations were identified in PubMed and Embase databases. 736 potentially relevant articles were selected through title/abstract screening, of which 14 studies remained for qualitative synthesis after full-text screening (**Figure 1**).

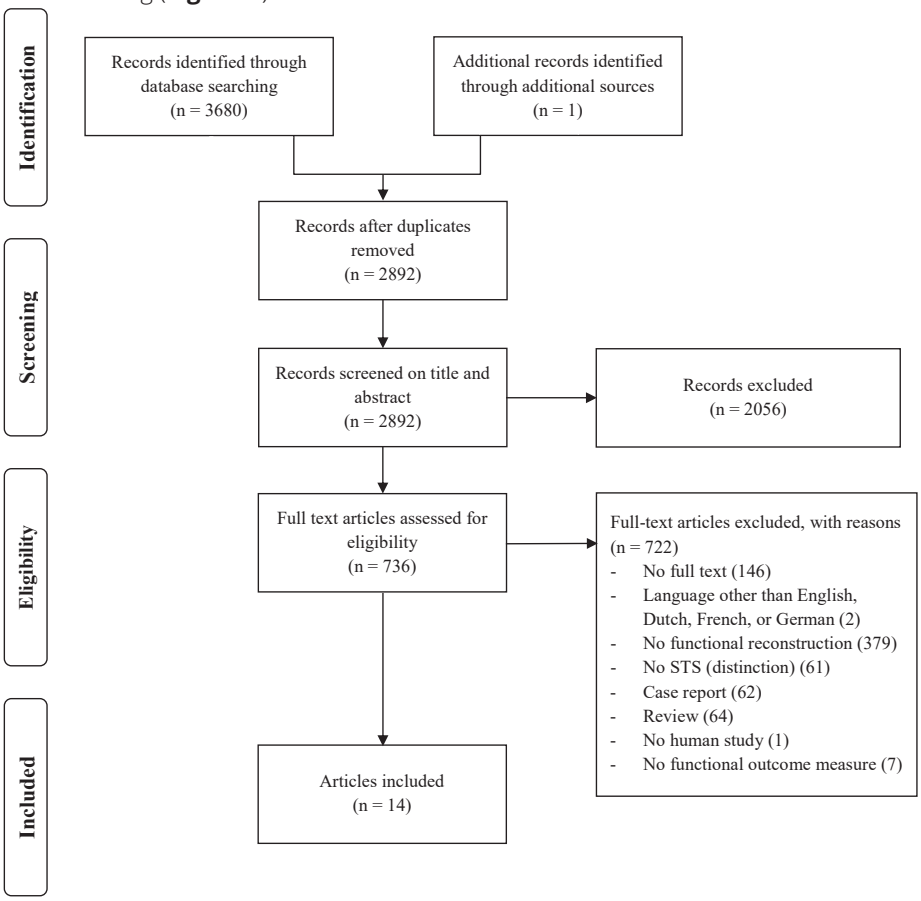


Figure 1 Flowchart depicting study selection

Study characteristics and multimodal treatment

All studies were small retrospective cohort studies or case series describing a total of 134 patients with any form of functional reconstruction after extremity STS resection (**Table 1**). Of all reconstructions 26 % were performed in the upper extremity and 74.9% in the lower extremity, which is in line with the anatomical distribution of sarcomas. Reconstructions were generally performed if loss of a major muscle was anticipated or present due to large or complete muscle group resection, tendon resection, or major nerve resection. Free functioning muscle transfers were used in 41.0% of all cases,

tendon reconstructions in 58.2%, and nerve reconstructions in 12.7%. Most studies included patients with high grade sarcomas, which resulted in 60.3% (range: 0-100%) of all cases using radiotherapy, and 49.4% (range: 0-70%) chemotherapy. A wide variety of functional outcome measures were used, of which the Musculoskeletal Tumor Society scoring system (MSTS) and Medical Research Council muscle grade (MRC) were most commonly used.

Shoulder and upper arm

Four different studies included reconstructions of shoulder and upper arm functions in 13 patients (**Table 2**). The deltoid muscle was most commonly reconstructed with a pedicled innervated latissimus dorsi flap (LD), but a free functioning tensor fascia lata (TFL) flap was also described. Both operations yielded good muscle grades (M4), good range of motion in shoulder abduction, and high MSTS scores (both >90%). Loss of elbow flexion was commonly reconstructed with the use of a pedicled LD,[13,31] but a free functioning gracilis transfer has also been performed.[31] Although relatively low MSTS scores were seen on average in one study (63.3%), patients did regain M4 elbow flexion.[31] Toronto Extremity Salvage Scores (TESS) were however excellent in another study (98.7%).[13] The latter study also presented one patient with loss of elbow extension reconstructed with the use of a pedicled LD as well yielding good results (TESS = 100%).[13] All studies that evaluated muscle grade, showed that all patients regained at least M3 muscle power, regardless of multimodal therapy.

Forearm

Functional reconstructions in forearm compartments are described in four studies in nine patients. Loss of function in the flexor compartment was either reconstructed by tendon transfers[13] or a free LD flap.[32] Lost extensor compartment function, leading to either loss of wrist extension, finger extension, or a combination, was reconstructed with a free gracilis flap,[32,33] a free LD flap,[32] or a composite anterolateral thigh flap (ALT).[34] A composite ALT may contain part of the vastus lateralis, TFL, and iliotibial band. All patients regained reasonable muscle grade (M3-4) and reasonable to excellent MSTS scores (66.7-100%) and TESS (61.3-92.6%).[34] No nerve reconstructions have been described in these studies.

Table 1 Study characteristics of included studies.

Study, year	Patients			Reconstructions			High grade tumors	Other treatment		Functional outcome measure	F-U (mo)
	Total	UE	LE	FFMT	Tendon	Nerve		RTx	Cx		
Doi 1999	17	11.8%	88.2%	100%	29.4%	5.9%	Yes	0%	64.7%	MSTS, MRC, ROM lag, walking aid	60 (27-106)
Fischer 2015	43	0%	100%	0%	100%	0%	*NA*	41.2%		ROM, strength, Karnofsky, QoL, satisfaction, walking aid	66 (22-107)
Grinsell 2012	18	16.7%	82.3%	100%	0%	11.1%	Yes	100%	0%	MSTS, MRC, LEFS, DASH	18 (6-42)
Gunterberg 1980	2	0%	100%	0%	100%	0%	No	NA	NA	ROM, strength	40 (36-44)
Innocenti 2009	10	0%	100%	100%	40%	0%	Yes	80%	70%	MSTS, MRC	69 (21-136)
Mehrara 2008	7	100%	0%	0%	71.4%	57.1%	*NA*	28.6%	0%	MSTS	47 (*NA*)
Melendez 2001	6	0%	100%	0%	0%	100%	*NA*	83.3%	50%	MRC, S	12 (5-42)
Mirous 2016	3	100%	0%	0%	100%	66.7%	Yes	33.3%	66.7%	MSTS, DASH, VAS	54 (12-156)
Mundinger 2014	12	100%	0%	0%	100%	0%	Yes	83.3%	*NA*	TESS	43 (*NA*)
Muramatsu 2009	4	100%	0%	100%	0%	0%	Yes	0%	*NA*	MSTS	69 (12-173)
Muramatsu 2014	4	100%	0%	0%	100%	0%	Yes	*NA*	*NA*	MSTS, MRC, ROM	50 (12-106)
Stranix 2017	4	0%	100%	100%	0%	0%	Yes	*NA*	*NA*	MSTS	22 (20-36)
Tokumoto 2018	2	0%	100%	0%	0%	100%	Yes	*NA*	*NA*	MRC, S	12 (3-24)
Walley 2017	2	0%	100%	100%	0%	0%	Yes	100%	50%	MSTS, KSS, ROM, MRC, walking aid	19 (17-21)
Total	134	26.1%	74.9%	41.0%	58.2%	12.7%		60.3%	49.4%		

Cx: chemotherapy DASH: disability of arm, shoulder, and hand, FFMT: free functioning muscle transfer, F-U: follow-up, KSS: knee society score, LE: lower extremity, mo: months, MRC: medical research council muscle grade, MSTS: musculoskeletal tumor society rating scale, N: number of, NA: not available, No. pt: number of patients, QoL: quality of life, ROM: range of motion, RTx: radiotherapy, S: sensibility, TESS: Toronto extremity salvage score, UE: upper extremity, VAS: visual analog scale

Table 2 Average functional outcomes in upper extremity reconstructions.

	Study	Flaps (N)	Objective measures[a]		Subjective measures[a]			
			MRC	ROM	MSTS	DASH	TESS	VAS
Shoulder& upper arm		*Deltoid*						
	Doi 1999	TFL (1)	4.0	0° lag	93.3%			
	Muramatsu 2014	Pedicled LD (4)	3.8	164°	91.5%			
		Trapezius						
	Grinsell 2012	Pedicled LD (1)	5.0		100%	0		
		Biceps						
	Grinsell 2012	Pedicled LD (1), gracilis (1)	4.0		63.3%	22.5		
	Mundinger 2014	Pedicled LD (3)					98.7%	
		Triceps						
	Mundinger 2014	Pedicled LD (1)					100%	
Forearm		*Flexor compartment*						
	Mundinger 2014	TT: FDS to FCR (1), PL to FPL (1)					77.0%	
	Muramatsu 2009	LD (1)			83.3%			
		Extensor compartment						
	Doi 1999	Gracilis + PL (1)	3.0	30°	93.3%			
	Muramatsu 2009	Gracilis (2), LD (1)	4.0[b]		88.9%			
	Stranix 2017	Composite ALT (1)			80%			
Hand & wrist		*Hand*						
	Mehrara 2008	Toe-to-thumb (1) TT: FDS to FPL (2), ECR to EPL (1), FPL to P1 (1) LABCN (2), sural nerve (1)			95.2%			
	Mirous 2016	Allografts: finger flexion (2) TT: PL to ECRL and ECRB (1), EIP to EPL (1), hemiFCR to APL (1) Sural nerve (2)			75.3%	21.3		0
	Mundinger 2014	Allografts: finger flexion (1), finger extension (1), wrist extension (1)					65.1	

[a] = DASH: disability of the arm, shoulder, and hand questionnaire (0-100 points, higher score correlates to larger disability), MRC/MMT: medical research council muscle grade / manual muscle testing (0-5), MSTS: musculoskeletal tumor society scale (0-30 points, higher score correlates to higher function), ROM: range of motion (degrees), TESS: Toronto extremity salvage score (0-150 points, high score correlates to higher function), VAS: visual analog scale (0-10), [b] = MRC outcome only given in one case.

APL: abductor pollicis longus DN: digital nerve, ECRB: extensor carpi radialis brevis, ECRL: extensor carpi radialis longus, EIP: extensor indicis proprius, EPL: extensor policis longus, FCR: flexor carpi radialis, FDS: flexor digitorum superficialis, FPL: flexor pollicis longus, LABCN: lateral antebrachial cutaneous nerve, LD: latissimus dorsi flap, P1: first phalanx, PL: palmaris longus, TFL: tensor fascia lata flap, TT: tendon transfer

Hand and wrist

Defects after STS in hand and wrist area are diverse and according to each specific deficit three different studies describe their reconstructions performed in 13 patients.[13,35,36] One study specifically reported on thumb reconstructions after STS.[35] These were commonly reconstructed with tendon transfers, but a successful toe-to-thumb reconstruction has also been described. On average, high MSTS scores were yielded (95.2%). Other deficits of the hand occurred after tendon resections or resection of digital nerves. Tendon defects of other fingers could often be reconstructed with the use of allografts or tendon transfers.[13,36] Functional results were variable, but of the three unfavorable outcomes, one was related to tendon rupture.[13] Digital nerve defects and median nerve defects were reconstructed with the use of sural nerve grafts or lateral antebrachial cutaneous nerve grafts.[35,36] In one study, no neuropathic pain was observed after nerve reconstruction.[36] No other sensibility outcome measures were described. No study reported cases of nerve transfers used to restore sensation in the hand.

Upper leg and hip

Eight studies reported a total of 89 patients with reconstructions of upper leg and hip functions (**Table 3**). After resection of the complete hamstrings, knee flexion was regained with the use of free innervated LD flaps, resulting in good functional outcomes (M3-4, MSTS 63.3-86.7%).[31,33] One patient did not regain active knee flexion (M2) which resulted in the use of a static knee brace and the lowest MSTS score (63.3%).[33] Loss of knee extension function was most commonly reconstructed with a free LD flap as well, but a gracilis or sartorius tendon transfer was concomitantly performed in cases with complete quadriceps resection.[33,37] Outcomes were variable ranging from M2-5. A total of 3/17 patients did not regain more than M2 muscle power, most of which resulted in a fair MSTS score. In one patient with flap failure, knee extension was completely absent and a poor MSTS score was observed.[37] Two studies evaluated the effect of a contralateral composite ALT flap, which showed good muscle grade (M4-5) and reasonable MSTS scores (63.3-80%).[34,38] A free rectus femoris flap, transverse abdominal muscle flap (TRAM), and free gracilis flap have also been described all of which yielded high functional outcomes (M4-5, MSTS 100%).[31] Tendon transfers using the biceps femoris tendon for reconstruction of knee extension have been described in one study which resulted in an M4 muscle grade on average.[39] These tendon transfers sometimes included a gracilis or semitendinosus tendon as well, depending on surgeon preference. However, such additional tendons did neither increase power nor functionality, but did increase wound dehiscence and lymph edema rates.[39] Adductor muscles of the leg were reconstructed using either a free LD, free gracilis, or a free rectus abdominis flap.[31,33] All of which regained reasonable to excellent muscle power (M3-5) and good MSTS scores (86.7-96.7%). Reconstruction of the gluteal muscle after STS resection has also been described in one study.[31] Either a free LD flap or TRAM was used, both resulting in M5 hip extension and 100% MSTS scores. Sciatic nerve

Table 3 Average functional outcomes in lower extremity reconstructions.

	Study	Flaps (N)	Objective measures[a]			Subjective measures[a]				
			MRC	ROM	S	MSTS	KSS	LEFS	SF-36	K-scale
Upper leg & hip				*Hamstrings*						
	Doi 1999	LD (5)	3.2	20° lag		82.7%				
	Grinsell 2012	LD (4)	4.0			91.2%		63.5		
				Quadriceps						
	Doi 1999	LD (6) + gracilis (3), RF + gracilis (1)	3.7	9° lag		90.5%				
	Fischer 2015	BF (17) +/- gracilis or semitendinosus (6)	4.0	66%					78%	82
	Grinsell 2012	Gracilis (1), TRAM (2)	5.0			100%		72.3		
	Innocenti 2009	LD (10) + sartorius (4)	2.8			Good[b]				
	Stranix 2017	Composite ALT (1)				76.7%				
	Walley 2017	Composite ALT (2)	4.5	5-75°		71.7%	77			
				Adductors						
	Doi 1999	LD (1)	3.0	0°		96.7%				
	Grinsell 2012	Gracilis (1), RA (1)	4.5			86.7%		69.0		
				Gluteus						
	Grinsell 2012	LD (1), TRAM (1)	5.0			100%		80.0		
				Sciatic nerve						
	Melendez 2001	Peroneal nerve (5) +/- sural nerve (3)	Knee: 5.0 Ankle: 2.0		Protective					
	Tokumoto 2018	Vascularized sural nerve (2)	Knee: 4.0 Ankle: 1.0		Protective					
Lower leg				*Anterior compartment*						
	Doi 1999	Gracilis (2)	3.5	0° lag		95.0%				
	Grinsell 2012	Gracilis (1)	5.0			100%		78.0		
	Gunterberg 1980	TT: TP to EDL and PT (2)		0-5°						
	Stranix 2017	Composite ALT (2)				85.0%				
				Posterior compartment						
	Grinsell 2012	LD (1), gracilis (1), parascapular + sural nerve(1)	4.0			91.1%		55.0		

[a] = DASH: disability of the arm, shoulder, and hand questionnaire (0-100 points, higher score correlates to higher disability), K-scale: Karnofsky performance status scale (0-100, higher score correlates to higher function), KSS: knee society score (0-100 points, higher score correlates to higher function), LEFS: lower extremity functional scale (0-80 points, higher score correlates to higher function), (0-5), MRC/MMT: medical research council muscle grade / manual muscle testing (0-5), MSTS: musculoskeletal tumor society scale (0-30 points, higher score correlates to higher function), ROM: range of motion (degrees), SF-36: short-form 36 (8 subdomains, total: 0-100%, higher score correlates higher well-being), [b] = no specified percentages.
ALT: anterolateral thigh flap, BF: biceps femoris muscle transfer, EDL: extensor digitorum longus, KSS: knee society score, LD: free functioning latissimus dorsi muscle flap, LEFS: lower extremity functional scale, MRC: medical research council muscle grade, MSTS: musculoskeletal tumor society rating scale, N: number of, PT: peroneus tertius, ROM: range of motion, RA: rectus abdominis muscle flap, RF: free functioning rectus femoris muscle flap, SF-36: short-form 36, TESS: Toronto extremity salvage score, TFL: tensor fascia lata flap, TP: tibialis posterior muscle, TRAM: transverse abdominal muscle flap, TT: tendon transfer

reconstruction after STS resection was described in two studies.[40,41] Gaps of 11-19 cm were reconstructed using peroneal nerves or (vascularized) sural nerves. Both studies combined, more than half of all patients regained protective sensation of the foot sole, but all patients regained some protective sensation in any part of the foot at least one year postoperatively.[40,41] Also, while motor function of the lower leg commonly sustained, knee flexion was often unharmed. In one study, only two patients regained M3-4 dorsiflexion and plantar flexion.[40]

Lower leg

Functional deficits of the lower leg were reconstructed in four studies describing 10 patients. The anterior compartment of the lower leg mainly provides foot and hallux dorsiflexion and has been reconstructed in seven patients. Both free flaps and tendon transfers were performed. Two studies described a free gracilis transfer resulting in good muscle power (M3-5), and excellent MSTS scores (90-100%).[31,33] Composite ALTs also resulted in good results in one study.[34] A tendon transfer of the tibialis posterior to the extensor digitorum longus and peroneus tertius showed that the foot could remain in neutral position, but dorsiflexion beyond that point was minimal.[42] The posterior compartment's primary function is plantar flexion. One study describes reconstructions of this compartment using either a free LD, gracilis or parascapular flap and sural nerve.[31] These reconstructions generally provided good motor function (M3-5) and high MSTS score (83.3-100%).

Surgical complications

A total of 31 patients (23.8%) had postoperative complications. Most of these complications (67.7%) were wound-related, such as superficial infections, wound dehiscence, and seroma. Other complications that occurred were lymph edema (n = 5), venous thrombosis (n = 2), fistula (n = 1), hematoma (n = 1), and femoral fracture (n = 1). Most complications (51.6%) were reported by a single study using different biceps femoris transfer for the restoration of knee extension.[39] Overall, flap failure occurred in two patients. [31,37] One patient had a pedicled LD for reconstruction of arm flexion which was replaced with a free gracilis flap after which an M4 muscle grade was obtained.[31] The other patient ended up with poor functional outcomes.[37] Tendon rupture after reconstruction of the hand occurred in one patient as well, which also resulted in a poor MSTS score.[13] Both patients did not receive radiotherapy or chemotherapy in any modality, but do show that failed reconstructions give poor functional outcomes.

Discussion

Functional reconstructions in extremity STS are uncommon, yet good muscle grades and high functional outcome scores can be expected when performed even if radiotherapy and chemotherapy are used. Poor outcomes are seen after flap failure,

which are not restricted to patients with multimodal therapy. Reconstructions are most commonly used after resection of a complete muscle group. The type of reconstruction depends mainly on the defect size and location. While large muscles in proximal extremities will need larger muscle transfers to restore function, more distal defects often require tendon repair by transfer or grafting. Nerve reconstructions using grafts or transfers are also possible in selected cases, yet have rarely been described. Such reconstructions are especially of interest in distal extremities to restore both motor and sensory function.

Reconstructions in STS

As limb salvage surgery has emerged as standard of care over the past decades and reconstructive possibilities have increased, an increasing amount of extremity STS patients survive with salvaged limbs. However, in a few cases resection of neurovascular bundles and/or complete muscle compartments is inevitable.[19] Depending on location and extent of muscle resection different degrees of disability will arise. Unfortunately, almost no studies report on the difference in functionality between patients undergoing a resection for STS only and patients that undergo functional reconstruction alongside resection. One study showed that in lower extremity STS receiving functional reconstructions had improved function.[18] Moreover, it was shown that albeit slightly longer operative times and length of hospital stay, functional reconstructions added up to be cost-effective.[18] Selection of ideal candidates is however important when considering functional reconstructions preoperatively. Resection of many muscles and tendons and even some nerves do not result in significant functional deficits. For instance in upper leg STS, only resection of three or four heads of the quadriceps muscle or the complete hamstring compartment will result in a considerable impairment as remaining muscles are not able to fully compensate for the resected muscle.[16,33] However, few cases in this study that have poor muscle function because of a 'failed' reconstruction, do show that MSTS scores are lower compared to their 'successful' counterparts and more commonly require postoperative use of braces. Reconstruction of the sciatic nerve also remains a topic of debate. Whereas some authors do not advocate restoring it,[43,44] others do recommend it.[40,41,45] Indeed, recovery of motor function should not be anticipated, especially of the peroneal compartments,[46] but studies included in this review do show that protective sensation of the foot can be acquired within little over a year.[40,41] Sural nerve grafts are commonly used because of their length, easy harvest, and low donor site morbidity as they generally only supply sensation to a part of the lateral foot and lower leg.[47] However in nerve reconstructions of large gaps, higher patient age should be considered as a contraindication because of its notorious negative effect on nerve regeneration.[48] The use of postoperative radiotherapy should on the other hand not necessarily be considered as a hard contraindication for nerve reconstruction, as it may not significantly affect functional outcomes.[49] However, nerve reconstruction itself may be complicated by preoperative radiotherapy which should be considered when planning a treatment plan. Timing

of functional reconstructions is difficult, but direct reconstruction (within 2-3 weeks) seems to be preferred over a delayed surgical reconstruction.[50–53] This ensures an early start of rehabilitation, which is even more important to obtain good results after such reconstructions.[51–53] Additionally, less complications occur and fibrosis is not yet present which complicates delayed reconstructions since adequate vessels and nerves may be difficult to find.[50–53] In high-grade STS achieving clear margins may be essential before performing any type of reconstruction. Also, one must consider that nerve regeneration in FFMT and nerve reconstructions can take several months before reaching its target.[33] In contrast, tendon transfers result in immediate function restoration and could be considered in cases where early recovery is needed.[54] Nerve transfers are also increasingly used in traumatic nerve injuries and are becoming standard of care in brachial plexus surgery.[55,56] These reconstructions provide the opportunity to restore nerve function distal to the defect, thus decreasing the time to recovery. In extremity STS this may also imply reconstructing outside of possible radiation fields.

Multimodal treatment and reconstruction in STS

Although LSS is performed for functionality purposes, in STS oncologic treatment should of course have priority in almost any case. This means that clear margins are essential, especially in high grade STS. Studies have however shown that the early participation of a plastic surgeon can yield higher rates of clear margins if free flaps are considered at an early stage.[57,58] The effect of chemotherapy and radiotherapy in functional reconstructions has not been thoroughly investigated. Studies included in this review however showed that all but one flap survived, and generally only minor complications occurred. One study did report radiotherapy induced fractures which ultimately affected functional outcomes.[37] Another series showed no negative effect of radiotherapy on functional outcomes after biceps femoris transfer for the reconstruction of knee extension.[39] In LSS generally, multiple studies have shown that preoperative radiotherapy does not increase complications when flaps are used.[59–63] These studies are however in contrast to the trial by O'Sullivan et al.[11] and other LSS studies.[7–10] In case postoperative radiotherapy is administered, free flap surgery can facilitate early start of treatment.[64] Also, complications may possibly be diminished when flaps are used compared to no flap usage.[61,63–65] Besides, restoration of function may alleviate the need for orthoses,[33] which are difficult to wear on irradiated skin. Overall, the use of functional reconstructions does not seem to impede the use of either pre- or postoperative radiotherapy. The effects of chemotherapy are less frequently addressed in literature, but its use in LSS does not seem to increase complications regardless of sequence.[66,67]

Strengths and limitations

Main limitations to our study include the large heterogeneity among studies and their patients, as well as the low amount of patients treated with functional reconstructions. Direct comparison between studies and flaps used is complicated due to the different

defects being reconstructed and the diversity in outcome measures used. Also, with only a small amount of cases with differing tumor grades, location, and indications for multimodal treatment may have differed. As such, investigating the correlation of multimodal treatment to functional outcomes is impaired. Nonetheless, this study shows encouraging outcomes for the use of functional reconstructions. These results may stimulate sarcoma teams to incorporate early participation of experienced reconstructive plastic surgeons and rehabilitation teams. Such cooperation may result in facilitating wider tumor excision as well as planned preservation of certain structures needed for reconstruction. In order to increase our understanding of outcomes, future studies on limb salvage in STS patients should preferably differentiate functional reconstructions from soft-tissue coverage only. Additionally, when investigating outcomes of functional reconstructions, future studies are to be stimulated using both objective outcome measures assessing true muscle or sensory function and subjective outcome measures. This may further help elucidate expected outcomes and select ideal candidates. As such, sarcoma teams will increasingly be capable to incorporate functional reconstructions as part of their treatment strategy in extremity STS.

Conclusion

Functional reconstructions in extremity STS are uncommon in literature. However, resection of major nerves or complete muscle groups can lead to loss of specific functions. Reconstructions of nerves, muscles, and tendons can potentially improve function. As numerous options exist, the choice of reconstruction depends mainly on patient and tumor characteristics, such as size and location. Multimodal treatment does however not preclude successful restoration of function. A patient-tailored approach is needed to balance appropriate oncological resections with optimal functional outcome.

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Supplemental Table 1 Search syntax for PubMed and Embase databases

PubMed search: 26-6-2018	(Reconstruction[tiab] OR flap*[tiab] OR neurotization[tiab] OR nerve graft[tiab] OR nerve crossover[tiab] OR limb salvage[tiab] OR ((muscle[tiab] OR nerve[tiab] OR tendon[tiab]) AND (transfer[tiab] OR reconstruction[tiab] OR transplantation[tiab])) OR Free Tissue Flaps[MeSH Terms] OR Tendon transfer[MeSH Terms] OR Nerve Transfer[MeSH Terms] OR Limb Salvage[MeSH Terms]) AND ((Sarcoma[tiab] OR soft tissue neoplasm[tiab] OR soft tissue cancer[tiab] OR tendinous tissue neoplasm[tiab] OR tendinous tissue cancer[tiab]) OR Sarcoma[MeSH Terms] OR Soft Tissue Neoplasm[MeSH Terms])) AND (Extremity[tiab] OR extremities[tiab] OR limb[tiab] OR limbs[tiab] OR plexus[tiab] OR shoulder[tiab] OR shoulders[tiab] OR arm[tiab] OR arms[tiab] OR hand[tiab] OR hands[tiab] OR finger[tiab] OR fingers[tiab] OR digit[tiab] OR digits[tiab] OR thumb[tiab] OR thumbs[tiab] OR hip[tiab] OR hips[tiab] OR leg[tiab] OR legs[tiab] OR ankle[tiab] OR ankles[tiab] OR foot[tiab] OR feet[tiab] OR toe[tiab] OR toes[tiab])
Embase search: 26-6-2018	(Reconstruction:ti,ab OR flap*:ti,ab OR neurotization:ti,ab OR nerve graft:ti,ab OR nerve crossover:ti,ab OR limb salvage:ti,ab OR ((muscle:ti,ab OR nerve:ti,ab OR tendon:ti,ab) AND (transfer:ti,ab OR reconstruction:ti,ab OR transplantation:ti,ab)) OR 'free tissue graft'/exp OR 'tendon transfer'/exp OR 'tendon transplantation'/exp OR 'nerve transplantation'/exp OR 'limb salvage'/exp) AND (Sarcoma:ti,ab OR soft tissue neoplasm:ti,ab OR soft tissue cancer:ti,ab OR tendinous tissue neoplasm:ti,ab OR tendinous tissue cancer:ti,ab OR 'sarcoma'/exp OR 'soft tissue cancer'/exp) AND (Extremity:ti,ab OR extremities:ti,ab OR limb:ti,ab OR limbs:ti,ab OR plexus:ti,ab OR shoulder:ti,ab OR shoulders:ti,ab OR arm:ti,ab OR arms:ti,ab OR hand:ti,ab OR hands:ti,ab OR finger:ti,ab OR fingers:ti,ab OR digit:ti,ab OR digits:ti,ab OR thumb:ti,ab OR thumbs:ti,ab OR hip:ti,ab OR hips:ti,ab OR leg:ti,ab OR legs:ti,ab OR ankle:ti,ab OR ankles:ti,ab OR foot:ti,ab OR feet:ti,ab OR toe:ti,ab OR toes:ti,ab) AND ([article]/lim) AND ([Embase]/lim)

9

A Systematic Review of Functional Outcomes after Nerve Reconstruction in Extremity Soft Tissue Sarcomas: a Need for General Implementation in the Armamentarium

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Dullaart MJ
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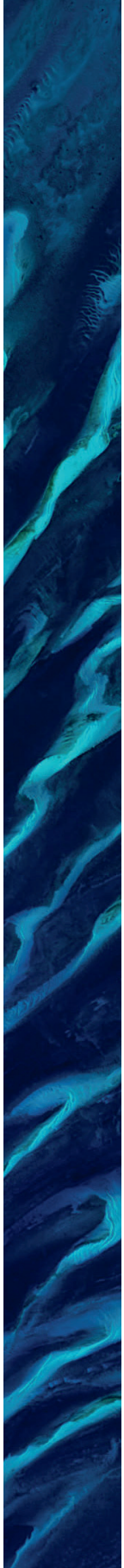

Abstract

Background Resection of nerves in extremity soft tissue sarcomas (STS) can lead to large functional deficits. Nerve reconstructions are rarely performed and little is known on their outcomes and indications for their use even though they are essential in restoring sensation in limb salvage procedures. This study investigated current knowledge on functional outcomes and considerations to be taken before performing such reconstructions after sarcoma resection.

Methods A systematic search was performed in July 2018 in PubMed and Embase databases according to PRISMA guidelines. Search terms related to 'soft tissue sarcoma' and 'nerve reconstruction' were used. Studies evaluating functional outcomes after nerve grafting or nerve transfers in extremity soft tissue sarcomas were included. Qualitative synthesis was performed on all studies.

Results Nineteen studies were included after full-text screening, describing 26 patients. The majority of patients had a nerve reconstruction in the upper extremity (65%). Perioperative radiotherapy was administered in 67% of patients and perioperative chemotherapy in 29%. Nerve grafting was most commonly performed (n=23) and nerve transfers were performed in six patients. A wide variety of outcome measures were used. Most patients recovered at least some motor function and sensation, but success rates were higher after upper than lower extremity defects. Multimodal treatment did not preclude successful reconstructions.

Conclusion Nerve reconstructions in extremity STS allow the restoration of sensation in limb salvation, even motor nerve function can be restored with satisfactory function. The use of multimodal therapy does not seem to interfere with success. Nerve reconstructions should therefore be considered in STS patients.

Introduction

Soft tissue sarcomas (STS) are rare cancers occurring in approximately 4 cases per 100,000, half of which arise in extremities.[1,2] Ideal treatment of localized disease generally includes wide resection, radiotherapy, and in some cases chemotherapy.[3] Clear surgical margins are critical for decreasing local recurrence rates.[3,4] In extremity soft tissue sarcoma, limb-salvage surgery (LSS) has become standard of care as its combination with radiotherapy does not impair local control, yet improves functionality.[5,6]

Although amputation rates have fallen in the last decades, major neurovascular involvement of STS in extremities is still seen as a reason for amputation.[7–9] In part, this may be due to the lack of literature on reconstruction of such nerve defects. Even though resection of nerves is rare in STS generally, their resection leads to significant functional deficits.[10,11] Reported rates of any nerve resection, excluding amputations, vary from 1.2-12%.[9,10,12–17] Incidence of nerve resection increases when sarcomas arise from nerve structures, like malignant peripheral nerve sheath tumors (MPNSTs), who have reported postoperative loss of motor function in up to 30%.[18] While rates of nerve reconstructions are as low as 0.4%.[19] As STS has a relatively high incidence at a younger age and treatment options are slowly improving, the amount of long-term survivors with life-long disabilities will increase.[20]

The relatively rare nature of nerve resections is probably not the only cause of the paucity of literature. STS research has primarily focused on improving oncological outcomes and decreasing complications and the primary role of plastic surgery has traditionally only included soft tissue coverage while nerve reconstructions are not common practice.[21–23] Secondly, knowledge on nerve reconstructions is still growing, especially on the use of nerve transfers and nerve conduits.[24] Lastly, STS treatment will often involve the use of radiotherapy and chemotherapy which have uncertain effects on nerve regeneration, which already is notorious for being slow.[25] Altogether, these factors may preclude clinicians to consider nerve reconstructions as a possibility in STS management, even though the resection of nerves may cause both motor and sensory deficits. Contrarily, nerve reconstructions have been shown to increase quality of life after other tumor-ablative surgeries, for example in mastectomies or head and neck cancers.[26–29]

This review set out to summarize all cases on nerve reconstruction in extremity STS and assess functional outcomes albeit the use of multimodal treatment. Consequently, indications of their use and considerations to be taken may be elucidated. As such, reconstructive surgeons can ameliorate their choice of reconstruction which should be in concurrence with oncological treatments proposed in sarcoma teams.

Methods

Literature search

A systematic search was performed in both PubMed and Embase databases according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines, in order to identify all potentially relevant articles as of July 2018. A search string was built with the help of a professional librarian using search terms related to "soft tissue sarcoma" and "nerve reconstruction". The exact search syntaxes for PubMed and Embase are shown in **Supplementary Table 1**. All clinical studies evaluating outcomes after nerve reconstructions in extremity STS were included. All nerve transfers and nerve grafts were considered nerve reconstructions, unless an interposition graft was used to innervate a free functioning muscle transfer. Exclusion criteria included articles not stratifying outcomes for STS, no functional outcome measures presented, and STS not localized in extremities. The initial review was conducted by two independent authors (E.M. and M.J.D.). Disagreements were solved through discussion, in which one additional author was involved (J.H.C.).

Data extraction and synthesis

All data was extracted on individual patient level and included tumor grade (high/low), tumor site, radio- and chemotherapy use, reconstruction(s) performed, oncologic and functional outcomes, and length of follow-up. Patients with bone sarcomas or non-extremity sites were excluded from qualitative synthesis, as well as patients with incomplete outcome data. Results were summarized and stratified by nerve reconstructed. Objective outcome measures scales included strength measured in weight-bearing, grasp power, grip/pinch strength and in the Medical Research Council muscle grade (MRC: M0-M5), range of motion, use of ambulatory devices, and sensation measured in the Medical Research Council sensory grade (MRCS: S0-S4) using two-point discrimination or with Semmes-Weinstein monofilament testing. Subjective outcome measures included the musculoskeletal tumor society scale (MSTS: 0-30), a visual acuity scale for pain (VAS: 0-10), and the disability of the arm, shoulder, and hand questionnaire (DASH: 0-100).

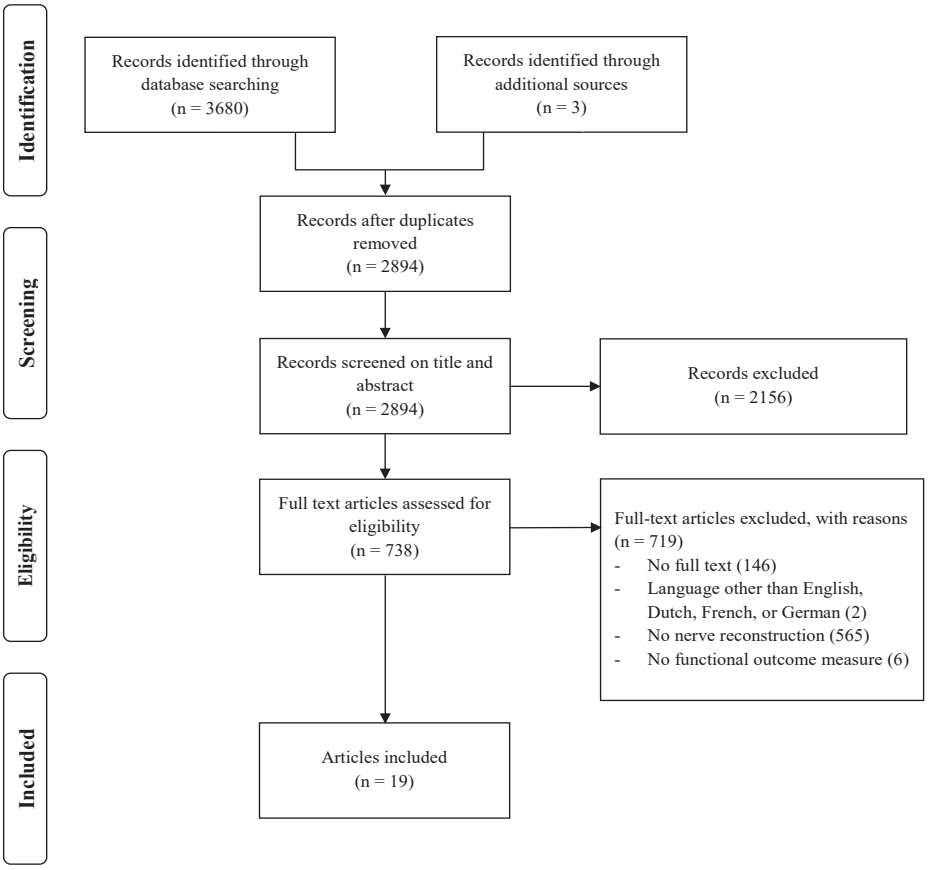

Figure 1 Flowchart depicting study selection

Results

After removal of duplicates, a total of 2894 citations were identified in PubMed and Embase databases. Potentially relevant articles were selected through title/abstract screening, of which 19 studies remained for qualitative synthesis after full-text screening (**Figure 1**). A total of 26 patients were described (**Table 1 and 2**). Nerve reconstructions were most commonly performed after upper extremity STS resections (65%). Two thirds of all patients received any modality of radiotherapy (14/21) and chemotherapy was administered in six patients. Four patients did not receive any (neo)adjuvant therapies.

Brachial plexus

Two different studies evaluated reconstructions of the brachial plexus in two patients (**Table 1**).[30,31] Both nerve transfers and nerve grafts were used. The first case described

resection of the upper trunk after neoadjuvant radiotherapy.[30] Subsequently, sural nerve interposition grafts were placed from C5 to the anterior division of the upper trunk. Secondly, the spinal accessory nerve was connected to the suprascapular nerve using a sural nerve graft. Lastly, to optimize abduction, a radial branch to the long head of the triceps, was sutured to the non-functional axillary nerve. The reconstruction yielded excellent elbow flexion and shoulder abduction, even some sensation in C5-6 was achieved at 36 months postoperatively, all despite neoadjuvant radiotherapy. The second case described an en bloc excision of the brachial plexus, after which the patient was left with a flail arm. To restore function, an ulnar nerve graft was used to connect the radial nerve to both C5 and C7 roots, a sural nerve graft was placed between C5 and the median nerve, and the 4th to 6th intercostal nerves were harvested and anastomosed to the musculocutaneous nerve. Despite these efforts the patient remained paralysed.[31]

Median nerve

The resection and reconstruction of a median nerve was described in four case reports.[32–35] All defects occurred in the proximal forearm. Three defects were reconstructed with the use of grafts,[33–35] the other with a transfer of the superficial radial nerve (RSN).[32] Sensation was restored adequately in all patients (protective or S3+-S4). Grasp power or finger flexion were recorded in three patients, of which all were functional.[32,34,35] Loss of motor function was reconstructed with tendon transfers and a free functioning muscle transfer.[32,34] In one case wrist flexion was reconstructed with a partial ulnar nerve transfer to the flexors, however no postoperative muscle grade was measured.[33] All reconstructions were successful albeit the use of neoadjuvant radiotherapy in one patient[34] and a combination of adjuvant and neoadjuvant administration of chemotherapy in another.[32]

Radial nerve

The reconstruction of the radial nerve was described in three case reports.[36–38] Two defects were at the level of the hand,[37,38] while the other was more proximal.[36] All nerve reconstructions used grafts and were performed for reversal of sensory loss. Either the lateral antebrachial cutaneous nerve (LABCN) or sural nerve was used as grafts. Recovery of sensation was good (S3-S3+) in both cases reporting an objective outcome.[36,37] Subjective outcome measures were excellent in both studies describing this.[37,38] Motor defects were reconstructed with tendon grafts in one case.[37] Two cases received radiotherapy, of which one was brachytherapy; both cases had good outcomes.[37,38]

Table 1 Functional outcomes reconstructions upper extremity.

Study, year	Reconstruction	Histology type	Functional outcome[a]						Adjuvant therapy & FU (months)
			Objective measures			Subjective measures			
			Strength	ROM	Sensation	MSTS	DASH	VAS	
			Brachial plexus						
Spiliopoulos 2011	C5 to ADUT with SN grafts + SAN transfer to SSN + triceps branch transfer to AN	MPNST	Shoulder abduction: M4 Elbow flexion: M5 Elbow extension: M5	40° abduction	C5 & C6: S2				nRTx; 20
Tan 2003	GF + C5 & C7 to RN with UN graft + C5 to MN with SN graft + IN to MCN	Fibrosarcoma	Paralysis						aCTx; 144
			Median nerve						
Fujii 2009	Tendon transfers + RSN transfer to MN	Epithelioid sarcoma	50% grasp power of contralateral hand		50% of contra-lateral hand		22.5		nCTx & aCTx; 42
Koshima 2003	ALT + FN graft for MN + UN graft to forearm flexors	Rhabdomyosarcoma			MN: S3+				*NA*; 30
Koulaxouzidis 2016	MN to ON branch of GF + tendon transfer + SN grafts for sensation	Epithelioid sarcoma		Full finger flexion	MN: Protective				nRTx; 60
Rinehart 1989	RAF + SN graft for MN	Synovial sarcoma		Full finger flexion/ extension	D1-3: S3+ D4-5: S4 and S3+				*NA*; 8

Table 1 Continued.

Study, year	Reconstruction	Histology type	Functional outcome[a]						Adjuvant therapy & FU (months)
			Objective measures			Subjective measures			
			Strength	ROM	Sensation	MSTS	DASH	VAS	
			Radial nerve						
Cugola 1985	SN graft for RN	Synovial sarcoma	Wrist extension: M4 Finger extension: M4		RN: S3				None; 8
Lohman 1998	RRF + tendon grafts + LABCN to split RSN	Malignant fibrous histiocytoma	8,6 kg (wrist); 3.3 kg (key); 2.9 kg (D1-tip)	Wrist flexion: 50° Wrist extension: 30°	Flap: S3+	Excellent			nRTx; 8
Mehrara 2008	RRF + LABCN graft for RSN	Epithelioid sarcoma				97%			BRt; mean 47
			Ulnar nerve						
Nicoli 2015	Compound LD and groin flap + SN graft for UN	High-grade liposarcoma	Elbow extension: M4 Wrist flexion: M3 Finger flexion: M3		UN: S3				aRTx; 12
			Digital nerve(s)						
Atiyeh 1996	FRFF + LABCN transfer to UDN D1	Fibrohistiocytic sarcoma		Thumb full ROM	Protective				aRTx; 12
Boorman 1987	CFF + LABCN graft for D1	Myxoid liposarcoma			UDN: S4 RDN: S0				*NA*; 9

Table 1 Continued.

Study, year	Reconstruction	Histology type	Functional outcome[a]						Adjuvant therapy & FU (months)
			Objective measures			Subjective measures			
			Strength	ROM	Sensation	MSTS	DASH	VAS	
Mehrara 2008	RRF + tendon transfers + LABCN grafts for digital nerves	Epithelioid sarcoma				100%			None; mean 47
Mehrara 2008	RRF + SN graft for D1-2	Myofibroblastic tumor				97%			None; mean 47
Mirous 2016	2-stage Hunter + SN grafts for D1-2 + RDN D3-4	MPNST				53%	43	0	aRTx; 66
Mirous 2016	2-stage Hunter + SN grafts for D1-2 + RDN D3	Synovial sarcoma				80%	21	0	nCTx & aCTx; 132
Seal 2005	FRFF + LABCN to PBMN + SN graft for D3-5, silicon rods D4-5	Epithelioid sarcoma		D4&D5: 90-30-30°	D3-5 & flap: S3-S4				nRTx; 16

[a] = DASH: disability of the arm, shoulder, and hand questionnaire (0-100 points, higher score correlates to larger disability), MSTS: musculoskeletal tumor society scale (0-30 points, higher score correlates to higher function), ROM: range of motion (degrees), Sensation: when possible medical research council sensory grade (S0-S5), Strength: when possible medical research council muscle grade / manual muscle testing (0-5), VAS: visual analog scale (0-10) of pain.

aCTx = adjuvant chemotherapy, ADUT = anterior division of upper trunk, ALT = anterolateral thigh flap, AN = axillary nerve, aRTx = adjuvant radiotherapy, BRt = brachiotherapy, CFF = chinese forearm flap, DASH = disabilities of arm, shoulder and hand (score), D = digit, FRFF = free radial forearm flap, FU = follow-up, GF = gracilis flap, IN = intercostal nerve, kg = kilogram, LABCN = lateral antebrachial cutaneous nerve, LD = latissimus dorsi flap, MABCN = medial antebrachial cutaneous nerve, M = Medical Research Council muscle grade, MCN = musculocutaneous nerve, MN = median nerve, MPNST = malignant peripheral nerve sheath tumour, MSTS = musculoskeletal tumor society score, NA = not available, nCTx = neoadjuvant chemotherapy, nRTx = neoadjuvant radiotherapy, ON = obturator nerve, PBMN = palmar cutaneous branch of median nerve, RAF = rectus abdominis flap, RDN = radial digital nerve, RN = radial nerve, RRF = reverse radial forearm flap, RSN = radial sensory nerve, S = sensation, SAN = spinal accessory nerve, SN = sural nerve, SSN = suprascapular nerve, STSG = split-thickness skin graft, UDN = ulnar digital nerve, UN = ulnar nerve

Ulnar nerve

One study reported the reconstruction of 10 centimeter ulnar nerve defect with the use of sural nerve grafts after resection of a sarcoma at the level of the elbow.[39] Restoration of finger and wrist flexion and sensation in the distribution of the ulnar nerve were adequate (M3 and S3 respectively) 12 months postoperatively. The elbow extension deficit was reconstructed with an innervated latissimus dorsi flap. This patient also received adjuvant radiotherapy.

Digital nerve(s)

Five studies reported on seven patients having undergone reconstruction of one or more digital nerve(s).[38,40–43] Most reconstructions (6/7) were performed using a nerve graft, either the LABCN or sural nerve grafts. All but one digital nerve did not recover good sensation (protective or S3-S4).[40,41,43] MSTS scores were good to excellent (80-100%) in three patients,[38,42] while one patient did not obtain good function postoperatively (MSTS 53%, DASH 43).[42] Concomitant tendon defects were reconstructed using transfers or silicon rods.[38,42,43] One study reported a VAS pain outcome score which was 0 in both patients.[42] The use of adjuvant therapy did not result in failed reconstructions in at least three out of four patients.[40,42,43]

Sciatic nerve

Three studies reported a total of seven patients with reconstructions of the sciatic nerve (**Table 2**).[44–46] All reconstructions were performed using nerve grafts, using the sural nerve, the (superficial) peroneal nerve or a combination of both. Preoperative sensory and motor deficits differed between patients, most likely depending on location of defect. Recovery of motor function was functional in only one patient,[46] while two others regained M1 dorsiflexion.[44,45] No recovery of motor function was seen in any of the other patients.[44] Sensation ameliorated in 6 out of 7 patients, all of which gave at least slight protection in some part of the foot. The other patient had a positive Tinel's sign 18 centimeters distally from the reconstruction site at 12 months. Slight protective and protective sensation of the foot sole was gained in three patients only.[44,45] All patients had some form of multimodal treatment.

Peroneal nerve

One patient was reported to have a reconstruction of the deep peroneal nerve at the level of the ankle.[47] A composite gracilis flap was used and the anterior obturator nerve was used to reconstruct the peroneal nerve defect. The gracilis muscle was used for reconstruction of ankle and toe motion. Both motor and sensory recovery were good at seven months postoperatively.

Table 2 Functional outcomes reconstructions lower extremity.

Study, year	Reconstruction	Histology type	Functional outcome[a]					Adjuvant therapy & FU (months)
			Objective measures				Subjective measures	
			Strength	ROM	UAD	Sensation	MSTS	
Sciatic nerve								
Lee 1993[b]	SN & superficial PN grafts for SCN	High-grade spindle cell sarcoma	Dorsiflexion: M3			Positive Tinel's sign 18cm below nerve repair site		nRTx & aRTx; 12
Melendez 2001[b]	SN & PN grafts for SCN	Spindle cell sarcoma	Dorsiflexion: M0		Ankle device	Slight protective (dorsal surface)		nRTx; 4,5
Melendez 2001[b]	PN grafts for SCN	Spindle cell sarcoma	Dorsiflexion/plantar flexion: M3/M4		Ankle device	Slight protective (dorsal surface)		nCTx & aRTx; 12
Melendez 2001	PN grafts for SCN	Spindle cell histiocytoma	Dorsiflexion/plantar flexion: M3/M3		Ankle device	Slight protective (dorsal & plantar surfaces)		nRTx & aCTx; 12
Melendez 2001	SN & PN grafts for SCN	Fibromyxoid sarcoma	Knee flexion/ extension: M3/M5 Dorsiflexion/plantar flexion: M0/M1 Eversion/inversion: M0/M0 Toe flexion/extension: M0/M0		None	Protective (dorsal and lateral plantar surfaces)		nRTx; mean 24
Melendez 2001	SN & PN grafts for SCN	Unclassified sarcoma	Knee flexion/ extension: M5/M5 Dorsiflexion/plantar flexion: M0/M0 Eversion/inversion: M0/M0 Toe flexion/extension: M0/M0		Ankle device	Protective (mediodorsal surface)		nRTx & aCTx; 8

Table 2 Continued.

Study, year	Reconstruction	Histology type	Functional outcome[a]					Adjuvant therapy & FU (months)
			Objective measures				Subjective measures	
			Strength	ROM	UAD	Sensation	MSTS	
Tokumoto 2018	SN grafts for SCN	MPNST	Knee flexion/ extension: M4/M4 Dorsiflexion/plantar flexion: M1/M1			Slight protective (plantar surface of foot)		*NA*; 24
Peroneal nerve								
Deune 2001	GF + anterior branch ON graft for deep PN	Sarcoma, indeterminate type	Full weight-bearing	Full (ankle & great toe extension)	None	Protective (1st web space)		*NA*; 7
Tibial nerve								
Nishio 2012	ALT & fascia lata + SN graft for TN	Myxoid liposarcoma					97%	None; 84

[a] = MSTS: musculoskeletal tumor society scale (0-30 points, higher score correlates to higher function), ROM: range of motion (degrees), Sensation: when possible medical research council sensory grade (S0-S5), Strength: when possible medical research council muscle grade / manual muscle testing (0-5), UAD: use of ambulatory device; [b] = Died of disease.
aCTx = adjuvant chemotherapy; ALT = anterolateral thigh flap; aRTx = adjuvant radiotherapy; cm = centimeters; FU = follow-up in months; GF = gracilis flap; M = Medical Research Council muscle grade; MPNST = malignant peripheral nerve sheath tumour; MSTS = musculoskeletal tumor society (score); NA = not available; nCTx = neoadjuvant chemotherapy; nRTx = neoadjuvant radiotherapy; ON = obturator nerve; PN = peroneal nerve; ROM = range of motion; SCN = sciatic nerve; SN = sural nerve; TN = tibial nerve; UAD = use of ambulatory devices

Tibial nerve

One patient was reported to have a reconstruction of the tibial nerve at the level of the ankle.[48] A defect of the ankle and foot flexors was reconstructed with fascia lata strips, which was covered with an anterolateral thigh flap. Seven years postoperatively MSTS score was excellent (97%).

Complications

A total of four complications were reported, of which three were wound-related problems.[38,42,44] One patient developed wound dehiscence after a reconstruction of the RSN with an LABCN graft and the use of brachytherapy.[38] Two wound complications occurred after the reconstruction of the sciatic nerve in one study.[44] One patient developed radiation-induced hand lesions which impaired hand function.[42] No patient was reported to have developed neuropathic pain. Unfortunately, a total of three patients died within the first year after surgery due to distant metastases.[44,46]

Discussion

Nerve reconstructions by either grafting or transfers can aid in avoiding postoperative muscle weakness and recover loss of sensation. Nerve reconstructions after resection of soft tissue sarcomas in extremities have nevertheless had little attention in literature and are irregularly carried out. When performed they seem to be successful in a selected group of patients and the use of multimodal treatment does not seem to impair these outcomes. Success rates were however higher in upper extremity defects as opposed to lower extremity defects. Neuromas and neuropathic pain may possibly also be avoided.

Preservation of nerves

Before considering any nerve reconstruction, surgeons should always consider strategies to preserve nerve structures. The resection of nerves significantly decreases functional outcomes.[9,10,12–14,16,17] Adequate preoperative imaging may help surgical planning by demonstrating the extent of nerve involvement. Recently, the use of diffusion tensor imaging (DTI) has shown promising results in facilitating three-dimensional images of nerve involvement.[49] Furthermore, in the past decades several techniques have shown to significantly reduce the need for nerve resection. Neoadjuvant treatment can possibly reduce tumor size prior to surgery. Firstly, in large previously unresectable extremity sarcomas, isolated-limb perfusion (ILP) can be administered.[50,51] During this process the perfusion of an extremity is isolated and intra-arterial chemotherapy is infused, decreasing tumor size. Secondly, while neoadjuvant radiotherapy does not only have smaller long-term toxicities compared to adjuvant therapy, it may also reduce size preoperatively, especially in myxoid liposarcoma.[52] And lastly, epineural dissection has been shown effective to avoid resection of major nerves

without impairing local control.[53–55] In the latter case, when STS encase nerves by less than three quarters of their circumference, dissection of epineurium only suffices. However, as this means a 'close' margin was achieved, postoperative radiotherapy is indicated.[53–55]

Nerve reconstruction versus no reconstruction in LSS

Nerve reconstructions are only carried out in 0.4% of all STS patients,[19] even though nerve resections occur in 1.2-12%.[9,10,12–17] Reasons for surgeons to not reconstruct nerves may vary, including the paucity of literature of its use in ablative surgery and therefore expected outcomes, not involving reconstructive surgeons with familiarity of nerve reconstruction options in surgical planning, insufficient knowledge of the impact of neuropathic pain and insensate extremities on functionality, and the uncertainty of outcomes of nerve reconstruction when using radiotherapy and chemotherapy. Reconstruction of a sciatic nerve defect has been subject of debate in the last decades. Whereas sciatic nerve involvement of STS used to be a hard contraindication for limb salvage, because of extensive loss of both motor and sensory function, nowadays it is not. Several studies have shown that its resection without reconstruction could lead to acceptable functionality and patients prefer this over amputation.[56] As a result, many discourage reconstructing the sciatic nerve as outcomes of reconstruction were reportedly poor. Three studies included in this review do indeed show that muscle function of the lower leg will most likely not recover, but most patients will regain some protective sensation in the foot.[44,45] Three out of seven patients even had recovery of plantar foot sensation, even though follow-up of patients was less than a year in some cases, possibly underestimating final outcomes. Restoration of sensation in the foot has repeatedly been shown to reduce rates of foot ulcers in diabetic patients and thus decrease the need for amputation.[57] This is not a phenomenon reserved for diabetic feet solely, it has also been reported to have caused secondary amputation in STS as well.[13] Although restoration of motor function was not seen in the aforementioned cases, after reconstruction in traumatic patients, some did regain distal motor function, especially in children.[58] Altogether, reconstruction of the sciatic nerve may therefore be beneficial in some cases and restoration of sensation should be considered as its primary goal. Although resection of the femoral nerve without reconstruction show similar functional outcomes as sciatic nerve resections, one study showed that fractures occurred commonly as a result from loss of knee extension.[9] Therefore reconstruction of knee extension should strongly be considered. In case more than half of the quadriceps muscle is intact, reconstruction of the femoral nerve could be considered, otherwise a biceps femoris transfer or free functioning latissimus dorsi flap may recover lost function.[59–61] In STS overall, as LSS has become standard of care, functional extremities are extremities that also have sensation, especially in the hand and foot sole. While motor defects may also be reconstructed using tendon transfers or free functioning muscle transfers, sensory loss can only be compensated with nerve reconstructions.[61] Furthermore, after resection of nerves, neuropathic pain is not rare

in STS.[62,63] One study reported a prevalence of 25% of surgically treated sarcomas.[63] In these patients functional outcomes were worse in these patients, with significantly lower Toronto Extremity Salvage Score (TESS) and MSTS scores. This further underlines the importance of preventing neuropathic pain as its occurrence has a disabling impact and is not limited to trauma only. Although many techniques are available to treat neuromas, nerve reconstruction is known to prevent neuropathic pain as it decreases the risk of neuroma formation,[64] which may be the reason no patient was reported to have it in this study.

Multimodal treatment and nerve regeneration

Although LSS is performed for functionality purposes, in STS oncologic treatment should be prioritized in almost any case. This means that clear margins are essential, but radiotherapy also remains an important in treating extremity STS.[3] The effect of multimodal treatment on the regeneration of nerves has had little attention in a clinical setting, which has made clinicians cautious when combining the two. The effect of chemotherapy on the regenerative capacity of nerves has been studied in one study in mice and did however not show any adverse effect.[65] Other preclinical studies have shown that both adjuvant as well as neoadjuvant radiotherapy do not impair function in mice after nerve reconstruction.[66–69] It is nonetheless advocated that whenever nerve reconstructions are performed in an irradiated wound bed, fibrous tissue is removed.[70] Additionally, free tissue transfers for wound coverage are commonly performed after STS resection and also form a good wound bed for nerves as they are unirradiated. This study shows that indeed functional outcome may not necessarily be impaired by multimodal treatment, nor has its timing. These findings are also supported when evaluating the success rate of neurotization in free functioning muscle transfers in extremity STS.[61]

Nerve reconstruction options in extremity STS

Reconstructive strategies applied in an extremity STS patient should ideally be discussed during surgical planning in a multidisciplinary setting in order to review all possible options for both the tumor ablative surgery, e.g. close margin surgery, as well as reconstructive options. Including a wide range of reconstructive options and diverse presentation of patients no one tool will suffice in STS patients and ideal reconstruction should be discussed case-by-case. However, some general rules may be taken into consideration. If the resection of a nerve seems inevitable, grafting or distal nerve transfers may restore lost function. Distal nerve transfers are increasingly being used in trauma cases, showing good functional restoration and diminishing the time of a nerve to reach its end target.[24,71] Theoretically, nerve transfers can be of great use in sarcoma surgery as well, especially in cases of proximal nerve defects such as partial plexus resections. Secondly, distal nerve transfers offer the option of providing a reconstruction outside of the operation and radiation field. This may particularly be interesting in case of an extensively scarred tissue bed due to repeat surgeries or

neoadjuvant radiotherapy administration. To date, many nerve transfers have been proposed in the literature, most commonly in upper extremity lesions.[24,71,72] But nerve transfers in the leg are also possible in certain cases.[73] In case nerve transfers are not preferred or not a viable option, grafting procedures are possible. Traditionally autografts are used and depending on the caliber of the resected nerve sural nerve grafts can be used as single strands or as cable grafts, but in smaller nerves such as digital nerves the posterior interosseous nerve, medial antebrachial cutaneous nerve, or LABCN may be used depending on ease of harvest and surgical preference. In rare cases of short defects nerve conduits can have a potential role as well, avoiding the need of a donor nerve and thus avoiding donor site infections, hematomas, and a sensory deficit.[74] However, because of the need for wide margins, larger defects are more common and in case of minimal nerve involvement the possibility of epineural dissection still remains the preferred option. In larger defects however, autografts have superior outcomes.[75] Decellularized nerve grafts may also play a role, especially in cases of large defects and insufficient autologous grafts.[76]

Strengths and limitations

As only a small of amount of cases have been described in literature; this study is inherently subdued to limitations. As patient characteristics, treatment modalities, and outcome measures used varied widely across studies, direct comparisons of reconstruction outcomes and the effect of multimodal treatment were impaired. Also, no study has yet been able to study functional outcome differences between comparable patients who did and did not undergo nerve reconstruction, which makes interpretability of the additional benefit difficult. Additionally, as nerves regenerate slowly, adequate follow-up is essential to truly observe final outcomes. This may especially be of importance in proximal defect reconstruction, such as sciatic nerve reconstruction, of which some cases had less than 12 months follow-up. Overall however, this study does show that nerve reconstructions can be successful after extremity soft tissue sarcoma resections. Reconstruction of sensation in the hand and foot is possible and important for good functional extremities. Yet surgical teams should always consider patient's age, anticipated tumor defect, life expectancy, smoking, and diabetes for the success of a nerve reconstruction. In case fast recovery of function is needed, tendon transfers should also be considered.[77] Large defects will likely also need additional muscle for recovery of muscle function. Future studies should be stimulated to use both objective outcome measures such as MRC grades adjacent to more subjective outcome measures such as MSTS, DASH, or the PROMIS-extremity. To effectively consider the additional value of functional reconstructions and the reconstruction of nerve defects specifically, patients should be stratified from other LSS patients and amputees from large STS databases.

Conclusion

Nerve reconstructions in extremity STS have rarely been described, yet may yield good results in LSS. Restoration of sensation in LSS is possible when performing nerve reconstruction and best results are seen after upper extremity defects. Reconstruction of motor nerve function can also restore satisfactory function without the use of free functioning muscle flaps. The use of multimodal therapy does not seem to preclude failure. Therefore nerve reconstructions should be considered as part of a reconstructive surgeon's armamentarium after STS resection.

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Supplemental Table 1 Search syntax for PubMed and Embase databases

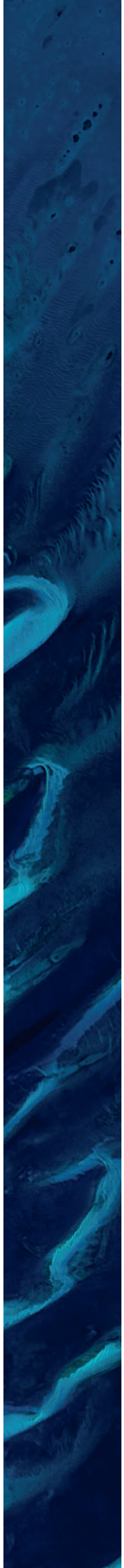
PubMed search: 26-6-2018	(Reconstruction[tiab] OR flap*[tiab] OR neurotization[tiab] OR nerve graft[tiab] OR nerve crossover[tiab] OR limb salvage[tiab] OR ((muscle[tiab] OR nerve[tiab] OR tendon[tiab]) AND (transfer[tiab] OR reconstruction[tiab] OR transplantation[tiab])) OR Free Tissue Flaps[MeSH Terms] OR Tendon transfer[MeSH Terms] OR Nerve Transfer[MeSH Terms] OR Limb Salvage[MeSH Terms]) AND ((Sarcoma[tiab] OR soft tissue neoplasm[tiab] OR soft tissue cancer[tiab] OR tendinous tissue neoplasm[tiab] OR tendinous tissue cancer[tiab]) OR Sarcoma[MeSH Terms] OR Soft Tissue Neoplasm[MeSH Terms])) AND (Extremity[tiab] OR extremities[tiab] OR limb[tiab] OR limbs[tiab] OR plexus[tiab] OR shoulder[tiab] OR shoulders[tiab] OR arm[tiab] OR arms[tiab] OR hand[tiab] OR hands[tiab] OR finger[tiab] OR fingers[tiab] OR digit[tiab] OR digits[tiab] OR thumb[tiab] OR thumbs[tiab] OR hip[tiab] OR hips[tiab] OR leg[tiab] OR legs[tiab] OR ankle[tiab] OR ankles[tiab] OR foot[tiab] OR feet[tiab] OR toe[tiab] OR toes[tiab])
Embase search: 26-6-2018	(Reconstruction:ti,ab OR flap*:ti,ab OR neurotization:ti,ab OR nerve graft:ti,ab OR nerve crossover:ti,ab OR limb salvage:ti,ab OR ((muscle:ti,ab OR nerve:ti,ab OR tendon:ti,ab) AND (transfer:ti,ab OR reconstruction:ti,ab OR transplantation:ti,ab)) OR 'free tissue graft'/exp OR 'tendon transfer'/exp OR 'tendon transplantation'/exp OR 'nerve transplantation'/exp OR 'limb salvage'/exp) AND (Sarcoma:ti,ab OR soft tissue neoplasm:ti,ab OR soft tissue cancer:ti,ab OR tendinous tissue neoplasm:ti,ab OR tendinous tissue cancer:ti,ab OR 'sarcoma'/exp OR 'soft tissue cancer'/exp) AND (Extremity:ti,ab OR extremities:ti,ab OR limb:ti,ab OR limbs:ti,ab OR plexus:ti,ab OR shoulder:ti,ab OR shoulders:ti,ab OR arm:ti,ab OR arms:ti,ab OR hand:ti,ab OR hands:ti,ab OR finger:ti,ab OR fingers:ti,ab OR digit:ti,ab OR digits:ti,ab OR thumb:ti,ab OR thumbs:ti,ab OR hip:ti,ab OR hips:ti,ab OR leg:ti,ab OR legs:ti,ab OR ankle:ti,ab OR ankles:ti,ab OR foot:ti,ab OR feet:ti,ab OR toe:ti,ab OR toes:ti,ab) AND ([article]/lim) AND ([Embase]/lim)

10

Surgical Strategies and the Use of Functional Reconstructions after Resection of MPNST: an International Survey on Surgeons' Perspective

Martin E
Slooff WBM
van Houdt WJ
van Dalen T
Verhoef C
Coert JH

Submitted



Abstract

Background Malignant peripheral nerve sheath tumors (MPNST) are aggressive and possibly morbid sarcomas because of their origin in nerve tissue. However, postoperative functional status has had little attention in literature. The reconstruction of lost function after excision of any soft tissue sarcomas has also infrequently been described, but research does show that such reconstructions may be beneficial. This study investigated how surgical considerations and the use of functional reconstructions differed among surgeons treating MPNST.

Methods Multiple national and international surgical societies were asked to distribute this survey amongst their members. Survey responses were analyzed overall and between surgical subspecialties (surgical oncology/neurosurgery/plastic surgery/other).

Results A total of 30 surgical oncologists, 30 neurosurgeons, 85 plastic surgeons, and 29 'others' filled out the survey. Surgical oncologists had the highest case load ($p<0.001$). Functional status was usually considered preoperatively among all subspecialties (65.1%); 42.2% never considered performing less extensive resections to preserve function. Neuropathic pain and motor deficits are seen in 40.9±22.9% and 36.7±25.5% respectively. Functional reconstructions for motor and sensory deficits were more commonly considered by plastic surgeons and 'others'. Relative contraindications for reconstructions did not differ between subspecialties ($p>0.05$). Most surgeons would reconstruct directly or directly unless radiotherapy would be administered (62.7%). On average, surgeons would consider functional reconstructions when estimated survival is 3.0±2.0 years.

Conclusion Surgical treatment of MPNSTs differs slightly among subspecialties. Neuropathic pain, motor deficits, and sensory deficits are commonly acknowledged postoperative morbidities. Functional reconstructions are varyingly considered by surgeons. Surgical oncologists and neurosurgeons treat most patients, yet may be least likely to consider functional reconstructions. A multidisciplinary surgical and reconstructive approach may be beneficial in MPNSTs.

Introduction

Malignant peripheral nerve sheath tumors (MPNST) are rare and aggressive soft tissue sarcomas (STS) that can occur at any anatomical site.[1] MPNSTs occur more commonly in neurofibromatosis type 1 (NF1) patients, accounting for approximately 25-50% of all patients.[2–5] Surgical resection of these tumors is essential to increase survival, while radiotherapy and chemotherapy mainly increase progression-free survival.[6,7] Despite curative intents of aggressive treatment, local recurrences and distant metastases are common and survival remains poor.[5,6]

In general, MPNSTs are treated equally to other STS, and for extremity tumors limb salvage procedures have become standard of care.[8] Combining radiotherapy with limb-sparing surgery has been proven to increase functionality without impairing oncological outcomes.[8,9] For extremity tumors not resectable without morbid surgery or amputation, isolated limb perfusions followed by resection can increase the limb salvation rates.[10] Resecting nerves is sometimes, however, inevitable when operating on any STS and has repeatedly been reported to increase morbidity.[11–13] This is still frequently a reason for amputation in case of major neurovascular involvement.[14,15] The resection of MPNSTs always requires the resection of a nerve, but thus far, postoperative functionality and reconstructions in MPNSTs have had little attention in literature, even though reported rates of motor deficits are as high as 30%.[16] Moreover, functional reconstructions are still not common practice in any STS, both for sensory and motor deficits.[17–19] Aside from functional deficits, neuropathic pain can develop postoperatively also resulting in disability and psychological distress.[20] This phenomenon has not previously been studied in MPNSTs, nor has it widely been studied in sarcoma literature.[21] As neuropathic pain is commonly caused by neuroma formation in transected nerves,[22] MPNST patients may be even more prone to its development.

Not only are MPNSTs rare tumors, but they are also operated by different surgical subspecialties due to their tissue of origin. Altogether, more can therefore be learned on surgeons' operative and reconstructive considerations. This study is not aiming to address the ideal surgical specialty for operating these patients, but aims to investigate considerations for function preservation and reconstruction among these specialties by means of an international survey. Additionally, variation between subspecialties is assessed.

Methods

Study design and survey instrument

A survey was constructed by two authors (E.M. and J.H.C.) and tested internally with all co-authors from different surgical subspecialties. A secure electronic data capturing tool (REDCap) provided by the Dutch Plastic Surgery Society (NVPC) was used to construct the survey. This study is part of a larger survey addressing both surgical and non-surgical treatment considerations for localized MPNST. A total of 22 questions (30 in total) were used for this study, of which seven were demographic. The complete survey can be found in **Supplementary File 1 of Chapter 5**. Approval for this study was obtained from our institutional review board.

Study population

Several surgical societies were asked to distribute the survey link by email among their members with an accompanying text explaining the purpose of the research. Anyone involved in the surgical management of MPNSTs was asked to fill out the survey. A reminder email was sent thereafter. The survey was sent to the members of the Dutch Society of Surgical Oncology (NVCO), the Dutch Society for Surgery of the Hand (NVVH), the peripheral nerve section of the Dutch Society for Neurosurgery (NVVN), the American Society for Peripheral Nerve (ASPN), the peripheral nerve section of the European Association of Neurosurgical Societies (EANS), and the Soft Tissue and Bone Sarcoma Group of the European Organization for Research and Treatment of Cancer (EORTC). Survey responses were filled out anonymously and no person identifying data was inquired.

Statistical analysis

Responses were summarized per surgical subspecialty: surgical oncology, neurosurgery, plastic surgery, and other surgical subspecialties. Differences were calculated with χ^2-tests for categorical data; for continuous data either unpaired student t-tests (two groups) or one-way analysis of variance tests (more than two groups) were used. P-values <0.05 were considered statistically significant. Statistical analyses and data visualization were conducted using R version 3.6.0 (R Core Team, 2019).

Results

Demographics of survey responders

A total of 174 respondents filled out the survey, most of which were European surgeons (**Figure 1**). The most common surgical subspecialty was plastic surgery (48.9%, **Figure 2**). The 'other' surgical subspecialty group consisted mainly of non-oncologic orthopedic and general surgeons other than surgical oncologists. On average, respondents had 14.2 years (±9.5) of surgical experience, of which the largest proportion (38.2%) finished their surgical training less than 10 years ago (**Table 1**). Fellowship experience differed between subspecialties ($p<0.001$) and neurosurgeons most commonly classified themselves as peripheral nerve surgeons ($p<0.001$). Highest caseloads were performed by surgical oncologists ($p<0.001$). What tumor locations surgeons operate differed between subspecialties ($p<0.05$), except for the brachial plexus (41.9%) and extremities which were operated by most surgeons (87.2%, both $p>0.05$).

Postoperative functional status

Most surgeons observe a combination of neuropathic pain, motor disability, and sensory loss after resection of MPNSTs (69.7%, **Figure 3**). On average, surgeons reported 36.8±25.5% of patients presenting with a motor deficit and 40.9±22.9% with neuropathic pain postoperatively, with no differences reported between subspecialties (both $p>0.05$). Conservation of function is always considered preoperatively by 52.8% of respondents, more commonly by plastic surgeons (65.5%, $p>0.05$, **Table 1**). Others consider it only in some cases based on localization (n = 3), in case it does not interfere with oncologic resection (n = 1), in case of multiple lesions (n = 1), if another nerve bundle

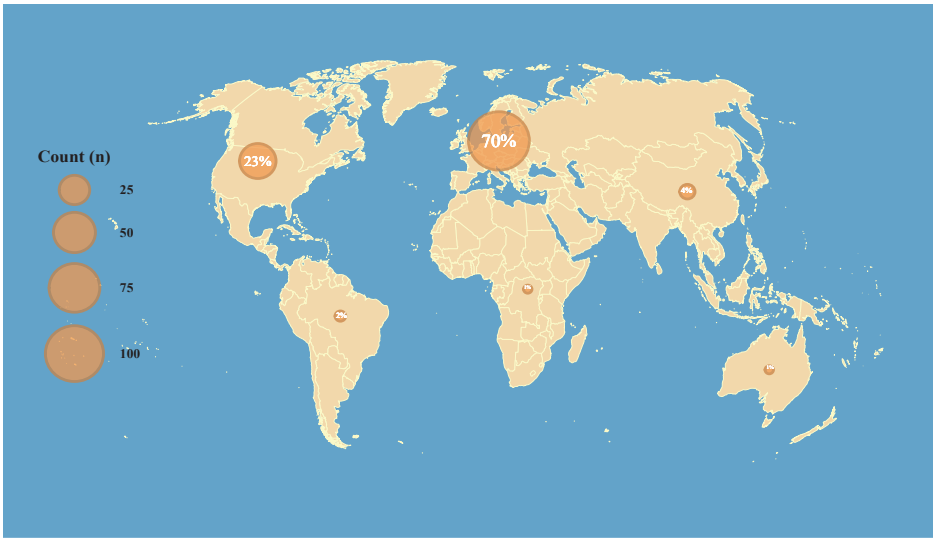


Figure 1 World map showing survey respondents' country of origin. The size of each bubble is proportional to amount of respondents.

is separable (n = 1), and depending on tumor grade (n = 1). The largest proportion of surgeons would never resect less extensively in order to preserve function (42.1%), regardless of subspecialty (p>0.05). A smaller proportion would only resect less in case free margins are not presumed possible (36.1%).

Table 1 Respondents'experience nad nerve handling.

Variable		Overall	Oncologic Surgery	Neuro-surgery	Plastic Surgery	Other Specialties	P
Number of participants		174	30	30	85	29	
Experience	0-10 years	58 (38%)	8 (29%)	10 (37%)	31 (43%)	9 (36%)	
	10-20 years	56 (37%)	14 (50%)	10 (37%)	25 (35%)	7 (28%)	0.585
	20+ years	38 (25%)	6 (21%)	7 (26%)	16 (22%)	9 (36%)	
	Mean (SD)		15.64 (±9.31)	13.26 (±8.64)	13.49 (±9.81)	15.64 (±10.13)	0.603
PNS	No	56 (37%)	21 (78%)	4 (15%)	23 (32%)	8 (32%)	**<0.001**
	Yes	95 (63%)	6 (22%)	23 (85%)	49 (68%)	17 (68%)	
Fellowships	PNS	53 (35%)	1 (4%)	15 (56%)	23 (32%)	14 (56%)	
	Sarcoma	29 (19%)	23 (85%)	0 (0%)	4 (6%)	2 (8%)	**<0.001**
	Other/none	84 (56%)	8 (30%)	12 (44%)	53 (74%)	11 (44%)	
Consider function preoperatively	No	29 (35%)	7 (28%)	7 (39%)	9 (31%)	6 (54%)	
	Sometimes	7 (78%)	4 (16%)	2 (11%)	1 (3%)	0 (0%)	0.403
	Yes	47 (53%)	14 (56%)	9 (50%)	19 (66%)	5 (46%)	
Collaborate with PNS	No	38 (46%)	8 (32%)	7 (39%)	14 (50%)	9 (82%)	
	Sometimes	20 (24%)	14 (56%)	1 (6%)	4 (14%)	1 (9%)	**<0.001**
	Yes	24 (29%)	3 (12%)	10 (56%)	10 (36%)	1 (9%)	
Intraoperative nerve conduction test	No	23 (28%)	13 (52%)	2 (12%)	5 (18%)	3 (27%)	
	Sometimes	22 (27%)	7 (28%)	3 (18%)	9 (32%)	3 (27%)	**0.023**
	Yes	36 (44%)	5 (20%)	12 (71%)	14 (50%)	5 (46%)	
Look for nerve of origin	No	5 (6%)	2 (8%)	0 (0%)	2 (7%)	1 (9%)	
	Sometimes	16 (20%)	5 (20%)	4 (24%)	3 (11%)	4 (36%)	0.539
	Yes	60 (74%)	18 (72%)	13 (77%)	23 (82%)	6 (55%)	
Nerve end handling	Nothing	15 (25%)	7 (29.2%)	3 (21%)	2 (12%)	3 (50%)	
	Bury	24 (39%)	11 (46%)	7 (50%)	4 (24%)	2 (33%)	
	End closure	9 (15%)	4 (17%)	1 (7%)	3 (18%)	1 (17%)	0.284
	TMR	6 (10%)	1 (4%)	1 (7%)	4 (24%)	0 (0%)	
	Other	7 (12%)	1 (4%)	2 (14%)	4 (24%)	0 (0%)	

PNS: peripheral nerve surgeon

Intraoperative nerve handling

In general, most respondents always look for the nerve of origin (74.1%, p>0.05, **Table 1**). Those who do not, question the relevance of the nerves from which MPNSTs originate. The largest proportion of surgeons (46.3%) never collaborates with a peripheral nerve surgeon when operating MPNSTs, while 29% of all respondents will always collaborate with one. The use of intraoperative nerve conduction testing (NCT) also differs significantly between subspecialties (p<0.05), generally surgical oncologists never use it (52.0%), while neurosurgeons most commonly responded 'always' (70.6%).

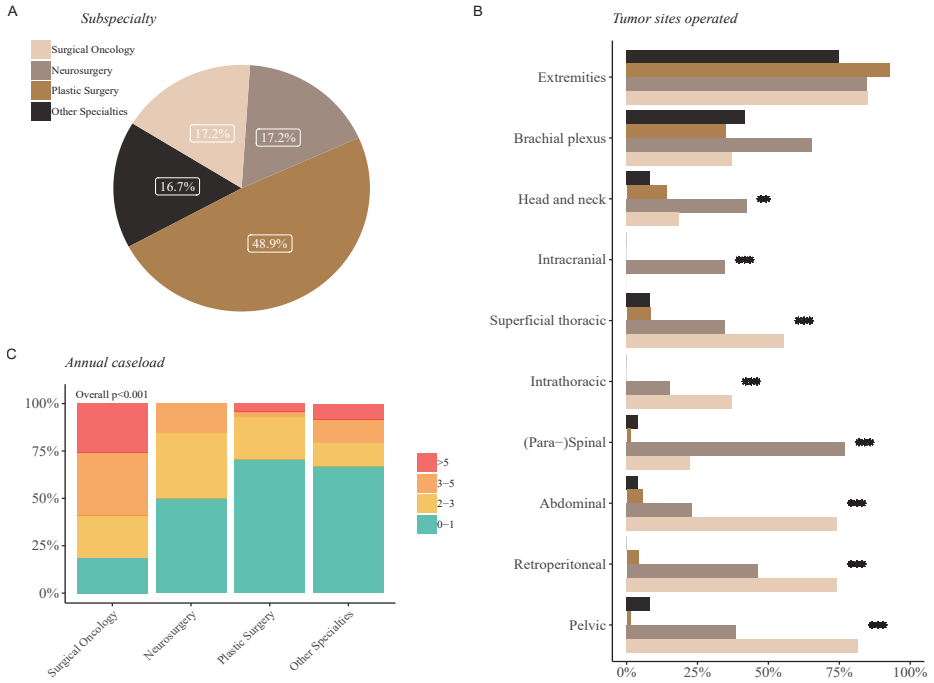


Figure 2 Demographic distributions of surgical subspecialties. A) Distribution of respondents' surgical subspecialty B) Distribution of tumor locations operated per subspecialty C) Distribution of annual surgical caseload per subspecialty; p-values: * = <0.05, ** = <0.01, *** = <0.001

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Preferred handling of the transected nerve varied among all subspecialties, but overall did not differ from each other (p>0.05). Plastic surgeons were however least likely to do nothing (11.8%). The preferred method of neuroma prevention is burying the stump in a bone, muscle, or vein (39.3%). Variation exists within all subspecialties, but did not differ from each other (p>0.05).

Functional reconstructions

Overall, 39.2% always considers functional reconstructions when a motor deficit is anticipated (**Figure 4**). Plastic surgeons were most likely to always consider functional reconstructions in these cases (66.7%, p<0.05). Functional reconstructions were less commonly considered whenever a sensory deficit was to be anticipated (15.2%). Plastic surgeons were most likely to always consider a functional reconstruction in such a case (33.3%, p<0.05). A total of 14.1% of surgeons did not consider any MPNST patient eligible for functional reconstruction, none of whom were plastic surgeons. Of surgeons that did consider functional reconstructions, preferences for timing of reconstruction differed, but not between subspecialties (p>0.05). Most would reconstruct directly or directly unless adjuvant radiotherapy is administered (62.7%), in which case the reconstruction would be performed after radiotherapy administration. The type of reconstructions

surgeons regard as eligible for MPNST patients differed between subspecialties (all p<0.05, **Figure 5**). Plastic surgeons most commonly considered nerve reconstructions, nerve transfers, tendon transfers, and free functioning muscle transfers (FFMT) to be possibilities to reconstruct function in MPNST patients (all >80%). Neurosurgeons and surgical oncologists were both most likely to answer that they do not know, and most commonly considered options ineligible. Relative contraindications for functional reconstructions in MPNST patients with a functional deficit did not differ between subspecialties (p>0.05). Most contraindications were only checked by less than a third of all respondents. Overall, 20.5% of respondents did not deem slow rehabilitation after reconstruction, slow nerve regeneration, the use of radiotherapy, a non-extremity tumor site, the general poor prognosis of MPNST patients, or the nerve of origin as a 'sick' nerve relative contraindications for functional reconstructions in MPNST patients. Responses did not differ significantly between subspecialties except for general low survival of MPNST patients (p<0.05). Neurosurgeons (70.6%) and plastic surgeons (40.7%) most commonly considered the latter a reason to not reconstruct lost function. All surgeons agreed that on average, a patient needs to have a life expectancy of at least 3.0 ± 2.0 years to be considered eligible for reconstruction. (p>0.05, **Figure 4C**).

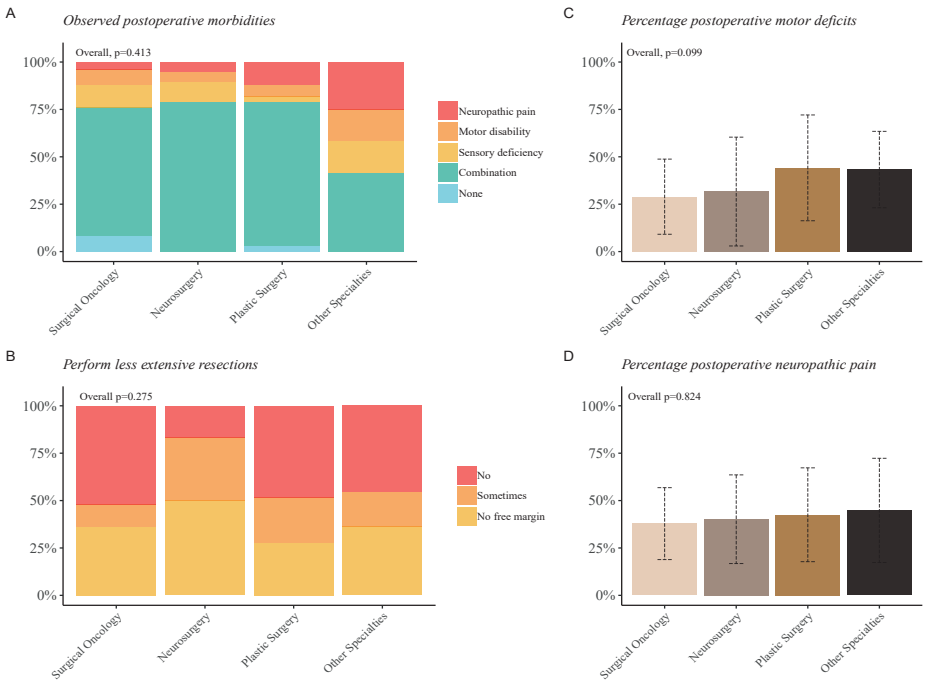

Figure 3: Complications after MPNST resections. A) Most common postoperative complication per subspecialty B) Considering resecting less tumor per subspecialty C) Mean postoperative prevalence of motor deficits per subspecialty D) Mean postoperative prevalence of neuropathic pain per subspecialty.

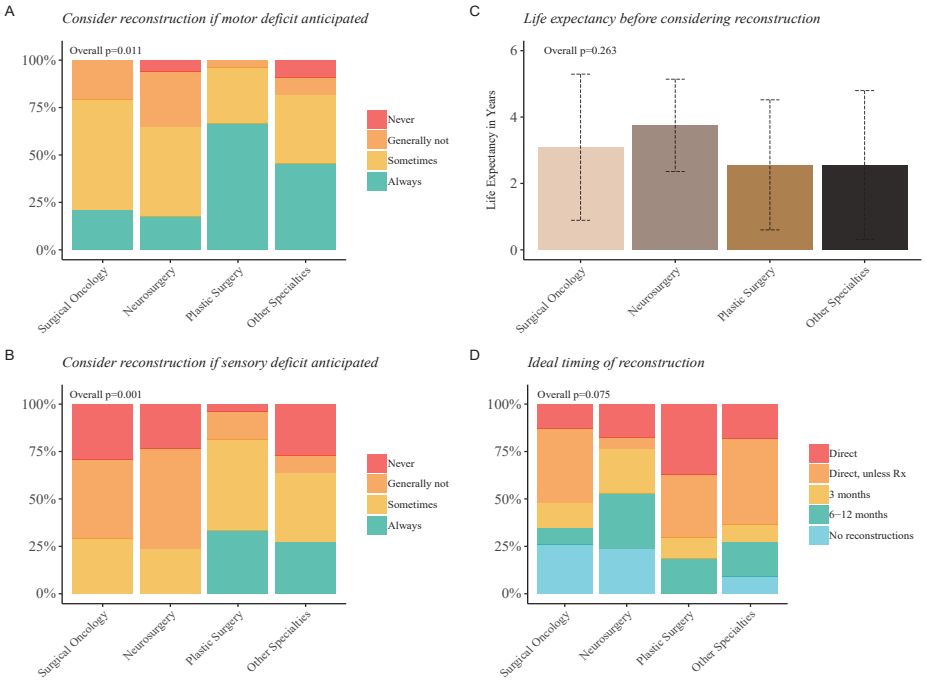

Figure 4 Considerations for performing functional reconstructions in MPNST. A) Distribution per subspecialty considering a functional reconstruction when a motor deficit is anticipated B) Distribution per subspecialty considering a functional reconstruction when a sensory deficit is anticipated C) Mean life expectancy before considering a functional reconstruction per subspecialty D) Ideal timing of functional reconstruction per subspecialty, Rx = radiotherapy.

Discussion

Practice variation exists both within as well as between surgical subspecialties treating MPNSTs. Although neuropathic pain, motor deficits, and sensory deficits are common postoperative morbidities among all surgical specialties, little consensus is present on ideal balancing of functional and oncological outcomes. Highest surgical caseloads are among surgical oncologists and neurosurgeons, yet these subspecialties are least likely to consider functional reconstructions in MPNST patients. Conversely, there is little difference in opinion between subspecialties on relative contraindications.

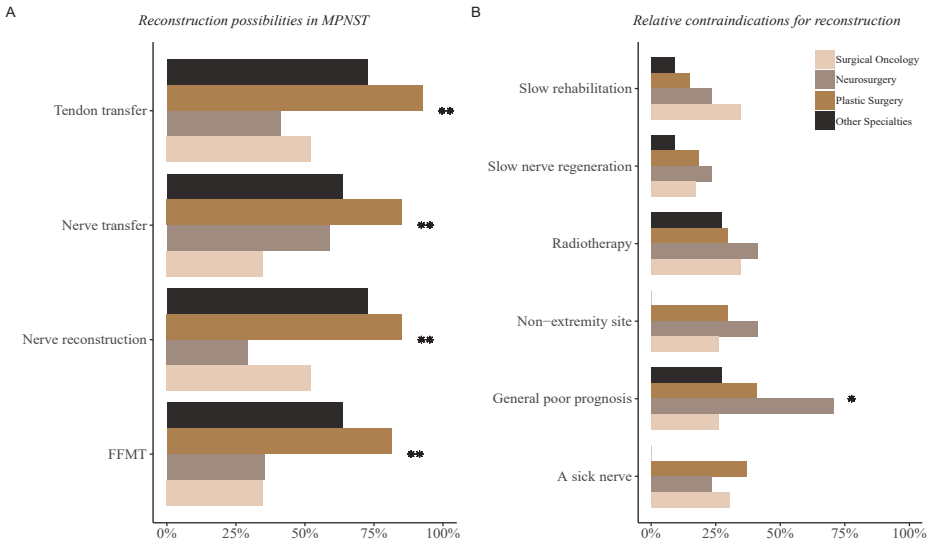

Figure 5 Functional reconstructions. A) Percentage of respondents per subspecialty considering type of reconstruction as an option in MPNST patients, FFMT = free functioning muscle transfer B) Percentage of respondents per subspecialty considering a factor as relative contraindication for functional reconstruction; p-values: * = <0.05, ** = <0.01, *** = <0.001.

Functional reconstructions in MPNST

Despite the fact that oncological treatment should generally be prioritized in the treatment of any MPNST, early considerations on the preservation of function preservation may benefit patients, especially in the era of limb salvage treatment. Fortunately, not every MPNST will need functional reconstructions as not all MPNSTs arise in major nerves or require the resection of adjacent nerves, tendons, or large muscle bellies. This is reflected in a study reporting a rate of 30% motor deficits after resection of MPNSTs.[16] Fortunately, studies have shown that microscopically positive resection margins do not significantly decrease overall survival in MPNSTs.[4–6] For MPNSTs arising in the brachial and sacral plexus this implies that when adjacent nerve bundles that are not completely encased by the tumor epineural dissection and postoperative radiotherapy may suffice.[23] Reconstructive surgeons are generally equipped with several options for functional reconstructions, yet some do not consider all options suitable in MPNST patients. The selection of the reconstruction is patient- and tumor-site specific, but when large muscle resections are required FFMTs need to be considered, while more distal defects may be restored with the use of tendon transfers.[17,24] Nerve reconstructions are rarely performed in any STS and only few cases have been described in the literature, yet may result in good outcomes.[19] Nerve reconstructions are also crucial for restoring sensation. Although the reconstruction of the sciatic nerve is controversial, protective sensation of the foot

sole is feasible recovering after just more than a year.[25,26] Not only will patients have more than just a warm leg, foot ulcers and secondary amputations may be avoided, which is not a phenomenon reserved for diabetic patients.[11] However, while functional reconstructions may well provide good restoration of function, candidate selection is of utmost importance. Indeed, as some reconstructions require a long rehabilitation and as nerves only regenerate slowly, a patient's life expectancy should be adequate for reconstructions to be purposeful. Clinical studies have shown that localized MPNSTs have a median survival of 5-8 years.[3,4,6] This is considerably longer than the 3 years, that respondents to our survey agreed upon before considering functional reconstructions.

Multimodal treatment and timing of reconstruction

As sarcomas commonly require the use of radiotherapy and sometimes chemotherapy, some surgeons consider this to be a contraindication for performing functional reconstructions. The effect of multimodal therapy on outcomes after functional reconstructions has however had little attention in literature. In available case series on functional reconstructions, negative effects of multimodal therapy are not evident, not even when performing nerve reconstructions.[17] Negative effects on nerve regeneration are also not seen in animal studies.[27,28] However, the use of neoadjuvant radiotherapy may complicate nerve reconstruction and fibrous tissue should ideally be removed in order to create a well vascularized wound bed.[29] As more research emerges on the use of nerve transfers in trauma patients,[30,31] their implementation in tumor surgery can be studied further. Nerve transfers can provide the opportunity to restore function outside of irradiated tumor fields and shorten the time of nerves to reach their end targets compared to nerve grafting.[30,31] The ideal timing of reconstruction also remains a topic of debate, which is reflected in this survey. As MPNSTs are high-grade sarcomas in almost any case, obtaining free margins remains crucial before performing any reconstruction. However, after obtaining these margins, direct reconstruction has shown superior results over delayed surgical reconstruction.[32–34] Early reconstruction is surgically less complex as fibrosis is not yet extensive, ameliorating nerve and vessel identification, thus decreasing possible complications.[32–34] Also, rehabilitation can be started earlier, which then may improve functional outcomes.[32–34]

Neuropathic pain in MPNST

Neuropathic pain, the loss of sensation in combination with paradoxal allodynia and hyperalgesia, can be highly disabling. This has shown to significantly decrease functional outcome in sarcoma patients.[21] This postoperative complication is even less studied than motor deficits. On the other hand, 25% of all sarcoma patients are reported to have at least mild neuropathic pain.[21] Supposedly, in MPNSTs this may be as high as 40% of all patients, but this has, to the authors knowledge, not been studied in patients previously. Postoperative neuropathic pain is commonly caused by neuroma formation and preventive measures may decrease rates of neuropathic pain.[35,36] A meta-analysis showed that once present, only 77% of neuroma surgeries are effective, underlining

the importance of prevention.[36] Interestingly, in a recent systematic review of functional outcomes after nerve reconstructions in extremity STS, none of the patients were reported to have neuropathic pain.[19] A wide variety of surgical techniques are described, most of which rely on guiding the transected nerve to tissue in which to grow.[35,36] To date, no single technique has repeatedly shown to be superior to others. Ideal nerve stump handling will therefore need to be assessed on a case-by-case base, taking the anatomical location and particular nerve in consideration. Novel techniques such as targeted muscle reinnervation have shown promising results, especially in amputees.[37] As observed in our study, this is not yet widely used, but has the most interest among plastic surgeons. In order for surgeons to perform neuroma preventive actions, precarious dissection will aid in identifying neighboring nerves and the nerve from which the MPNST originated. Intraoperative nerve conduction testing may further help discriminate between sensory and motor fascicles as well, which in turn aids in fascicular dissection: motor fascicles can be possibly spared and sensory nerves can be appropriately handled for preventing neuroma formation. However, neuroma preventive measures are not studied in MPNST and sarcoma surgery since oncological outcomes are prioritized in both clinical and research settings.

Strengths and limitations

This survey does have its methodological inherent limitations. Respondent bias is always present as only physicians who are interested will fill out the survey. Also, as we restricted our distribution to a selected list of surgical societies, selection bias may be present as surgeons that do operate MPNSTs but are not members of these societies were excluded from participation. Additionally, this paper does not assess the effect of volume and surgical discipline on oncological and functional outcome. In general, it has been found that oncological outcome is better when patients are treated in sarcoma centers with ample experience with sarcoma patients.[38] It seems advisable to collaborate between surgical subspecialties, such as surgical oncologists, peripheral nerve surgeons, and reconstructive surgeons to optimize both oncological and functional outcome, especially when motor or mixed nerves are involved. Although current literature is still limited on the use of functional reconstructions and prevention of neuropathic pain in STS, the high rates of postoperative morbidity in MPNSTs are acknowledged and most surgeons agree that restoration of function is warranted. Overall survival of localized disease varies depending on size, location, and grade of the tumor, but combining responses to this survey with the knowledge that localized MPNSTs have a median survival of at least 5 years, the consideration for function preservation seems justifiable. And while there is no specific prognostic tool for MPNSTs specifically, calculators for all STS do exist which could be helpful in the decision making process.[39,40] Future studies should nonetheless be encouraged to evaluate functional outcomes in MPNSTs specifically, in order to elucidate techniques in minimizing morbidity.

Conclusion

Practice variation exists both within as well as between surgical subspecialties treating MPNSTs. Neuropathic pain, motor deficits, and sensory deficits are common to cause postoperative morbidity in MPNST patients. Consensus has yet to be reached on the preservation and reconstruction of function in MPNST. Surgical oncologists and neurosurgeons see the most patients, but these subspecialties are least likely to consider functional reconstructions in MPNST patients even though relative contraindications are similar between subspecialties. Surgeons agree that functional reconstructions may be considered in local MPNSTs with a life expectancy of more than three years.

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11

Morbidity and Functional Reconstructions in Malignant Peripheral Nerve Sheath Tumors

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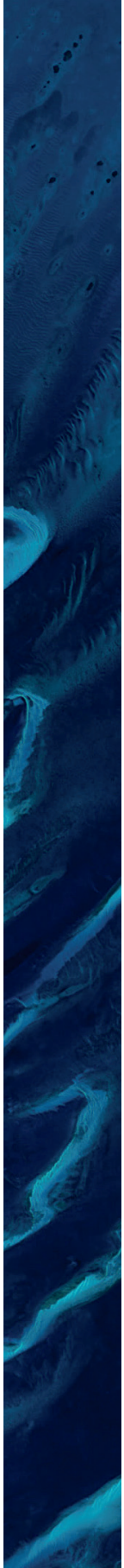
Submitted



Abstract

Background Malignant peripheral nerve sheath tumors (MPNSTs) are aggressive soft tissue sarcomas and their resection may lead to serious morbidity. Postoperative motor and sensory deficits are under-reported in the literature and functional reconstruction is infrequently carried out. This study aimed to identify the incidence of postoperative motor and sensory deficits in malignant peripheral nerve sheath tumors (MPNST) and patient risk factors for these deficits. A secondary objective was investigating the outcomes of functional reconstructions.

Methods Postoperative function and treatment of MPNSTs diagnosed from 1988-2019 in 10 cancer centers was obtained. Patients with and without function loss were compared, defined by <M3 motor grade or critical sensory loss. Critical sensation was defined as partial or complete loss of hand, foot, or buttocks sensation.

Results Seven-hundred-fifty-six patients (33.4% neurofibromatosis type 1, NF1) were included. MPNSTs originated in 34.4% from a major nerve. Of 658 surgically treated patients, 27.2% had <M3 muscle power and 24.3% critical sensory loss. Amputations were carried out in 61 patients. Risk factors for motor and sensory loss included patients with NF1, symptomatic, large (≥5cm), deep-seated, extremity, and plexus tumors originating from major nerves (all $p<0.05$). Twenty-six patients underwent functional reconstructions. The majority (64%) of these patients regained at least M3 muscle power and 33% M4 despite 86% receiving multimodal therapy.

Conclusion Resection of MPNSTs commonly results in motor and sensory deficits. Patients with NF1, symptomatic, large, deep-seated tumors, and arising from major nerves were at higher risk for developing postoperative morbidity. Functional reconstructions are infrequently performed, but can improve functional outcomes.

Malignant peripheral nerve sheath tumors (MPNSTs) are rare soft tissue sarcomas (STS) and comprise approximately 2% of all STS subtypes.[1] Neurofibromatosis type 1 (NF1) patients account for approximately 25-50% of MPNSTs; others occur sporadically or are radiation-induced.[2–5] Because of their origin in nervous tissue they may occur at any anatomical site. Treatment recommendations for localized disease follow general high-grade STS guidelines.[6] Surgical resection increases survival in MPNSTs and radiotherapy may be used to decrease local recurrences.[2–5] The role of chemotherapy in localized disease is being investigated, but remains controversial.[7,8] Despite aggressive treatment, the prognosis remains poor.[3]

Oncological outcomes remain the focus in both STS and MPNST literature, and functional outcomes are infrequently described. The resection of any nerve in STS leads to significant decrease in function and quality of life.[9,10] MPNSTs have poor oncological outcomes and are particularly prone to major functional deficits after resection, yet little is known on the incidence and prevention of such morbidity. The resection of nerves, in contrast to only muscle tissue as in STS, may lead to both motor and sensory deficits. These deficits may be restored using functional reconstructions, yet such reconstructions are still rarely performed.[11–14] Reasons for this may be multifactorial, including the major focus on oncological outcomes, the unawareness of reconstructive possibilities, or the uncertainty of the effects of radiation and chemotherapy on the outcomes of reconstructions. Although amputation numbers have drastically fallen the last decades, major neurovascular involvement is still seen as a reason for amputation, commonly because of anticipated functional deficits.[15–17]

The purpose of this study was to 1) investigate the incidence of postoperative motor and sensory deficits in MPNSTs; 2) identify patients at increased risk for such deficits; and 3) assess the use and outcomes of functional reconstructions.

Methods

Patient population

MPNST patients diagnosed from 1988-2019 and receiving treatment in 10 cancer centers were included in this study. Follow-up was available until March 2020. Uncertain diagnoses were excluded based on pathological reports and available information during follow-up in patient files. The data request was approved by all ethical committees of participating centers.

Covariates

Patient-, tumor-, and treatment-specific covariates were retrospectively extracted from electronic patient files. Tumor sites were categorized into extremity, brachial plexus, head and neck (including intracranial sites), pelvic, core (including superficial and deep

thoracic, abdominal, and retroperitoneal sites), and unknown tumor site. Tumor size was categorized into <5cm, 5-10cm, and ≥10cm. Tumors originating from below the deep fascia were categorized as deep-seated. Whenever the nerve of origin was known it was categorized into motor, sensory, or mixed nerves. These were all considered major nerves. Surgical margins were defined as tumor-free (R0), microscopically positive (R1), and macroscopically positive (R2). Postoperative function loss was deducted from both clinical notes as well as surgical and pathological reports clarifying if nerves were completely excised. Motor deficits were graded according to the Medical Research Council muscle scale from M0 to M5. Sensory deficits were defined as any sensory deficit. Critical sensation was defined as partial or complete sensory loss of hand, plantar foot, or buttocks. Only motor and sensory deficits directly related to the MPNST and its resection were included. Sites of amputation were recoded into forequarter, above elbow, below elbow, hand, and finger for the upper extremities, and into hemipelvectomy, above knee, below knee, foot, and toe for the lower extremities. Functional reconstructions were defined as reconstructions aimed at restoring function of resected structures and may include: free functioning muscle transfers (FFMT), tendon reconstruction using transfers or grafts, or any nerve reconstruction using either grafts or transfers. Pedicled muscle transfers as a functional reconstruction were seen as tendon transfers.

Outcomes and statistical analysis

Qualitative assessment was performed for the presence and persistence of preoperative motor and sensory deficits, newly formed motor and sensory deficits, and outcomes of functional reconstructions. Baseline and treatment differences were assessed between patients with and without less than M3 postoperative motor deficits and between patients with and without critical sensory deficits using χ^2-tests for categorical variables. Cases with unknown deficits were excluded from these comparisons. P-values <0.05 were considered statistically significant. Statistical analyses and data visualization were conducted using R version 4.0.0 (R Core Team, 2020).

Table 1 Patient characteristics and presenting symptoms of all patients.

Variable		Overall	
N		756	
Age (years)			
	0-18	72	(9.5%)
	19-60	512	(67.7%)
	60+	172	(22.8%)
	Mean (SD)	44.3 (±19.4)	
Male gender		400	(53.0%)
MPNST			
	Sporadic	441	(58.3%)
	NF1	253	(33.4%)
	Radiation-induced	62	(8.2%)
Tumor site			
	Extremities	286	(37.8%)
	Brachial plexus	52	(6.9%)
	Head and neck	92	(12.2%)
	Pelvic	68	(9.0%)
	Core	248	(32.8%)
	Unknown	10	(1.3%)
Major nerve of origin			
	Any	260	(34.4%)
	Motor	15	(4.1%)
	Mixed	190	(80.7%)
	Sensory	51	(15.2%)
Tumor size			
	<5cm	155	(27.0%)
	5-10cm	221	(36.3%)
	≥10cm	191	(36.7%)
	NA	189	
	Mean (SD)	8.6cm (±5.6)	
Tumor depth			
	Superficial	83	(18.2%)
	Deep	373	(81.8%)
	NA	25	
Synchronous metastasis		99	(13.4%)
Symptoms at diagnosis			
	Mass	273	(56.8%)
	Pain	349	(48.8%)
	Motor deficit	114	(15.8%)
	Sensory deficit	101	(13.4%)
	Other	94	(13.4%)
	NA	72	
Multiple symptoms			
	1 symptom	350	(58.5%)
	2 symptoms	169	(28.3%)
	>2 symptoms	79	(13.2%)
	NA	158	

N: number of patients, NA: not available, NF1: neurofibromatosis type 1, SD: standard deviation

Table 2 Function loss after MPNST surgery.

Variable		Overall	
Surgically treated patients		658	
Motor deficit			
	Any	199	(34.7%)
	None	375	(65.3%)
	NA	81	
Motor grade			
	Less than M4	168	(29.1%)
	Less than M3	157	(27.2%)
	Unknown grade	23	
Sensory deficit			
	Any	171	(54.6%)
	None	142	(45.4%)
	NA	342	
Critical sensory loss			
	Any	76	(24.3%)
	Complete hand	5	(6.6%)
	Partial hand	28	(36.8%)
	Complete foot	30	(39.5%)
	Partial foot	10	(13.2%)
	Buttocks	3	(3.9%)
Amputation			
	Any	61	(9.3%)
	At initial surgery	34	(55.7%)
	At recurrence surgery	27	(44.3%)
Level of amputation			
Upper extremity	Forequarter	12	(60.0%)
	Above elbow	4	(20.0%)
	Below elbow	2	(10.0%)
	Hand	0	(0.0%)
	Finger	2	(10.0%)
Level of amputation			
Lower extremity	Hemipelvectomy	20	(48.8%)
	Above knee	12	(29.3%)
	Below knee	5	(12.2%)
	Foot	1	(2.4%)
	Toe	3	(7.3%)
Prosthetic or orthoses			
	No	30	(60.0%)
	Yes	20	(40.0%)
	NA	138	
Walking aid			
	Any	14	(22.6%)
	No	48	(77.4%)
	NA	111	

M: Medical Research Council muscle grade, NA: not available

Results

Patient population

A total of 756 patients were treated at the participating centers. The mean age was 44.3 years including 72 children (**Table 1**). Fifty-three percent of the patients were male. NF1 patients comprised 33.4% of all patients. Most tumors were large (73.0% ≥5cm) and deep-seated (81.8%). MPNSTs most commonly occurred at extremity sites (37.8%) and 34.4% were known to originate from a major nerve. Patients presented in 13.4% of cases with synchronous metastases. A mass or spontaneous pain were the most common presenting symptoms, but 15.8% of patients presented with motor deficits and 13.4% with sensory deficits (**Table 1**). Of patients with a neurologic deficit, 48.3% presented with both motor and sensory deficits.

Function loss

Postoperative motor deficits were present in 199 patients (34.7%), of which 157 patients (27.2%) were known to have a deficit with less than M3 muscle power of the nerve's target muscles or an adjacently resected structure (**Table 2**). Most patients that presented with motor deficits (58%) had persisting motor deficits with less than M3 muscle power after tumor resection (**Table 3**). NF1 patients, larger, and deep-seated tumors were also associated with an increased risk of developing postoperative motor deficits (all $p<0.001$). Extremity tumors will develop postoperative motor deficits in 37.1% of cases, but brachial plexus tumors (57%) and pelvic tumors (55%) have the highest risk for persistent motor deficits ($p<0.001$). MPNSTs originating from major nerves more commonly had postoperative motor deficits (<0.001); incidence of motor deficits were 64.1% for those originating from motor or mixed nerves. Surgical resection margins were associated with motor grade ($p = 0.04$). Sensory deficits were postoperatively present in 171 patients (54.6%). Almost half (44.4%) of these cases had at least partial sensory loss of the hand or feet. Patients presenting with sensory loss had persistent loss of critical sensation in 55%. NF1 patients, larger, and deep-seated tumors were associated with loss of critical sensation (all $p<0.05$). Extremity tumors will develop critical sensory loss in 32.0% of cases, but brachial plexus tumors (63%) and pelvic tumors (44%) were at highest risk for developing critical sensory loss ($p<0.001$). Peripheral nerve surgeons were more commonly involved in cases with motor and sensory deficits ($p<0.001$), but were not involved in 64.2% and 60.5% of cases respectively. Amputations were carried out in 61 patients at any point in time. Most amputations (56%) were carried out during initial surgery. For the upper extremity, forequarter amputations were most commonly performed; for the lower extremity, hemipelvectomies were most common. The use of prosthetics, orthoses, and walking aids were commonly unknown.

Table 3 Differences between patients with and without function loss.

Variable		At least M3		Less than M3		P	No loss of critical sensation		Loss of critical sensation		P
N		393		157			228		76		
Age (years)											
	0-18	32	(8.1%)	19	(12.1%)		29	(12.7%)	8	(10.5%)	
	19-60	271	(69.0%)	113	(72.0%)	0.10	147	(64.5%)	60	(78.9%)	**0.04**
	60+	90	(22.9%)	25	(15.9%)		52	(22.8%)	8	(10.5%)	
Male gender		201	(51.1%)	88	(56.4%)	0.31	124	(54.6%)	34	(44.7%)	0.19
NF1		102	(27.3%)	78	(52.0%)	**<0.001**	78	(35.6%)	36	(50.0%)	**0.04**
Tumor site											
	Extremities	141	(35.9%)	83	(52.9%)		87	(38.2%)	41	(53.9%)	
	Brachial plexus	19	(4.8%)	25	(15.9%)		11	(4.8%)	19	(25.0%)	
	Head and neck	56	(14.2%)	7	(4.5%)	**<0.001**	35	(15.4%)	0	(0.0%)	**<0.001**
	Pelvic	17	(4.3%)	21	(13.4%)		14	(6.1%)	11	(14.5%)	
	Core	156	(39.7%)	20	(12.7%)		77	(33.8%)	5	(6.6%)	
Major nerve of origin		95	(24.2%)	105	(66.9%)	**<0.001**	59	(34.7%)	46	(86.8%)	**<0.001**
Nerve type											
	Motor	6	(6.5%)	2	(1.9%)		10	(10.4%)	0	(0.0%)	
	Mixed	49	(52.7%)	96	(92.3%)	**<0.001**	59	(61.5%)	65	(94.2%)	**0.02**
	Sensory	38	(40.9%)	6	(5.8%)		27	(28.1%)	4	(5.8%)	
Tumor size											
	<5cm	97	(35.3%)	24	(18.0%)		54	(29.0%)	14	(20.6%)	
	5-10cm	106	(38.5%)	60	(45.1%)	**0.001**	65	(34.9%)	34	(50.0%)	0.09
	≥10cm	72	(26.2%)	49	(36.8%)		67	(36.0%)	20	(29.4%)	
Deep-seated tumor		157	(69.4%)	101	(96.2%)	**<0.001**	141	(82.2%)	51	(96.2%)	**0.02**
Motor deficit at presentation		35	(9.5%)	49	(32.0%)	**<0.001**	33	(15.1%)	27	(36.5%)	**<0.001**

Table 3 Continued.

Variable		At least M3		Less than M3		P		No loss of critical sensation		Loss of critical sensation		P
Sensory deficit at presentation		37	(9.4%)	40	(25.5%)	**<0.001**	25	(11.0%)	30	(39.5%)		**<0.001**
Surgical margins												
	R0	224	(57.0%)	98	(62.4%)	**0.04**	125	(54.8%)	47	(61.8%)		0.33
	R1	84	(21.4%)	41	(26.1%)		64	(28.1%)	18	(23.7%)		
	R2	47	(12.0%)	12	(7.6%)		26	(11.4%)	10	(13.2%)		
	Unknown	38	(9.7%)	6	(3.8%)		13	(5.7%)	1	(1.3%)		
Local recurrence		101	(28.0%)	50	(33.1%)	0.29	64	(29.9%)	21	(28.4%)		0.92
Involvement of PNS		63	(19.2%)	49	(35.8%)	**<0.001**	49	(23.8%)	30	(44.8%)		**0.002**

M: medical research council muscle grade, N: number of patients, NA: not available, NF1: neurofibromatosis type 1, PNS: peripheral nerve surgeon

Functional reconstructions

A total of 26 patients (4.0%) underwent functional reconstructions (**Table 4**), including 7 NF1 patients. Twenty-one of these reconstructions (80.8%) were part of initial treatment plan. Seven of these patients received immediate reconstruction, while the others were performed in a delayed fashion (delay 13-1076 days). Four patients had a functional reconstruction after a first local recurrence, while case 14 had the reconstruction after resection of a second local recurrence. Six reconstructions were performed for deficits of the lower extremity, 12 in the upper extremity, 5 of the brachial plexus, and 3 of the head and neck. The MPNST originated from a major nerve in 18 cases, in other cases an adjacent nerve or muscle was sacrificed. A total of 11 nerve grafting procedures, 4 nerve transfers, 9 tendon transfers, 3 tendon grafts, and 2 free functioning muscle transfers (FFMT, including a rotationplasty) were performed. All but 4 patients received additional oncological treatment; chemotherapy and radiotherapy were administered in 38% and 62% of cases respectively. Four patients received both chemo- and radiotherapy. Of known outcomes in motor function of extremity tumors, 10/15 had improvements in motor function. One patient had an unknown MRC grade, but 9/14 patients regained at least M3 motor function. Excluding the facial nerve reconstruction, 4/13 patients regained M4 muscle grade or more. The five patients that did not regain at least M3 power either needed to undergo re-resection because of a local recurrence (Case 14 and 22), inadequate margins (Case 16), or an amputation after prolonged deep wound infections of a megaprosthesis (Case 17). One patient had less than 6 months follow-up after reconstruction (Case 2). Ten nerve grafting procedures were performed to (in part) improve critical sensation, but 3 reconstructions resulted in unfavorable outcomes for the aforementioned reasons and follow-up of sensory function was not available for the remaining 7 patients.

Table 4 Functional reconstructions performed in MPNST patients.

Case	Sex, age	YOD	NF1	Size	Tumor site	Treatment stage	Interval (days)*	Reconstructions	Other treatment	Motor outcome	Sensory outcome	Clinical outcome	F-U (months)
1	F, 30	2018	NF1	*NA*	Ulnar nerve	Initial treatment	0	AIN to motor ulnar and sural nerve grafts for ulnar	adRTx	*NA*	*NA*	ANOD	10
2	M, 11	2016	NF1	12.5cm	Tibial nerve	Initial treatment	1076	Sural nerve graft	neoCTx	Complete tibial nerve palsy	No recovery	ANOD	35
3	F, 42	2016	S	1.5cm	Medial cord	Initial treatment	34	ECRL to FDP II-V, BR to FPL, EIP to opponens	adCTx	*NA*	*NA*	LR, DOD	45
4	F, 10	2016	NF1	4.0cm	Quadriceps muscle	Recurrence	*NA*	Rotationplasty	neoCTx	*NA*	*NA*	ANOD	43
5	F, 11	2015	S	8.5cm	Radial nerve	Initial treatment	43	PT to ECRB, FDS III to EPL, FCR to EDC	None	*NA*	*NA*	ANOD	48
6	F, 48	2015	NF1	3.4cm	Median nerve	Initial treatment	*NA*	FDP II side-to-side FDP III-V, BR to FPL, EIP to opponens, RSN to UDN dig. I	neoRTx	*NA*	*NA*	DOD	22
7	M, 39	2014	S	*NA*	Ulnar nerve	Recurrence	*NA*	Sural nerve graft for ulnar nerve	RTx	*NA*	*NA*	DOD	65
8	F, 19	2013	S	6.0cm	Tibial nerve	Initial treatment	*NA*	Sural nerve graft	neoRTx, neoCTx	*NA*	*NA*	ANOD	6
9	F, 9	2013	S	3.8cm	Facial nerve	Initial treatment	659	Cross-facial nerve graft with gracilis muscle transfer	adRTx, adCTx	Amelioration in rest and smile	*NA*	ANOD	79
10	F, 12	2011	S	3.0cm	Hypoglossal nerve	Initial treatment	*NA*	Nerve graft	None	*NA*	*NA*	DOD	81
11	M, 58	2011	S	4.5cm	Radial nerve	Initial treatment	1025	PT to ECRB, FDS IV to EPL and EIP, FDS III to EDC, FCR to APL	neoRTx, adCTx	Finger extension M3, wrist extension M3	No recovery	LR, M, DOD	62

Table 4 Continued.

Case	Sex, age	YOD	NF1	Size	Tumor site	Treatment stage	Interval (days)*	Reconstructions	Other treatment	Motor outcome	Sensory outcome	Clinical outcome	F-U (months)
12	F, 60	2010	S	2.1cm	C5-6	Initial treatment	13	Ulnar to brachialis nerve, median to biceps to branch	neoRTx	*NA*	*NA*	DOD	22
13	F, 36	2010	NF1	10.0cm	Posterior cord	Initial treatment	159	PT to ECRB, FDS IV to EPL, FDS III to EDC IV/V, FCR to APL	adRTx	Finger extension M3, Wrist extension M2	No recovery	M, DOD	76
14	M, 57	2007	S	5.0cm	Deltoid muscle	Recurrence	*NA*	Pedicled LD	None	Shoulder abduction M0	No recovery	LR, M, DOD	61
15	M, 22	2006	NF1	5.5cm	Sciatic nerve	Initial treatment	0	Gracilis to semitendinosus	adRTx	Knee flexion M3	No recovery	ANOD	135
16	M, 49	2006	S	*NA*	MCN	Initial treatment	0	Sural nerve graft	adCTx	Elbow flexion M0	No recovery	ANOD	137
17	M, 73	2006	S	4.3cm	Tibial bone	Initial treatment	0	Tendon allograft for patella	None	Amputation	*NA*	ANOD	53
18	F, 4	2005	S	6.1cm	Brachial plexus	Initial treatment	0	Nerve grafting**: C5 to SSN, C6 to MCN, C6 and C7 to median nerve	neoCTx	Shoulder abduction M4,elbow flexion M4, wrist flexion M4, finger and thumb flexion M2-3	*NA*	LR, M, DOD	41
19	F, 31	2001	S	7.0cm	Lateral cord	Initial treatment	*NA*	Nerve graft and nerve transfer	neoRTx	Amelioration of function	*NA*	DOD	25
20	F, 59	2000	S	1.8cm	Parotid gland	Recurrence	*NA*	PL graft in FRFF for mouth corner anchorage	adRTx	Amelioration in rest	*NA*	LR, ANOD	239
21	F, 37	2000	S	7.5cm	Median nerve	Initial treatment	513	ECRB to FPL, EIP to APB, partial FDP IV/V to FDP II/III	ILP, adRTx	All hand function M4-5	No recovery	ANOD	200
22	F, 44	1998	S	7.5cm	Median nerve	Initial treatment	0	Sural nerve grafts	adRTx	Complete median nerve palsy	No recovery	LR, DOD	35

Table 4 Continued.

Case	Sex, age	YOD	NF1	Size	Tumor site	Treatment stage	Interval (days)*	Reconstructions	Other treatment	Motor outcome	Sensory outcome	Clinical outcome	F-U (months)
23	M, 22	1997	S	1.5cm	Palm of hand	Initial treatment	26	PL to FCU	adRTx	Normal hand function	*NA*	ANOD	162
24	F, 20	1993	NF1	22.0cm	Forearm	Recurrence	*NA*	Ulnar nerve graft for ulnar and median nerve	neoCTx	*NA*	*NA*	M, *NA*	*NA*
25	M, 29	1992	S	*NA*	Median nerve	Initial treatment	0	Nerve graft	adRTx	*NA*	*NA*	ANOD	332
26	M, 15	1992	S	*NA*	Subpatellar	Initial treatment	72	Tendon allograft for patella reconstruction	Brachytherapy	Knee extension M4+	*NA*	M, DOD	35

*Time interval between initial surgical resection and functional reconstruction in days; **Nerve grafts were: ulnar nerve, superficial radial nerve, and medial cutaneous nerve

adCTx = adjuvant chemotherapy, adRTx = adjuvant radiotherapy, ANOD = alive no evidence of disease, APB = abductor pollicis brevis, APL = abductor pollicis longus, BR = brachioradial, dig = digit, DOD = dead of disease, ECRB = extensor carpi radialis brevis, ECRL = extensor carpi radialis longus, EDC = extensor digitorum communis, EIP = extensor indicis proprius, FCR = flexor carpi radialis, FCU = flexor carpi ulnaris, FDP = flexor digitorum profundus, FDS = flexor digitorum superficialis, FPL = flexor pollicis longus, FRFF = free radial forearm flap, ILP = isolated limb perfusion, LD: latissimus dorsi, LR = local recurrence, M = metastasis, MCN = musculocutaneous nerve, neoCTx = neoadjuvant chemotherapy, neoRTx = neoadjuvant radiotherapy, NA: not applicable or unknown, NF1: neurofibromatosis type I, PL = palmaris longus, PT = pronator teres, RSN = superficial radial nerve, S = sporadic patient, SSN: suprascapular nerve, UDN: ulnar digital nerve, YOD: year of diagnosis

Discussion

This study found that postoperative motor and sensory deficits are common morbidities after resection of MPNSTs. In patients who presented with motor or sensory deficits, these morbidities will likely persist after resection, but not in all cases. MPNSTs originating from major nerves were commonly resected completely resulting in major deficits. NF1 patients, large and deep-seated tumors were at an increased risk for postoperative deficits, more so for MPNSTs originating in the brachial plexus and pelvic area.

Surgical treatment of MPNST

In general, MPNSTs are ideally resected with wide margins.[5,6,18,19] Nonetheless, MPNSTs recur relatively frequently even when R0 margins are obtained.[2,20,21] When an MPNST arises from a major nerve, achieving microscopically free margins requires the resection of the nerve; in plexal MPNSTs, the resection of adjacent nerves may be required. Performing nerve-sparing procedures may be possible in some cases as reflected in our series, but will likely result in R1 resections. However, when performing resections with planned microscopic positive margins in combination with radiotherapy, local recurrence rates do not differ from achieving clear surgical margins.[22,23] R1 resections have also not been proven to affect survival in MPNSTs.[3,5,24] Nonetheless, a recent survey showed that many surgeons operating on MPNSTs are hesitant to perform less extensive resections regardless of surgical subspecialty.[25]

Use of functional reconstructions in MPNST

Ideal reconstructive strategies depend on several factors including patient age, exact functional deficits, the need for soft tissue coverage, and available donors for nerve and tendon transfers. As prognosis remains poor in MPNSTs, oncological treatment should be prioritized. However, with median survival ranging between 5-8 years in localized disease,[3–5] patients may live a significant part of their remaining life with substantial morbidity and less independence in activities of daily living (ADL). This is of importance in pediatric patients with MPNSTs who have a better prognosis compared to adults and whose survival has improved the last decades.[26,27] Considering postoperative function early on in a multidisciplinary team can improve patient selection for function preservation and functional reconstruction planning. Fortunately, not all MPNSTs will result in functional deficits or in deficits that require reconstruction. One smaller study found a motor deficit rate of 30%,[28] which is in line with the rate found in this study of any surgically resected MPNST. Functional reconstructions are unfortunately not routinely incorporated in STS treatment.[11–13] Systematic reviews have shown that functional outcomes may be satisfactory after the resection of extremity STS with the majority of cases recovering at least M3 muscle grade and high functional scores, despite multimodal therapy even for nerve reconstructions.[13,14] This can also be concluded from cases presented in this study who would otherwise have M0 deficits.

Surgeons should be encouraged to incorporate functional reconstructions as part of their surgical treatment plan as it improves quality of life. **Table 5** summarizes general motor and sensory deficits that could be anticipated when resecting major nerves and general reconstructive options to restore these functions. Altogether, when major limb or hand function is lost due to nerve or musculotendinous resection, attempts to reconstruct motor function should be considered. Whenever loss of critical sensation takes place, attempts can be made at restoring sensation with the use of nerve grafting. The reconstruction of sciatic nerve defects have long been topic of debate. While it used to be a reason for amputation in the past, nowadays it is not.[29] Sciatic nerve defects tend to be large with long distance to their target muscles which is why many discourage reconstructing the defect. However, studies in STS specifically showed that the majority of patients are likely to recover at least protective sensation of the foot and is why some advocate its reconstruction even though motor function is rarely restored.[30–32] Additionally, the reconstruction of nerves may reduce neuropathic pain.[33]

Combining oncological treatment and reconstructions

The exact effect of multimodal therapy on outcomes of functional reconstructions has not been studied extensively. But to date, there has not been an indication of its use precluding successful results.[13,14] Even nerve regeneration does not seem significantly affected by the use of radiotherapy or chemotherapy in this study or other series. These findings are supported by preclinical studies in mice.[34–36] Ideal timing of reconstruction also remains controversial. Obtaining tumor-free margins may however be crucial not only for oncological outcomes, but also diminishing the need for additional resections after reconstruction. Some surgeons emphasize the need for fresh frozen coupes preoperatively or even resecting more of the originating nerve as skip lesions may be present.[2,25,37,38] Whenever adequate margins have been obtained, early reconstructions show superior results over delayed reconstructions.[39–41] Early reconstructions are generally less complex as tissue fibrosis is less extensive, which ameliorates nerve and vessel identification, in turn decreasing possible complications.[39–41] Rehabilitation can also start early, improving functional outcomes.[39–41]

Table 5 Possibilities for reconstruction

Location		Motor deficit	Reconstruction	Value[a]	Sensory deficit	Value[a]
			Upper extremity			
Brachial plexus[2]		Arm, shoulder, and hand function	TT, NT, NG, FFMT	++	Arm, shoulder, and hand	+
Musculocutaneous nerve		Biceps function	NT, NG, FFMT	++	Lateral lower arm	+/-
Axillary nerve		Shoulder abduction / stabilization	NT, NG, TT, FFMT	+	Lateral upper arm	+/-
Median nerve	Proximal	Wrist and finger flexion	TT, NT, NG, FFMT	++	Hand palm, dig. I-IV	+
	Distal	Thumb function	TT, NG, NT, FFMT	++	Hand palm, dig. I-IV	++
Radial nerve	Proximal	Triceps function, wrist and finger extension	TT, NT, NG, FFMT	++	Posterior arm and radiodorsal hand, dig. I	+
	Distal	*NA*	*NA*	*NA*	Radiodorsal hand, dig. I	+
Ulnar nerve		Hand function	TT, NT, NG, FFMT	++	Ulnar side arm and hand, dig. IV-V	++
			Lower extremity			
Lumbosacral plexus[3]		Gluteal, leg, ankle, and foot function	NG, NT, TT, FFMT	+	Complete leg, buttocks, foot	+/-
Sciatic nerve	Proximal	Biceps femoris, ankle, and foot function	NG, TT, FFMT	+/-	Dorsal proximal leg, laterodorsal distal leg, plantar and dorsal foot	+/-
	Distal	Ankle and foot function	NG	+/-	Laterodorsal distal leg, plantar and dorsal foot	+
Femoral nerve	Proximal	Quadriceps and iliopsoas function	NT, TT, NG, FFMT	++	Ventrolateral proximal leg, medial distal leg	+/-
	Distal	Quadriceps function	NT, TT, NG, FFMT	++	Medial distal leg	+/-
Obturator nerve		Adductors	TT, NG, FFMT	+/-	Medial proximal leg	+/-
Peroneal nerve		Foot and toe extension	TT, NT, NG, FFMT	++	Lateral lower leg, dorsum foot	+/-
Tibial nerve		Foot and toe flexion	NG, TT, NT, FFMT	+	Dorsal lower leg, plantar foot	++
			Head and neck			
Facial nerve		Facial expression	FFMT, TG, NG, NT	++	No	*NA*
Spinal accessory nerve		Trapezius function	NG, NT	+	No	*NA*
Hypoglossal nerve		Tongue function	NG	+	No	*NA*

[a]Value of reconstructing the defect based on functional gain and anticipated effect. +/-: uncertain value, +: possibly worthwhile, ++: worthwhile; 2In case of complete brachial plexus palsy, tendon transfers impossible; 3In case of complete lumbosacral plexus palsy, no reconstructions possible
dig.: digit, FFMT: free functioning muscle transfers, N: number of patients, NA: not applicable, NG: nerve grafting, NT: nerve transfers, TG: tendon grafts, TT: tendon transfers

Strengths and limitations

This study is limited by its retrospective nature. Functional outcomes were not routinely and completely registered resulting in common missingness of exact deficits, more so for sensory deficits. For this reason further in-depth analyses were avoided. Nonetheless, this study included a large dataset of patients. MPNSTs are rare and it is unlikely that prospective datasets will include more patients to give further insight. Furthermore, by including data from several centers this study was able to identify large number of MPNSTs and possibly reduce referral bias. In turn, it was able to identify patient groups that are at risk of persisting critical motor and sensory deficits. Based on the high prevalence of postoperative functional morbidities and low incidence of functional reconstructions identified in this study it could be concluded that combining expertise from surgical oncologists and peripheral nerve surgeons may be beneficial when resecting MPNSTs from major nerves or large MPNSTs. By including peripheral nerve surgeon expertise, both epineural dissection and reconstructive possibilities can be taken into consideration. Unfortunately, these collaborations are still rare. Future research should attempt to further identify ideal candidates for reconstruction who are anticipated to have reasonable oncological outcomes.

Conclusion

Surgical resection of MPNSTs commonly results in major motor deficits and loss of critical sensation. Loss of function is more likely when resecting MPNSTs in NF1 patients, large, and deep-seated tumors, and those arising from major nerves. Whenever patients present with motor or sensory deficits, these will likely persist. Peripheral nerve surgeons are more commonly involved in high-risk patients, but not in the majority of cases. Functional reconstructions are infrequently performed, but may result in good regain of function regardless of the use of multimodal oncological treatment.

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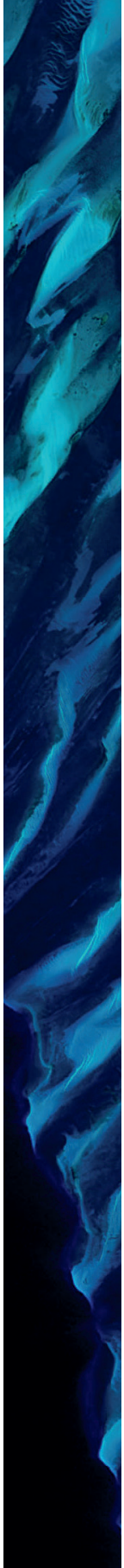
12

General Discussion and Future Perspective



The cover of this thesis is a satellite photo of the Great Bahama Bank. During the ice age, when sea levels were 120 meters lower than presently, the Banks were dry land. Ever since, currents have sculpted the underwater sediments in shallow waters into wavy patterns. The dark and deep water is an area known as the Tongue of the Ocean with depths of up to 4000 meters. The image may stand symbolic for our understanding of malignant peripheral nerve sheath tumors (MPNSTs). Over the last decades, many researchers have tried to understand this rare tumor and through their efforts we are increasingly seeing patterns. The deep and dark water in turn represents yet to be elucidated knowledge on tumor biology and ideal treatment of MPNSTs. The reader of this thesis, you, can be seen as the satellite that took the picture, observing what is known and what has yet to be brought to light. The overall aim of this thesis was to enhance our understanding of both oncological and functional outcomes in MPNSTs. By investigating both types of outcomes one could improve treatment considerations. In this chapter the main findings of this thesis are discussed and suggestions are made for future research efforts.

Getting the diagnosis right, on time

Timely diagnosis of MPNST is crucial as their prognosis remains relatively poor. Numerous studies, including **Chapter 2 and 3**, have repeatedly shown large tumor size to be of negative influence on survival.[1–3] Accurate diagnosis unfortunately seems difficult, especially in the neurofibromatosis type 1 (NF1) patient population. Even though NF1 patients are commonly under surveillance, they still commonly present with larger tumors than sporadic patients. Initial diagnosis is difficult as both clinical symptoms and radiological findings are overlapping with benign counterparts.[4,5] Additionally, intratumoral heterogeneity can cause sampling errors further delaying correct diagnosis. Contrarily, repeated biopsies are cumbersome, painful, and possibly damaging and therefore ideally avoided in benign lesions. Magnetic resonance imaging (MRI) should be used to characterize any lesion in case of newly formed pain, growing mass, or neurological symptoms and fortunately **Chapter 5** demonstrated that almost all surgeons utilize MRI. **Chapter 6** has shown that any lesion that presents with a target sign is highly unlikely to be an MPNST and therefore generally requires no further diagnostics. Conversely, not every lesion that lacks a target sign should undergo biopsy. Additional features including perilesional edema or ill-defined margins are highly suspect for malignancy. Alas, a significant proportion of MPNSTs do not show these characteristics and more features should be taken into account which complicates the identification of 'high-risk' lesions to minimize the need for biopsies. In NF1 patients, positron emission tomography (PET) in combination with computed tomography (CT) or MRI can result in higher accuracies for MPNST detection. The maximum standardized uptake volume (SUVmax) of ≥3.5 currently seems to yield highest accuracy across several populations, but lacks solid validation in a PET-scanner

that adheres to international guidelines (EARL criteria) and still results in a significant proportion of false positives. Nevertheless, it is advisable to offer PET scans to NF1 patients with newly symptomatic and suspicious lesions on MRI.

Future perspectives

Although it is clear that MRI's should be used in the characterization of nerve sheath tumors and there seems strong evidence that PET scans offer additional accuracy in NF1 patients, several questions remain unresolved. An ideal algorithm of MRI and PET characteristics to stratify lesions at high-risk of malignant transformation has yet to emerge in order to minimize biopsies and unnecessary resections. It may be that sporadic and NF1 patients require separate algorithms for MRI characterization as (ancient) schwannoma's are more common among non-NF1 patients. For PET-scans, ideal semi-quantitative features should be validated in a cohort that was scanned under a PET scan complying with EARL criteria. Diffusion weighted imaging and apparent diffusion coefficient mapping seem to be of true merit, but their incorporation in the diagnostic algorithm and possible replacement of PET scans needs further investigation. New imaging analyses such as radiomics are also interesting as radiomics has shown several purposes in other soft tissue sarcomas (STS) including distinction between benign and malignant as well as tumor grades. Yet no studies have been published using radiomics for nerve sheath tumors.

Aggressive therapy for MPNST, quo vadimus?

Radiotherapy

Chapter 2-4 offered us further insight to survival outcomes of large cohorts of MPNST patients. An association of chemotherapy or radiotherapy use with survival was not observed in any of the cohorts studied. This is in line with previous literature and partially the reason for practice variation seen in **Chapter 2-4**. However, these findings should be interpreted with caution as this thesis focused on overall survival only. MPNSTs have one of the highest rates of recurrence and metastasis in both adult STS and pediatric non-rhabdomyosarcoma STS (NRSTS).[6,7] Radiotherapy does decrease rates of local recurrences in microscopically positive margins and possibly in large tumors as well.[8–10] These indications are seemingly followed by most surgeons as seen in **Chapter 5**. MPNSTs nevertheless do recur even in cases that have completely been resected and received radiotherapy. Additional caution should be taken for its administration in children. The European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) treatment guidelines do implement radiation, but dosages have been modified from adult dosages, which is not supported by solid evidence and thus the efficacy may possibly be limited. Rates of radiotherapy administration in both adult and pediatric NF1-associated MPNST do not differ from sporadic MPNST. There is currently no guideline to treat NF1 patients differently to sporadic patients, yet we do

not know what the impact of radiotherapy is on recurrence rates in this population specifically, as radiation exposure more commonly may cause secondary malignancies in NF1 and MPNSTs commonly arise within plexiform neurofibromas.[11] The ideal timing of radiotherapy is not entirely clear either. Although neoadjuvant administration is gaining popularity in STS generally, surgeons other than surgical oncologists are still more likely to prefer postoperative administration in MPNST (**Chapter 5**). **Chapter 2-4** demonstrated that adjuvant radiotherapy is still more commonly the treatment of choice. Radiation dosage is smaller in neoadjuvant administration, but careful dissection may be more difficult in an irradiated field if one is planning to perform epineural dissection (peeling off epineurium) and nerve or tendon reconstructions require well vascularized wound beds. In vulnerable patient groups it has yet to be shown that radiotherapy is of additional value when an R0 resection can be performed.

Chemotherapy

The use of chemotherapy in localized adult MPNST is controversial, which is highlighted in **Chapter 5**. Ideally, doxorubicin and ifosfamide are used as chemotherapeutic regimen in MPNST.[12,13] But there is currently a lack of solid evidence to define the role of perioperative chemotherapy in any STS.[13–17] MPNSTs are known to be relatively chemoresistant STS, possibly even more so in NF1.[12,18] Administration of chemotherapy in adult localized disease is currently not widely employed (**Chapter 2, 3, and 5**). In pediatric MPNST however, a larger proportion of patients with localized disease receives perioperative chemotherapy with no difference between sporadic and NF1 patients (**Chapter 4**). The use of chemotherapy has been incorporated for pediatric NRSTS in the EpSSG and Children's Oncology Group (COG) guidelines and since 2005 doxorubicin and ifosfamide have become standard regimens. Survival has ameliorated after 2005 for pediatric MPNST in contrast to adult MPNST (**Chapter 3 and 4**), which begs to differ if incorporating chemotherapy in a selected group of adult patients would also be beneficial nonetheless. The increasing centralization of pediatric cancer healthcare in the Netherlands may have been an additional factor contributing to increasing survival prognosis in children. Recently, their treatment is further centralized in a single center, the Princess Máxima Center for pediatric oncology. In adult STS it has been shown that centralization ameliorates outcomes as well,[19] which would advocate further centralization of adult MPNST healthcare. Unfortunately, chemotherapy yields unsatisfactory response rates in metastasized MPNST, warranting new systemic therapies. **Chapter 7** highlighted that the search for these new therapies is arduous, but ongoing. So far no targeted therapy has yet proven effective in MPNST patients, despite compelling preclinical *in vivo* evidence. Ever since the publication of **Chapter 7**, the SARC023 trial has been published, investigating the addition of ganetespib (Hsp90 inhibitor) to sirolimus (mTOR inhibitor).[20] Alas, no responses were found.

Surgical margins

This thesis further emphasizes the need for macroscopic complete resections as it is the only treatment strategy proven to increase survival.[1,3,21] As seen in **Chapter 3**, it was even the most important predictor of survival in localized disease. When tumors are not amenable to complete resection, prognosis is almost similar to metastatic cases. Achieving R1 resections were nevertheless not associated with decreased survival in any of the cohorts studied in this thesis. Similar conclusions have been drawn in other studies as well.[1,3,21] **Chapter 5** did indicate that most surgeons are hesitant to perform less extensive resections in order to preserve function and one third never considers preservation of function before resection. As mentioned earlier, the MPNSTs have a high propensity to recur albeit free surgical margins and the use of radiotherapy. Some researchers have argued that due to their perineural origin and possibility of skip lesions an MPNST may stretch along the nerve of origin.[22] In **Chapter 5** half of all respondents felt that it may be beneficial to resect more of the nerve of origin whenever possible to decrease the rate of local recurrences. Additionally, obtaining multiple fresh frozen coupes of nerve endings may be indicated as well to ascertain complete resection.[2,3,22] These beliefs are not routine practice and demand further research.

Future perspectives

It goes without saying that careful planning by a comprehensive dedicated multidisciplinary team is necessary to weigh out all available options for oncological treatment in MPNST. In order to further enhance our understanding of treatment effects on outcomes, large international collaborations like the **MONACO** study are necessary to facilitate enough patients. Although disease-free survival was not studied in this thesis it should definitely be taken into account for optimal treatment allocation. Studies should be encouraged to establish safety and efficacy of radiotherapy in pediatric and NF1-associated MPNSTs. Similarly, the non-inferiority of less extensive R1 resections should be validated. As recurrence rates are high despite clear margins and the use of radiotherapy, it is of interest to investigate recurrence patterns along the nerve of origin. This could provide a foundation to perform more extensive resections of the originating nerve if it is already to be sacrificed. The use of chemotherapy in localized disease needs further investigation as well and may require a search for MPNST patients at highest risk of metastasis. At the same time a different approach to chemotherapy use between sporadic and NF1-associated MPNST requires further research. Evidently, new systemic therapies are needed and should include multiple targets because of high biologic heterogeneity in MPNST. Most preclinical evidence points towards mTOR and vascularization pathway targets, but other combinations are definitely possible. The use of immunotherapy and oncolytic viruses can be interesting as well, but also requires further investigation of MPNSTs' immune environment. Enrolling sufficient patients will be the bottleneck for any trial in MPNSTs specifically and therefore requires large multi-institutional collaborations.

How oncological and functional outcomes in MPNST could be balanced

Preservation of function

As oncological MPNST treatment generally follows STS guidelines, we have observed a tendency to resect all MPNSTs with wide margins. **Chapter 10** showed us that surgeons are well aware of the functional deficits caused by such an approach and some feel the need that functional status should be taken into account preoperatively. Nevertheless, both **Chapter 10** and literature reviews **Chapter 8 and 9** show that the reconstruction of lost function in MPNST and other extremity STS are rarely performed. Previously, few studies have been published on functional status after resection of MPNSTs. One study reported a 30% prevalence motor deficits,[23] which is almost in line with the 37% prevalence reported by surgeons in **Chapter 10.** Another study of 33 extremity MPNSTs, reported 21/33 MPNSTs arising from major nerves, of which 8 underwent complete nerve excision and 8 an amputation.[24] **Chapter 11** indeed proved that serious functional deficits are common after MPNST resections, including both motor and critical sensory deficits. Ideally, preventing functional deficits should initially be preferred over reconstruction. As stated earlier, R1 resections have not been associated with impaired survival in any MPNST.[1,3,21] Safety of planned close margin surgery also implies that epineural dissection can be performed in any MPNST. Whenever the MPNST does not encompass more than 50-75% of a nerve's circumference, epineural dissection could be considered, thus preserving nerve function.[25,26] This technique is important in brachial and lumbosacral plexus tumors as the resection of more nerves decreases function further and limits reconstructive options. Nerve tissue preservation is also important in sciatic nerve tumors. As observed in **Chapter 9,** sciatic nerve defects are difficult to restore and rarely result in motor function recovery when nerve reconstructions are performed. Moreover, low-grade MPNSTs are known have a very low rate of local recurrences and rarely metastasize even when performing R1 resections.[27] Likewise, benign atypical neurofibromas rarely recur after marginal resections.[27,28] The ability to reliably distinguish both these tumors from high-grade MPNSTs may therefore result in less aggressive surgical treatment overall. As suggested before based on **Chapter 6**, a new diagnostic algorithm would help in identifying patients at risk of malignant transformation based on imaging. Concurrently, for certain benign tumors the need for possibly harmful biopsies could be obviated and those requiring resection could be performed directly. Uncertain tumors, those exhibiting insufficient characteristics for high-risk or benign characterization, would still require biopsies. One could advocate that if the resulting biopsy is benign in a symptomatic lesion, a marginal resection should definitely be performed further reducing unnecessary morbidity.

Reconstruction of function loss

Still, many MPNSTs will require the complete resection of their originating nerve leading to serious morbidity. Fortunately, **Chapter 11** as well as **Chapter 8 and 9** show us

that both motor and sensory deficits can adequately be restored in MPNST and STS patients with lost function. Yet functional reconstructions are unfortunately still not standard of care. As highlighted in **Chapter 10**, many surgeons are still hesitant towards incorporating functional reconstructions in their surgical plan and a minority of surgeons always considers the use of functional reconstructions. **Chapter 10** shows that the problem is likely twofold. Firstly, surgical oncologists operate most patients, yet rarely involve reconstructive surgeons before surgical excision. This may be due to a lack of knowledge on the ability and outcomes of reversing function loss with reconstructions. Secondly, reconstructive surgeons may be too hesitant to perform the full range of reconstructive options due to a lack of knowledge on the oncological outcomes of STS and the impact of multimodal therapy on successful reconstructions. Nevertheless, both clinical and preclinical evidence do not suggest a negative impact of radiotherapy and chemotherapy on success rates of functional reconstructions. Whenever free tissue flaps are used in patients receiving radiotherapy, wound complications are minimized.[29,30] A multitude of reconstructive options are available and more options are increasingly being studied and applied in trauma cases. Selection of their use is based on numerous factors, including defect size and location, patient characteristics, functional deficits, and the need for soft tissue coverage. Yet, only nerve reconstructions and innervated skin flaps are capable of restoring sensation. Nerve transfers are increasingly being used over nerve grafting as they facilitate shorter time to reinnervation and possibly better functional outcomes.[31] Distal nerve transfers may be easier in case of irradiated wound beds and whenever a local recurrence occurs, the reconstruction is not necessarily at stake. The reconstruction of some deficits remains questionable nevertheless, including the reconstruction of sciatic nerve defects. Its resection leads to a flail and insensate distal leg and more proximally to loss of biceps femoris function as well. Only nerve reconstructions are available to reconstruct the defect, but rarely results in restoration of muscle function.[32,33] Sensation may however be regained, at least partially, and reconstructions can therefore be beneficial. As outcomes vary, it can be advocated that patients already prone to poor nerve regeneration should less likely be considered eligible for sciatic nerve reconstruction. Contrarily, younger patients, especially children, should be considered eligible for sciatic reconstructions as nerve reconstructions have significantly higher success rates.[34] Besides motor and sensory function loss, neuropathic pain can seriously affect functional status, but has had even less attention in STS literature. In any surgically treated STS, prevalence of neuropathic pain may be as high as 25%, which significantly lowers functional outcomes.[35] In **Chapter 10**, surgeons reported newly formed neuropathic pain in up to 41% of surgically treated MPNST patients, yet many surgeons still do not use neuroma preventive measures. True prevalence of newly formed neuropathic pain in MPNST patients has yet to be studied which could in turn support better nerve handling techniques such as ideal neuroma preventive measures and nerve conduction testing in selected cases. Nerve reconstructions are known to considerably diminish the risk of (painful) neuroma formation which is an

additional argument to consider nerve reconstructions.[36] Based on **Chapter 8-11**, surgeons should be encouraged to integrate functional reconstructions at an early stage, considering all available reconstructive techniques and determining an optimal surgical and reconstructive plan based on patient and tumor characteristics. Any patient with localized disease should be eligible and special attention should be paid to patients with extremity or plexus tumors, large and deep-seated tumors, and NF1 patients. In the era of limb salvage surgery, complete recovery of motor and sensory function and no neuropathic pain should be the goal whenever possible.

Future perspectives

Future studies should be encouraged to multicenter prospectively collect functional outcomes and indications for functional reconstructions in a multidisciplinary sarcoma team with close collaboration between oncological and reconstructive surgeons. Both objective and subjective outcome measures of motor and sensory function as well as pain should be registered at least until one year postoperatively. Trials are very unlikely to arise and the evidence provided in previous literature and this thesis is arguably strong enough to advocate an increase of the use of functional reconstructions and preservation of function in selected cases. However, to further elucidate ideal candidates and choice of reconstructive strategies, more can be learned by prospectively collecting functional outcomes in MPNST and STS. The risk stratification of lesion biology based on imaging proposed earlier can further help in diminishing wide resections and find patients suitable for direct marginal resections. The effect of consequent whoops excisions on oncological and functional outcomes can then be investigated as well. In order to decrease rates of postoperative neuropathic pain in MPNST, studies can already address the prevalence and risk factors for its development in retrospective cohorts. Despite the inherent limitations of its retrospective nature, this information is available in the **MONACO** study and could be utilized for this purpose as well.

Future perspectives of patient-tailored approaches to MPNST

With its diverse presentation, complex biology, and varying outcomes, patient-tailored approaches to MPNST treatment are justified. In other STS, recent calculators have been proposed for day-to-day use, including Sarculator and PERSARC for extremity STS.[37,38] However, these calculators may possibly be less applicable for general use in MPNST as, for instance, they do not incorporate NF1 disease nor all possible tumor sites. In **Chapter 2-4** we proposed several factors associated with decreased survival in MPNST and subgroups as pediatric and retroperitoneal MPNST. The **MONACO** study will hopefully aid in creating an online calculator for overall survival and disease-free survival specifically for MPNST patients. Future studies should be encouraged to use the resulting calculator and validate its usefulness. The calculator may help to

find clinical subgroups of patients each of which benefiting from different oncological treatment approaches; i.e. more/less aggressive resections, use of radiotherapy, and use of chemotherapy. Retroperitoneal MPNST for instance, had a drastically worse survival compared to non-retroperitoneal MPNST in **Chapter 3**, and are known to have the highest risk of recurrence and metastasis.[39,40] Safety of less extensive and function-preserving surgery in patients can subsequently be determined. Also, as depicted in **Chapter 10**, patients with a prognosis of at least three years can be calculated to whom functional reconstructions can be offered, even though **Chapter 2-4** already show promisingly longer overall median survival for localized MPNST. The resulting choice for reconstruction will depend on numerous factors, but ideal techniques are best discussed in the multidisciplinary setting involving both an oncological and a reconstructive surgeon. Preferably, a surgeon with knowledge of nerve reconstruction possibilities should be involved as well. Contrarily, in selected cases a wider excision can be planned, possibly avoiding the need for radiotherapy, when all possibilities are known to reconstruct anticipated deficits. Overall, such collaboration may lead to a balanced treatment strategy. While clinical characteristics are able to predict survival moderately-well, tumor-specific biology may enhance predictive value. Several studies have suggested that immunohistochemical markers and specific genetic alterations may improve prognostication in MPNST.[2,41,42] Future studies should be encouraged to test the most valuable of these markers in a large cohort of patients and ideally observe if it enhances prediction of the **MONACO** calculator. The somewhat somber outcomes of MPNST, both oncological and functional, raise the question if MPNST-related surgeries should be centralized even more than other STS. Other possibilities may include an MPNST-specific multidisciplinary team that is available for digital consultation to any STS-dedicated center.

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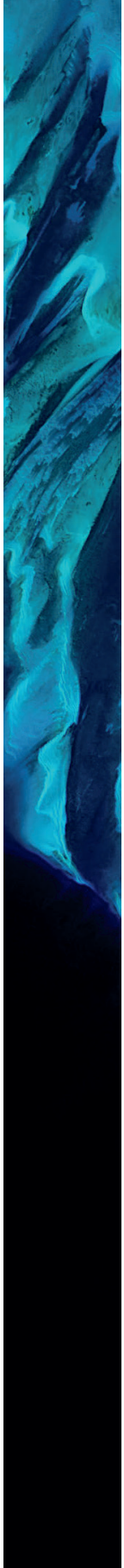
Appendices



SUMMARY

MPNSTs are rare soft tissue sarcomas (STS) that undergo aggressive treatment including resections with wide margins. Histotype-specific treatment and outcomes of MPNSTs have been studied infrequently. In contrast to other STS, resecting MPNSTs always requires the resection of nervous tissue making them prone to loss of function.

Part I Oncological Outcomes and Treatment of MPNST

In Part I, we elaborated on treatment differences, oncological outcomes, and risk factors of worse survival in MPNSTs. Although MPNSTs are rare, they may occur at any anatomical site that harbors peripheral nerves. Additionally, because of their origin in nervous tissue and the existence of benign counterparts that resemble malignancy, various surgical subspecialties may encounter and treat MPNSTs.

Chapter 2 Treatment and Survival Differences per Tumor Site
Several studies have reported differences in survival based on MPNST tumor site, however some tumor sites are rare and have been difficult to investigate on a larger scale. The SEER database, an American cancer registry, provided us the largest population to date including 3267 MPNST patients. Using this data we observed that treatment and outcomes vary according to tumor site. In concordance to previous studies worse survival was seen in patients with central tumors or tumors of the head and neck. Surprisingly, intracranial MPNSTs had a better prognosis. Also, children seemed to have a better prognosis compared to adults when controlling for several confounders. Furthermore, older age (60+), male gender, black race, high grade, and large tumors were associated with worse survival.

Chapter 3 Treatment and Survival in the Netherlands
Patients from the Dutch Cancer Registry were obtained to investigate treatment of MPNST in the Netherlands in a nationwide unselected cohort of patients. Because MPNSTs are difficult entities to diagnose pathologically, we also obtained all pathological reports related to these patients from the Dutch National Pathology Database to exclude uncertain diagnoses and obtain information on NF1 status which is not available in the Dutch Cancer Registry. In this study we excluded pediatric and metastatic patients at diagnosis as these are generally treated differently. A total of 629 MPNST patients were analyzed and stratified between retroperitoneal and non-retroperitoneal MPNST. This has rarely been done, but may be important, because we know that retroperitoneal soft tissue sarcomas (STS) are clinically more aggressive tumors. Retroperitoneal MPNSTs were more commonly unresectable and in resected cases radiotherapy was administered less frequently, but chemotherapy more frequently. We observed that in localized non-retroperitoneal adult MPNST, older age (60+), presence of NF1, irresectable, large, and deep-seated tumors were associated with worse survival.

Resectability of the MPNST was the most important factor predicting worse survival in localized disease. In retroperitoneal MPNST, older age (60+), male gender, and irresectable tumors were associated with worse survival. In non-retroperitoneal MPNST truncal tumor site was not associated with worse survival which may suggest that this association observed in other studies may be driven by retroperitoneal tumors. Furthermore, there was no difference between an R0 and R1 resection on survival in both retroperitoneal and non-retroperitoneal MPNST. This is important as it indicates that MPNSTs are eligible for function-sparing surgery with planned microscopically positive margins.

Chapter 4 Treatment and Survival in Pediatric MPNST

Using the same databases as **Chapter 3**, 70 pediatric patients were identified and investigated for treatment and survival. Pediatric MPNSTs are rare, treated by pediatric oncologists, and were found to be associated with increased survival in **Chapter 2**, therefore prompting further investigation. We observed that pediatric patients presented with similar clinicopathologic features as adult MPNSTs. In NF1 children, tumors tended to be larger at time of diagnosis, but were generally treated similarly to sporadic patients. Presence of NF1 was the only clinicopathologic feature associated with worse survival in localized pediatric MPNST. In contrast to adult MPNST, we observed that prognosis for localized pediatric MPNST has ameliorated after 2005. This may be due to the centralization of pediatric cancer health care in the Netherlands as well as the implementation of doxorubicin and ifosfamide as standard chemotherapy regimens. The use of radiotherapy and chemotherapy were not found to be associated with survival in any population analyzed in **Chapter 2-4**.

Chapter 5 Oncological Treatment Considerations

Because MPNSTs are rare and treated by several surgical subspecialties, variation in clinical decision-making may be present. Surgical oncologists treat MPNSTs as part of their sarcoma clinic, but peripheral nerve surgeons as a malignant form of nerve sheath tumors. By means of an international survey among several surgical societies, we evaluated how oncological treatment considerations varied as a whole and between surgical subspecialties. A total of 174 surgeons filled out the survey. Variation in cases and case load was evident between surgical subspecialties and surgical oncologists treated most patients. Diagnostic work-up differed between surgical subspecialties, but surgical oncologists adhered most commonly to sarcoma guidelines. (Pre) operative considerations for the preservation of function differed among all surgeons, many of which would not consider less extensive resections to preserve function. Indications for the use of radiotherapy did not differ between specialties, large tumor size (>10cm) and microscopically positive margins being the most common reasons for its administration. Sequence of administration differed significantly between specialties; surgical oncologists preferred neoadjuvant administration in contrast to other specialties. Indications for the use of chemotherapy in localized disease lacked

consensus among all surgeons. Although some differences may in part be explained by specialty bias, significant differences in work-up may occur based on initial presentation. A multidisciplinary approach combining knowledge from both surgical oncologists and peripheral nerve surgeons may be beneficial.

Chapter 6 Diagnostic Accuracy of Non-Invasive Tests

MPNSTs are impossible to differentiate from benign nerve sheath tumors (BPNSTs) based on clinical presentation. Moreover, sampling errors are common and repetitive biopsies are cumbersome and possibly damaging. It is therefore crucial to find non-invasive ways to detect tumors with the highest probability of malignant transformation. MRI's are widely used, but PET scans possibly offer additional value in NF1 patients. For this reason we systematically reviewed current literature of non-invasive tests that can be used to distinguish MPNSTs. This included conventional MRI, functional MRI, PET scans, and liquid biopsies. Diagnostic accuracy was quantified for several MRI and PET characteristics with Bayesian bivariate meta-analyses. These analyses allow for heterogeneity in threshold values even when combining a smaller sample of studies with few patients. The absence of a target sign was highly sensitive with a pooled negative likelihood ratio of 0.04 indicating high certainty of a BPNST when the target sign is present. However, the absence of a target sign is highly unspecific and additional characteristics such as ill-defined margins and perilesional edema should be taken into account to distinguish benign and malignant lesions. In NF1 populations PET scans offer higher accuracy. SUVmax and tumor-to-liver ratios are equally accurate. Ideal thresholds are lacking, but based on individual level data of 246 patients, meta-analyses suggested an ideal threshold for SUVmax at ≥3.5. Functional MRI's may provide equal accuracy as PET scans and are therefore of special interest in the sporadic patient population, but their implementation requires more research. Liquid biopsies currently hold no role in diagnostic work-up of MPNSTs but may potentially gain interest in the future.

Chapter 7 Emerging Therapeutic Targets

Current cytotoxic systemic treatment options yield limited responses and new therapeutic targets are desperately warranted. By means of a systematic review we summarized and investigated current literature of all non–cytotoxic treatment possibilities in MPNST. We included 60 *in vivo* studies and found that targeting the PI3K/Akt/mTOR pathway or vascularization may be promising, as well as the use of oncolytic viruses. Of 6 published trials, none has yet shown effective in MPNST. Currently 13 trials are still ongoing, recruiting MPNSTs in various degrees. Hopefully, some will provide further insights. A combination of drugs will most likely be pivotal to maximize treatment effect, because of the complex and heterogeneous biology of MPNSTs.

Part II Functional outcomes and possibilities for treatment in MPNST

In Part II, we explore options and outcomes of reconstructions to ameliorate postoperative functional status in extremity sarcomas and MPNST patients. To date, this has had remarkably less attention compared to oncological treatment and outcomes. Traditionally, the role of plastic surgeons has only been for soft tissue coverage, but functional reconstructions are increasingly being used in trauma cases. These may potentially play a similar role in sarcoma surgery.

Chapter 8 Functional Reconstructions in Extremity STS

Functional reconstructions include the reconstruction of nerves and tendons or replace lost function with free functioning muscle transfers. As extremity STS have a varying prognosis and commonly require additional therapies such as radiotherapy and chemotherapy, the feasibility and outcomes of functional reconstructions in these patients are not well known. For this purpose, we systematically reviewed all case series available on such reconstructions in extremity STS. A total of 14 different studies, describing 134 patients, were included. Tendon reconstructions (58.2%) and free functioning muscle transfers (41.0%) were most commonly used. Overall, we observed that most reconstructions adequately restored function. Most cases received additional therapy including radiotherapy (60.3%) and/or chemotherapy (49.4%). The use of such multimodal therapies did not preclude successful outcomes. The exact choice of reconstruction varies per patient and lesion as several factors play a role in determining an optimal strategy.

Chapter 9 Nerve Reconstructions in Extremity STS

Nerve reconstructions provide the opportunity to restore sensation and reduce the risk of neuropathic pain besides the restoration of motor function. Nevertheless, as we observed in **Chapter 8** these are rarely performed after resection of extremity STS. Nerves regenerate slowly which may be an additional factor precluding surgeons to use such reconstructions. We therefore reviewed all cases in literature on the use of nerve reconstructions after the resection of extremity STS. We found 19 studies describing outcomes of 26 patients. The majority of nerve reconstructions were performed in upper extremity cases in contrast to functional reconstructions in general. Nerve grafting procedures were most commonly employed. Most patients recovered at least some motor function and sensation. Successful reconstructions were more common in upper extremity reconstructions. We did not find a negative influence of multimodal therapy on functional outcomes of reconstructions.

Chapter 10 Current Attitudes towards Function Preservation

Because functional reconstructions are rarely performed and several surgical subspecialties operate or encounter MPNSTs, more could be learned on their attitudes towards integrating such reconstructions. In the same survey presented

in **Chapter 5**, we asked respondents questions regarding postoperative morbidity and the use of functional reconstructions in MPNST. In total, 174 surgeons filled out the survey. Surgeons reported high rates of neuropathic pain (40.9%) and motor deficits (36.7%) postoperatively without differences between surgical subspecialties. Functional reconstructions for either motor or sensory deficits were however more commonly considered by plastic surgeons and other hand surgeons. Nevertheless, relative contraindications for their use did not differ between surgical subspecialties. Many surgeons were hesitant to perform reconstructions whenever radiotherapy would be administered. Overall, surgeons agreed on an average life expectancy of 3 years before functional reconstructions should be considered. This shows that any surgeon acknowledges the extent of postoperative morbidity, yet surgical oncologists and neurosurgeons, who operate most patients, should incorporate a reconstructive surgeon early on.

Chapter 11 Function Loss in MPNST

The extent of postoperative morbidity has never been investigated on a large scale in MPNSTs before. This was in part the reason to start the MONACO study, an international collaboration of 10 Dutch cancer centers and the Mayo Clinic to retrospectively collect data on oncological and functional outcomes in MPNST patients. This study focused on the prevalence of postoperative motor deficits and sensory deficits of critical areas: the hand, foot sole, and buttocks. Also, the use and outcomes of functional reconstructions were assessed. We included 756 patients, of which 658 were surgically resected. Serious motor deficits (≤M3) were present in 27.2% after resection and 24.3% of patients had loss of sensation in the hands, feet or buttocks. Only 4.0% had a functional reconstruction. NF1 patients, symptomatic, large and deep-seated tumors, tumors arising from a plexus or extremities were at an increased risk for functional deficits. Peripheral nerve surgeons were involved in the minority of MPNST cases arising from major nerves. Functional reconstructions that were performed resulted in good outcomes regardless of the use of multimodal therapy. Unsatisfactory functional outcomes were mainly caused by oncological failure resulting in the need for re-resections. This study shows there is room for improvement of functional outcomes if functional reconstructions were to be considered more often.

NEDERLANDSE SAMENVATTING

MPNSTs zijn zeldzame weke delen tumoren (WDT) welke vaak agressieve therapie ondergaan met extensieve resecties. Histotype-specifieke behandeling en uitkomsten van MPNSTs zijn infrequent onderzocht. In tegenstelling tot andere WDT wordt er bij MPNSTs altijd zenuwweefsel gereseceerd, hierdoor zijn ze vatbaar voor functieverlies.

Deel I Oncologische Uitkomsten en de Behandeling van MPNST

In Deel 1 gaan we in op verschillen in behandeling, oncologische uitkomsten en risicofactoren van verminderde overleving in MPNSTs. Hoewel MPNSTs zeldzaam zijn kunnen ze op alle plekken in het lichaam ontstaan waar zenuwweefsel aanwezig is. Doordat MPNSTs bovendien uitgaan van zenuwweefsel en goedaardige tegenhangers van MPNSTs lastig te onderscheiden zijn, behandelen verschillende chirurgische specialismen deze tumor.

Hoofdstuk 2 Verschillen in Behandeling en Overleving per Tumor Locatie
Meerdere studies rapporteren verschillen in overleving op basis van tumor localisatie van MPNSTs, echter zijn sommige tumor locaties zeldzaam en lastig om op grotere schaal te onderzoeken. De SEER database, een Amerikaanse kankerregistratie, heeft ons voorzien van de grootste populatie tot op heden met 3267 MPNST patiënten. Met behulp van deze data zagen wij dat behandeling en uitkomsten variëren afhankelijk van tumor locatie. In samenspraak met eerdere studies hadden centraal-gelegen en hoofd-hals tumoren een slechtere prognose. Verrassend genoeg vonden wij dat intracraniële MPNSTs een betere prognose hadden. Kinderen leken ook een betere prognose te hebben. Daarnaast waren oudere leeftijd (60+), mannelijk geslacht, zwart ras, hoge tumorgraad en grote tumoren geassocieerd met een verminderde overleving.

Hoofdstuk 3 Behandeling en Overleving in Nederland
Patiënten uit de Nederlandse Kankerregistratie werden geïdentificeerd om behandeling en uitkomsten van MPNSTs in Nederland te bestuderen in een nationaal, niet geselecteerd cohort patiënten. Gezien MPNSTs pathologisch lastig te definiëren zijn, hebben wij ook alle pathologieverslagen van deze patiënten opgevraagd uit de Nederlandse Pathologie Database om zo onzekere diagnoses te excluderen. Daarnaast hebben wij NF1 status kunnen achterhalen aan de hand van deze pathologieverslagen. Dit wordt niet geregistreerd in de Nederlandse Kankerregistratie. In deze studie hebben wij kinderen en initieel gemetastaseerde patiënten geëxcludeerd, omdat deze anders behandeld worden. In totaal werden 629 MPNST patiënten geanalyseerd en gestratificeerd tussen retroperitoneaal en niet-retroperitoneale tumoren. Dit is tot op heden zelden gedaan, maar het verschil is belangrijk, omdat retroperitoneale WDT zich klinisch vaak agressiever gedragen. Retroperitoneale MPNSTs waren vaker irresectabel en in gereseceerde patiënten ontvingen ze minder vaak radiotherapie,

maar vaker chemotherapie. We vonden dat in gelokaliseerde niet-retroperitoneale volwassen MPNST patiënten oudere leeftijd (60+), NF1 status, irresectabele, grote en diepe tumoren geassocieerd waren met een verminderde overleving. Resectabiliteit was de belangrijkste voorspeller van slechtere prognose in gelokaliseerde ziekte. In retroperitoneale MPNSTs, oudere leeftijd (60+), mannelijk geslacht en irresectabele tumoren waren geassocieerd met verminderde overleving. In niet-retroperitoneale MPNSTs vonden wij geen associatie van centraal-gelegen tumoren met overleving die in andere studies wel werd gevonden. Mogelijk wordt deze associatie dus in andere studies voornamelijk veroorzaakt door retroperitoneale tumoren. Verder werd er geen verschil gevonden tussen R0 en R1 resecties op overleving in zowel retroperitoneale als niet-retroperitoneale MPNST. Dit is van belang, omdat het aangeeft dat MPNSTs in aanmerking komen voor functie-sparende chirurgie met geplande microscopisch positieve marges.

Hoofdstuk 4 Behandeling en Overleving van MPNST in Kinderen
Gebruikmakend van dezelfde databases als in **Hoofdstuk 3** hebben wij 70 kinderen geïdentificeerd en onderzoek gedaan naar behandeling en overleving. Gezien MPNSTs op de kinderleeftijd zeldzaam zijn, behandeld worden door kinderoncologen en geassocieerd waren met een betere overleving in **Hoofdstuk 2** gaf dit aanzet voor verder onderzoek. We vonden dat kinderen zich met vergelijkbare clinicopathologische karakteristieken presenteerden als volwassenen. NF1 kinderen presenteerden zich vaker met grotere tumoren, maar werden hetzelfde behandeld als sporadische patiënten. NF1 was de enige clinicopathologische karakteristiek die geassocieerd was met verminderde overleving in MPNST op kinderleeftijd. In tegenstelling tot volwassen MPNSTs zagen we een verbeterde prognose voor gelokaliseerde kinder MPNSTs na 2005. Dit kan deels veroorzaakt zijn door verdere centralisatie van kinderoncologie in Nederland, maar ook door de implementatie van doxorubicine en ifosfamide als standaard chemotherapeuticum. In geen enkele populatie onderzocht in **Hoofdstuk 2-4** was het gebruik van radiotherapie en chemotherapie geassocieerd met overleving.

Hoofdstuk 5 Overwegingen in Oncologische Behandeling
Omdat MPNSTs zeldzaam zijn en behandeld worden door verschillende chirurgische specialismen kan er variatie zijn in behandeloverwegingen. Oncologisch chirurgen behandelen MPNSTs als onderdeel van hun sarcoom kliniek, terwijl perifere zenuwchirurgen ze behandelen als maligne vorm van zenuwschedetumoren. Aan de hand van een internationale survey onder verschillende chirurgische verenigingen hebben wij variatie in behandeloverwegingen onderzocht, zowel in het geheel als ook tussen chirurgische subspecialisaties. In totaal hebben 174 chirurgen de survey ingevuld. Er was een duidelijke variatie tussen subspecialismen in casus presentatie en jaarlijks aantal behandelde patiënten waarbij oncologisch chirurgen gemiddeld de meeste patiënten behandelden. Diagnostische work-up varieerde tussen chirurgische subspecialismen, maar oncologisch chirurgen hielden zich het vaakst aan sarcoom

richtlijnen. (Pre)operatieve overwegingen om functie-sparend te opereren wisselde tussen chirurgen. Velen zouden minder extensieve resecties niet overwegen om functie te sparen. Indicaties voor het gebruik van radiotherapie verschilde niet tussen subspecialismen; grote tumoren (>10cm) en microscopisch positieve marges werden vaak als indicaties gekozen. Voorkeur voor volgorde van radiotherapie verschilde sterk tussen subspecialismen; oncologisch chirurgen prefereerden vaker neoadjuvante toediening. Er ontbrak overeenstemming over indicaties voor het gebruik van chemotherapie in gelokaliseerde ziekte. Ondanks dat verschillen deels verklaard kunnen worden door specialisatie bias kunnen significante verschillen ontstaan in work-up op basis van initiële presentatie. Het zou voordelig kunnen zijn om een multidisciplinaire aanpak te kiezen waarbij kennis van zowel oncologisch chirurgen als ook perifere zenuwchirurgen worden gecombineerd.

Hoofdstuk 6 Diagnostische Waarde van Niet-Invasieve Testen

MPNSTs kunnen op basis van kliniek onmogelijk onderscheden worden van benigne zenuwschedetumoren (BPNSTs). Bovendien treden er vaak sampling errors op en kunnen herhaaldelijke biopten hinderlijk en schadelijk zijn. Het is daarom van belang om manieren te vinden waarbij men tumoren kan identificeren die de grootste kans op maligne transformatie vertonen. MRI's worden over het algemeen gebruikt, maar PET scans kunnen mogelijk van meerwaarde zijn in NF1 patiënten. Daarom hebben wij de huidige literatuur systematisch onderzocht over niet-invasieve testen die gebruikt kunnen worden om MPNSTs te onderscheiden. Hierbij werden conventionele MRI, functionele MRI, PET scans en liquid biopsies meegenomen. De gevoeligheid van verschillende MRI en PET karakteristieken werden gekwantificeerd met behulp van Bayesiaanse bivariate meta-analyses. Dergelijke analyses laten heterogeniteit in afkapwaarden toe, zelfs wanneer men weinig studies met kleine populaties analyseert. De afwezigheid van een target sign was zeer sensitief met een negatieve likelihood ratio van 0.04 die wijst op een hoge waarschijnlijkheid van een BPNST wanneer een target sign wel aanwezig is. Echter is de afwezigheid van een target sign niet specifiek en moet men additionele karakteristieken in acht nemen zoals slecht gedefinieerde tumorranden en perilesionaal oedeem om benigne en maligne laesies van elkaar te onderscheiden. In NF1 patiënten bieden PET scans hogere accuraatheid. SUVmax en tumor-tot-lever ratio's zijn even gevoelig. Ideale afkapwaarden ontbreken, echter gebaseerd op individuele data van 246 patiënten suggereren onze meta-analyses dat de ideale afkapwaarde voor SUVmax ≥3.5 is. Functionele MRI's zijn mogelijk even gevoelig als PET scans waarmee ze erg interessant zullen zijn in de sporadische patiënten populatie, maar voor hun implementatie is nog meer onderzoek nodig. Liquid biopsies hebben tot op heden nog geen rol in de diagnostiek van MPNSTs, maar kunnen mogelijk interessant worden in de toekomst.

Hoofdstuk 7 Opkomende Therapeutische Doelwitten
Huidige cytotoxische systemische therapieën bieden matige effect waardoor nieuwe doelwitten voor therapie hard nodig zijn. Wij hebben daarom de huidige literatuur over niet-cytotoxische behandelmogelijkheden bij MPNSTs samengevat en onderzocht aan de hand van een systematische review. We includeerden 60 *in vivo* studies en vonden dat het richten van behandeling op de PI3K/Akt/mTOR pathway of vascularisatie veelbelovend is, zo ook het gebruik van oncolytische virussen. Er werden 6 gepubliceerde trials gevonden waarvan geen enkele effect toonde in MPNST. Momenteel zijn 13 trials actief waarbij MPNSTs in verschillende mate worden geïncludeerd. Hopelijk zullen zij ons van verdere inzichten voorzien. Gezien de complexiteit en heterogeniteit van MPNST biologie zal een combinatie aan middelen waarschijnlijk essentieel zijn om behandeleffecten te maximaliseren.

Deel II Functionele Uitkomsten en Behandelmogelijkheden in MPNST

In deel II verkennen wij opties en uitkomsten van reconstructies om postoperatieve functie te verbeteren bij extremiteit sarcomen en MPNST. Tot op heden heeft dit thema nog weinig aandacht gekregen ten opzichte van oncologische behandelingen en uitkomsten. Vroeger was de rol van de plastisch chirurg hoofdzakelijk voor weke delen bedekking, maar hedendaags worden in trauma casussen in toenemende mate ook functionele reconstructies uitgevoerd. Deze reconstructies kunnen mogelijk een zelfde rol vervullen in sarcoomchirurgie.

Hoofdstuk 8 Functionele Reconstructies in Extremiteit WDT
Functionele reconstructies omvatten zenuw- en peesreconstructies of het vervangen van functieverlies met vrije geïnnerveerde spierlappen. Gezien een extremiteit WDT een variërende prognose heeft en vaak additionele therapie zoals chemotherapie of radiotherapie benodigd, zijn de haalbaarheid en uitkomsten van functionele reconstructies in deze patiëntengroep nog onduidelijk. Daarom hebben wij een systematische review gedaan over alle case series over dergelijke reconstructies in extremiteit WDT. In totaal hebben wij 14 verschillende studies geïncludeerd die 134 patiënten beschreven. Peesreconstructies (58.2%) en vrije geïnnerveerde spierlappen (41.0%) werden het vaakst toegepast. We observeerden dat de meeste reconstructies in adequaat functieherstel resulteerden. De meeste patiënten ontvingen ook radiotherapie (60.3%) en/of chemotherapie (49.4%). Het gebruik van dergelijke multimodale therapie sloot succesvolle uitkomsten niet uit. De precieze keuze voor reconstructie strategie hangt af van verschillende patiënt- en laesie gerelateerde factoren.

Hoofdstuk 9 Zenuwreconstructies in Extremiteit WDT
Zenuwreconstructies bieden naast het herstel van motorische functie ook de mogelijkheid om sensibiliteit te herstellen en de kans op neuropathische pijn te verminderen. Desalniettemin zagen wij in **Hoofdstuk 8** dat zenuwreconstructies

zelden worden uitgevoerd. Zenuwen regenereren traag; dit kan mogelijk een extra reden zijn voor chirurgen om deze reconstructies niet te overwegen. Wij hebben voor die reden alle casussen in de literatuur gereviseerd die uitgevoerd zijn na de resectie van extremiteit WDT. We vonden 19 studies over 26 patiënten. De meeste zenuwreconstructies waren uitgevoerd in de bovenste extremiteiten, in tegenstelling tot functionele reconstructies over het algemeen. Zenuw graft procedures werden het vaakst toegepast. De meeste patiënten herstelden minstens iets aan motorfunctie en sensibiliteit. Reconstructies in de bovenste extremiteiten waren echter succesvoller dan in de onderste extremiteiten. We vonden geen invloed van multimodale therapie op functionele uitkomsten na zenuwreconstructies.

Hoofdstuk 10 Huidige Houding tegenover Functiebehoud

Gezien functionele reconstructies zelden worden uitgevoerd en verschillende chirurgische subspecialismen MPNSTs tegenkomen en opereren, kunnen we meer leren over de houding van chirurgen ten opzichte van dergelijke reconstructies. In dezelfde survey als in **Hoofdstuk 5** hebben wij respondenten vragen gesteld ten aanzien van postoperatieve morbiditeit en het gebruik van functionele reconstructies in MPNST. In totaal hebben 174 chirurgen de survey ingevuld. Chirurgen rapporteerden hoge prevalenties van postoperatieve neuropathische pijn (40.9%) en motorische uitval (36.7%). Er was geen verschil tussen verschillende specialismen. Functionele reconstructies voor het herstel van motorische of sensibele uitval werd echter alleen vaker door plastisch chirurgen overwogen. Desondanks waren de meningen gelijk verdeeld tussen specialismen betreffende relatieve contra-indicaties. Veel chirurgen waren onzeker over het uitvoeren van reconstructies indien radiotherapie werd toegepast. Gezamenlijk kwamen alle specialismen uit op een gemiddelde prognose van 3 jaar alvorens men functionele reconstructies zou moeten overwegen. Dit toont aan dat chirurgen wel de mate van morbiditeit erkennen, maar oncologisch chirurgen en neurochirurgen die de meeste patiënten behandelen, vaker een reconstructief chirurg in een vroeg stadium zouden moeten betrekken.

Hoofdstuk 11 Functieverlies in MPNST

Hoe vaak en ernstig postoperatieve morbiditeit is na resecties van MPNST is tot noch toe nooit onderzocht op grote schaal. Dit was deels de reden voor het opzetten van de MONACO studie, een internationale samenwerking tussen 10 Nederlandse kankercentra en de Mayo Clinic om retrospectief data te verzamelen over functionele en oncologische uitkomsten in MPNST patiënten. Deze studie focuste zich specifiek op de prevalentie van postoperatieve motorische uitval en sensibele uitval van kritieke gebieden: de hand, voetzool en het zitvlak. Daarnaast werd ook het gebruik en de uitkomsten van functionele reconstructies beoordeeld. We includeerden 756 patiënten, waarvan 658 chirurgische behandeling ondergingen. Serieuze motorische uitval kwam in 27.2% van de chirurgisch behandelde patiënten voor, sensibele uitval van de handen, voeten of billen in 24.3%. Daarvan had maar 4.0% een functionele reconstructie. NF1 patiënten,

symptomatische, grote en diep-gelegen tumoren als ook tumoren in de extremiteiten of een plexus hadden een verhoogd risico op functionele uitval. Perifere zenuwchirurgen waren echter in de minderheid van de MPNSTs uit grote zenuwen betrokken. De functionele reconstructies die zijn uitgevoerd resulteerde in de meerderheid in goede functie ondanks het gebruik van multimodale therapie. Onbevredigende uitkomsten werden hoofdzakelijk veroorzaakt door oncologisch falen en de daarop resulterende noodzaak voor re-resecties. Deze studie toont aan dat er ruimte voor verbetering is van functionele uitkomsten indien functionele reconstructies vaker overwogen worden.

REVIEW COMMITTEE

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Beste Bostonians, Chandler 106, huize RR, BSG, jullie hebben de weekenden in Boston onvergetelijk gemaakt; de huisfeesten, autotrips, brunches bij Appleton café, en Phoenix landing. Allen uniek. De Chinese diners op Thanksgiving moeten overigens blijven bestaan.

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LIST OF PUBLICATIONS

An overview of the prevalence of residual limb pain and symptomatic neuromas following lower extremity amputations: a systematic review and meta-analysis
List EB, Krijgh DD, **Martin E**, Coert JH. *Submitted.*

Prognostic significance of immunohistochemical markers and genetic alterations in malignant peripheral nerve sheath tumors: a systematic review
Martin E, Acem I, Grünhagen DJ, Bovée JVMG, Verhoef C. *Submitted.*

Morbidity and function loss after resection of malignant peripheral nerve sheath tumors
Martin E, Pendleton C, Verhoef C, Spinner RJ, Coert JH, MONACO Collaborators. *Submitted.*

A Bayesian approach for diagnostic accuracy of malignant peripheral nerve sheath tumors: a systematic review and meta-analysis
Martin E, Geitenbeek RTJ, Coert JH, Hanff DF, Graven LH, Grünhagen DJ, Verhoef C, Taal W. *Submitted.*

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LIST OF PRESENTATIONS

ORAL PRESENTATIONS

ASPN 2021	Morbidity and function loss after resection of malignant peripheral nerve sheath tumors. **Martin E**, Pendleton C, Verhoef C, Spinner RJ, Coert JH, MONACO collaborators.
ASPN 2021	A Bayesian approach for diagnostic accuracy of malignant peripheral nerve sheath tumors: a systematic review and meta-analysis **Martin E**, Geitenbeek RTJ, Coert JH, Hanff DF, Graven LH, Grünhagen DJ, Verhoef C, Taal W.
ASPN 2021	An overview of the prevalence of residual limb pain and symptomatic neuromas following lower extremity amputations: a systematic review and meta-analysis List EB, Krijgh DD, **Martin E**, Coert JH.
FESSH 2020	Oncological treatment considerations differ across surgical subspecialties treating malignant peripheral nerve sheath tumors: an international survey. **Martin E**, looff WBM, van Houdt WJ, van Dalen T, Verhoef C, Coert JH.
FESSH 2020	Do surgical strategies and the use of reconstructions after resection of MPNST differ between surgical subspecialties? An international survey **Martin E**, Slooff WBM, van Houdt WJ, van Dalen T, Verhoef C, Coert JH.
SSO 2020	A nationwide cohort study on treatment and survival in patients with malignant peripheral nerve sheath tumors. **Martin E**, Coert JH, Flucke UE, Slooff WBM, van Dalen T, van de Sande MAJ, van Houdt WJ, Grünhagen DJ, Verhoef C.
ASPN 2020	A nationwide cohort study on treatment and survival in patients with malignant peripheral nerve sheath tumors. **Martin E**, Coert JH, Flucke UE, Slooff WBM, van Dalen T, van de Sande MAJ, van Houdt WJ, Grünhagen DJ, Verhoef C.
ASPN 2020	Neurofibromatosis-associated malignant peripheral nerve sheath tumors in children have a worse prognosis: a nationwide cohort study. **Martin E**, Coert JH, Flucke UE, Slooff WBM, Grünhagen DJ, Verhoef C.
EANS 2019	Malignant peripheral nerve sheath tumors (MPNSTs): a Dutch nationwide cohort study on treatment and survival **Martin E**, Flucke UE, Slooff WBM, van Dalen T, Coert JH.

EANS 2019	The impact of early (<24h) surgical decompression on neurological recovery in thoracic spinal cord injury: a meta-analysis ter Wengel PV, **Martin E**, De Witt Hamer PC, Feller RE, van Oortmerssen JAE, van der Gaag NA, Öner FC, Vandertop WP.
NVPC 2019	Maligne perifere zenuwschedetumoren (MPNSTs): een nationale cohortstudie naar behandeling en overleving **Martin E**, Flucke UE, Slooff WBM, van Dalen T, Coert JH
FESSH 2018	Treatment and survival differences across tumor sites in malignant peripheral nerve sheath tumors: a SEER database analysis **Martin E**, Muskens IS, Smith TR, Broekman MLD
ASPN 2018	Treatment and survival differences across tumor sites in malignant peripheral nerve sheath tumors: a SEER database analysis **Martin E**, Muskens IS, Smith TR, Broekman MLD
EANS 2017	A nationwide analysis of 30-day readmission and adverse events after peripheral nerve surgery in extremities **Martin E**, Muskens IS, Senders JT, Cote DJ, Smith TR, Broekman MLD
EANS 2017	Timing of surgery in traumatic brachial plexus injury: a systematic review **Martin E**, Senders JT, Smith TR, Broekman MLD
EANS 2017	Randomized controlled trials in neurosurgery comparing surgery versus best medical treatment **Martin E**, Muskens IS, Senders JT, DiRisio AC, Smith TR, Broekman MLD

POSTER PRESENTATIONS

ASPN 2020	Do oncological considerations in malignant peripheral nerve sheath tumors differ among surgical specialties? An international survey. **Martin E**, Slooff WBM, van Dalen T, Verhoef C, Coert JH.
ASPN 2020	Different considerations across surgical subspecialties regarding functional reconstructions and nerve handling in malignant peripheral nerve sheath tumors: an international survey. **Martin E**, Slooff WBM, van Dalen T, Verhoef C, Coert JH.
ASPN 2020	A systematic review of functional outcomes after nerve reconstruction in extremity soft tissue sarcomas: a need for general implementation. **Martin E**, Dullaart MJ, Verhoef C, Coert JH.
EANS 2019	Treatment and survival of osteosarcoma and Ewing sarcoma of the skull: a SEER database analysis **Martin E**, Senders JT, ter Wengel PV, Smith TR, Broekman MLD

CNS 2017	A nationwide analysis of 30-day readmission and adverse events after peripheral nerve surgery in extremities **Martin E**, Muskens IS, Senders JT, Cote DJ, Smith TR, Broekman MLD
CNS 2017	Timing of surgery in traumatic brachial plexus injury: a systematic review **Martin E**, Senders JT, Smith TR, Broekman MLD
WPATH 2016	Meningiomas in three male-to-female transgender subjects using estrogens / progestagens and review of the literature ter Wengel PV, **Martin E**, Gooren L, Den Heijer M, Peerdeman SM
SNO 2016	Increased risk of meningiomas in male-to-female transgender subjects using estrogens / progestagens ter Wengel PV, **Martin E**, Gooren L, Den Heijer M, Peerdeman SM

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CURRICULUM VITAE

Enrico Martin was born on the 8th of January 1995 in Leiderdorp, the Netherlands, son of Didier Martin and Nathalie Martin. He grew up with one younger brother, Raoul. After graduating cum laude from his high school the Rijnlands Lyceum in Oegstgeest he started his study in Medicine at the University of Utrecht in 2012.

At the end of his Bachelor's degree in 2015 he got involved in research at the Department of Neurosurgery. He quickly gained interest in peripheral nerve surgery as it combined his fascination for complex anatomy and an underexplored field of plastic surgery and neurosurgery. In 2017 he went abroad for 4 months to do research at Brigham and Women's Hospital in Boston under the supervision of dr. T.R. Smith and dr. M.L.D. Broekman. He joined the Computational Neurosurgical Outcomes Center and started several studies with a main focus on peripheral nerve diseases. Upon his return, prof. dr. J.H. Coert provided him with the opportunity to start a PhD program on the treatment of malignant peripheral nerve sheath tumors (MPNSTs) at the Department of Plastic, Reconstructive, and Hand Surgery of the University Medical Center Utrecht (UMCU). Among others, he initiated an international multicenter collaboration, the **M**PNST **ON**cological **A**nd **C**linical **O**utcome Consortium (MONACO). He did most of his PhD alongside his clinical rotations under the supervision of prof. dr. J.H. Coert, prof. dr. C. Verhoef, prof. dr. M.A.J. van de Sande, and dr. W.J. van Houdt.

After obtaining his Medical Degree cum laude he finished his PhD thesis and extended his research in the field of MPNSTs for almost a year at the Erasmus Medical Center in Rotterdam under the supervision of prof. dr. C. Verhoef. During this time he started new collaborations to elaborate on ideal diagnostics and tumor biology of MPNSTs. That same year his research was awarded at the annual European Association of Neurosurgical Societies meeting and American Society for Peripheral Nerve meeting. In August 2020 he started as a resident not in training (ANIOS) at the Department of Plastic, Reconstructive, and Hand Surgery of the UMCU under the supervision of dr. A.H. Schuurman to continue his ambitions of becoming a plastic surgeon. Enrico currently lives in Amsterdam.