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Qualitative Study

Surgical strategies and the use of functional reconstructions after resection of MPNST: An international survey on surgeons' perspective

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ABSTRACT

Background: Malignant peripheral nerve sheath tumors (MPNST) are aggressive and possibly morbid sarcomas because of their tissue of origin. However, postoperative functional status of MPNST patients has been understudied. Reconstructions may play a role in restoring lost function, but are still infrequently carried out. This study investigated how surgical considerations and the use of functional reconstructions differed among surgeons treating MPNST.
Methods: This survey was distributed among members of multiple surgical societies. 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.
Conclusions: 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.

1. 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

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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.

2. Methods

2.1. 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 Appendix 1. Approval for this study was obtained from our institutional review board. The study has been reported in line with the Consolidated criteria for Reporting Qualitative Research (COREQ) criteria.

2.2. 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.

2.3. 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).

3. Results

3.1. Demographics of survey responders

A total of 174 respondents filled out the survey, most of which were European surgeons (Fig. 1). The most common surgical subspecialty was plastic surgery (48.9%, Fig. 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 $p > 0.05$).

3.2. Postoperative functional status

Most surgeons observe a combination of neuropathic pain, motor disability, and sensory loss after resection of MPNSTs (69.7%, Fig. 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 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%). A smaller proportion would only resect less in case free margins are not presumed possible (36.1%).

3.3. Intraoperative nerve handling

In general, most respondents always look for the nerve of origin (74.1%, 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%). 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 ($p > 0.05$).

3.4. Functional reconstructions

Overall, 39.2% always considers functional reconstructions when a motor deficit is anticipated (Fig. 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,

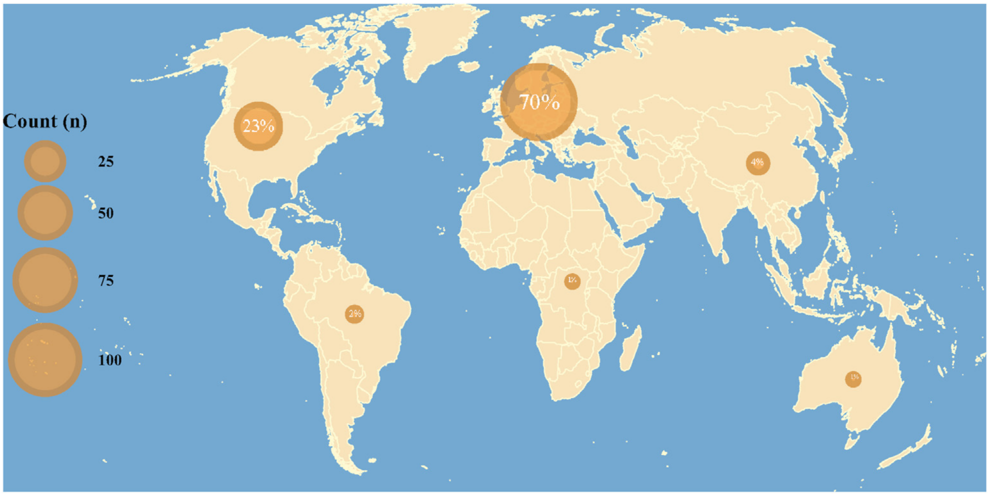

Fig. 1. World map indicating number of respondents per continent. The surface of each bubble corresponds to the number of respondents.

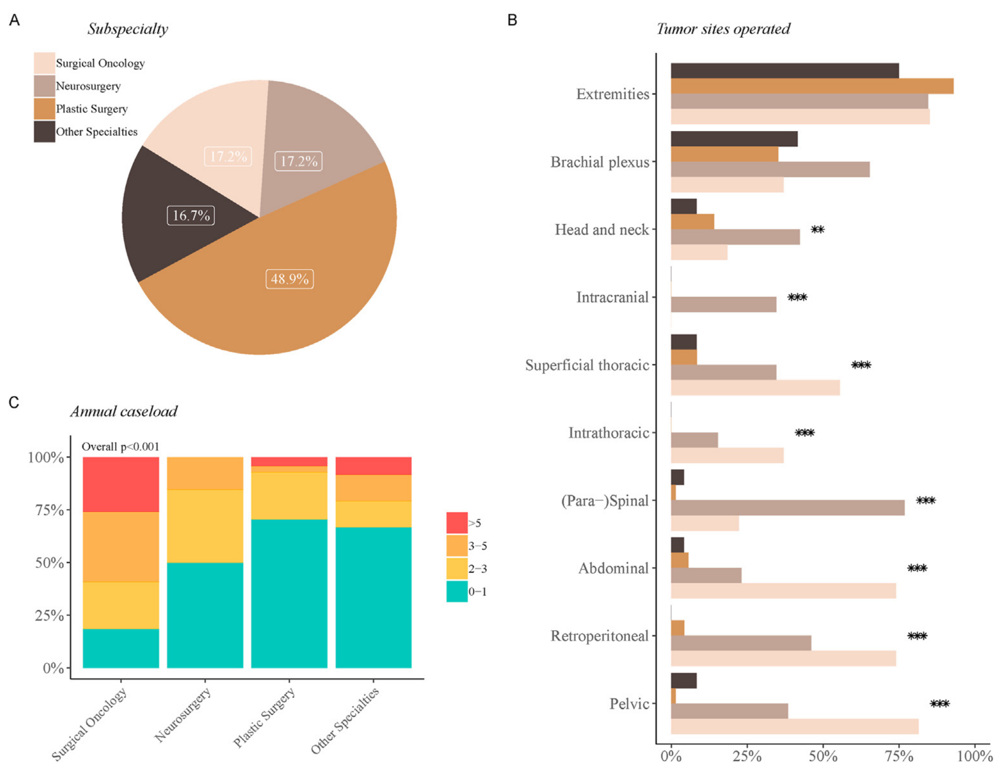

Fig. 2. Demographic distributions of surgical subspecialties. A) Distribution of respondents' surgical subspecialty. B) Distribution of tumor locations operated per subspecialty. C) Distribution of annual surgical caseload per subspecialty. p-values: * = <0.05, ** = <0.01, *** = <0.001.

preferences for timing of reconstruction differed. 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 $p < 0.05$, Fig. 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 ($p > 0.05$, Fig. 4C).

4. 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

Table 1
Experience and nerve handling among surgical subspecialties.

Variable	n	Overall	Oncologic Surgery	Neurosurgery	Plastic Surgery	Other Specialties	p-value
		174	30	30	85	29	
Experience	0–10 years	58 (38%)	8 (29%)	10 (37%)	31 (43%)	9 (36%)	0.585
	10–20 years	56 (37%)	14 (50%)	10 (37%)	25 (35%)	7 (28%)	
	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%)	**<0.001**
	Sarcoma	29 (19%)	23 (85%)	0 (0%)	4 (6%)	2 (8%)	
	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%)	0.403
	Sometimes	7 (78%)	4 (16%)	2 (11%)	1 (3%)	0 (0%)	
	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%)	**<0.001**
	Sometimes	20 (24%)	14 (56%)	1 (6%)	4 (14%)	1 (9%)	
	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%)	**0.023**
	Sometimes	22 (27%)	7 (28%)	3 (18%)	9 (32%)	3 (27%)	
	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%)	0.539
	Sometimes	16 (20%)	5 (20%)	4 (24%)	3 (11%)	4 (36%)	
	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%)	0.284
	Bury in bone/muscle/vein	24 (39%)	11 (46%)	7 (50%)	4 (24%)	2 (33%)	
	End closure	9 (15%)	4 (17%)	1 (7%)	3 (18%)	1 (17%)	
	Targeted Muscle Reinnervation	6 (10%)	1 (4%)	1 (7%)	4 (24%)	0 (0%)	
	Other	7 (12%)	1 (4%)	2 (14%)	4 (24%)	0 (0%)	

Bold denotes statistically significant.

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.

4.1. Functional reconstructions in MPNST

Despite the fact that oncological treatment should generally be

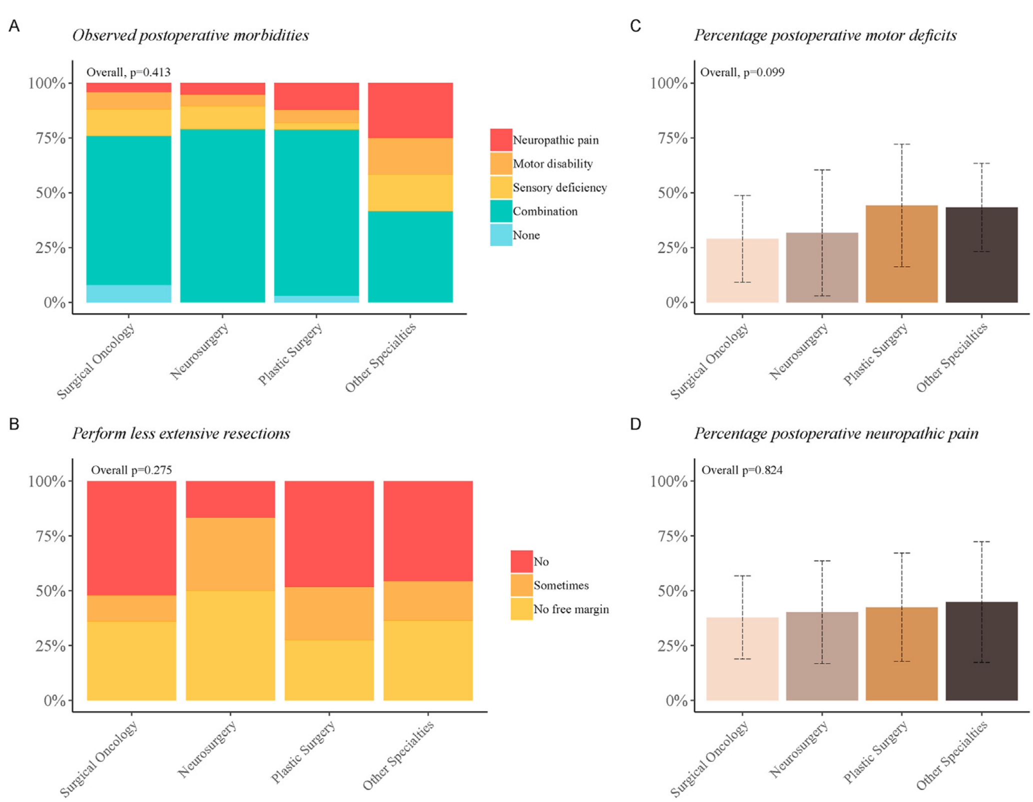

Fig. 3. Complications after MPNST resections. A) Most common postoperative complication per subspecialty. B) Considering resecting less tumor per subspecialty. C) Mean postoperative prevalence of motor deficits per subspecialty. D) Mean postoperative prevalence of neuropathic pain per subspecialty.

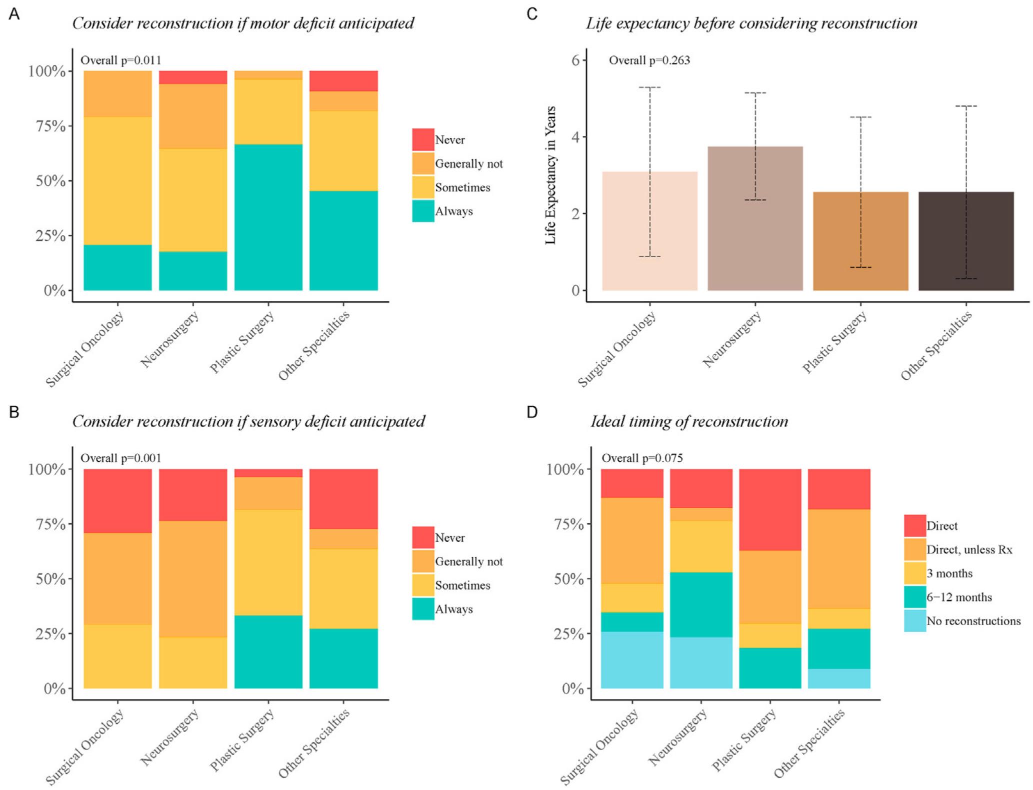

Fig. 4. Considerations for performing functional reconstructions in MPNST. A) Distribution per subspecialty considering a functional reconstruction when a motor deficit is anticipated. B) Distribution per subspecialty considering a functional reconstruction when a sensory deficit is anticipated. C) Mean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

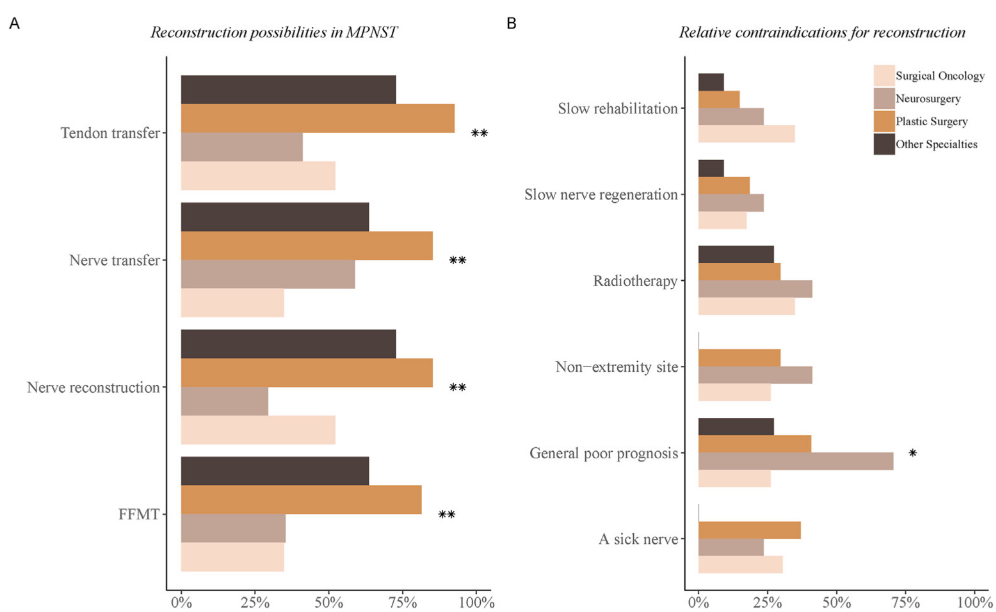

Fig. 5. Functional reconstructions. A) Percentage of respondents per subspecialty considering type of reconstruction as an option in MPNST patients, FFMT = free functioning muscle transfer. B) Percentage of respondents per subspecialty considering a factor as relative contraindication for functional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

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.

4.2. 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].

4.3. 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.

4.4. 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.

5. 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. A multidisciplinary surgical and reconstructive approach may possibly be beneficial in MPNST.

Conflicts of interest

None to declare.

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Ethical approval and consent

Approval for this study was obtained from our institutional review board (protocol number: 18–526/C, reference number: WAG/mb/18/026470).

Provenance and peer review

Not commissioned, externally peer-reviewed.

Author contribution

Conceptualization: EM, WBM, TD, CV, JHC.
Data curation: EM, JHC.
Formal analysis: EM, WJH, CV, JHC.
Funding acquisition: NA.
Investigation: EM, WBM, WJH, TD, CV, JHC.
Methodology: EM, WBM, WJH, TD, CV, JHC.
Project administration: EM, JHC.
Resources: EM, CV, JHC.
Software: EM, JHC.
Supervision: WJH, CV, JHC.
Validation: WBM, WJH, TD, CV, JHC.
Visualization: EM.
Roles/Writing – original draft: EM, JHC.
Writing – review & editing: EM, WBM, WJH, TD, CV, JHC.

Guarantor

E. Martin, J.H. Coert.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.orthop.2021.03.001.

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