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REVIEW

Treatment of neurofibromatosis 1-associated malignant peripheral nerve sheath tumors: a systematic review

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Abstract

Malignant peripheral nerve sheath tumors (MPNST) are a rare and aggressive group of tumors that are challenging to treat. Neurofibromatosis type 1 (NF-1)-associated MPNSTs have been associated with poorer clinical outcomes. The treatment options for NF-1-associated MPNSTs broadly include surgery (SG), chemotherapy (CT), and adjuvant radiotherapy (RT). Overall, the role and efficacy of CT and RT are unclear. Examination of existing literature for studies reporting on NF-1-associated MPNSTs and respective treatment-related outcomes was conducted. We conducted a systematic review according to PRISMA guidelines in PubMed/Medline and Cochrane databases of studies which reported treatment-specific outcomes in NF-1-associated MPNSTs. The literature search found 444 records after removal of duplicates. The present study included 50 patients across 12 observational studies. All of the included studies reported data on overall survival (OS 52%, $n = 26/50$) but mean follow-up in months among the studies and among patients varied widely, between 10.85 (SD, ± 10.38) and 192 (SD, ± 98.22). From the included studies, patients underwent either SG alone ($n = 21$), SG + CT ($n = 10$), SG + RT ($n = 7$), or SG + CT + RT ($n = 12$). The quality of evidence in the literature regarding optimal treatment options for NF-1-associated MPNSTs remains tenuous. Future retrospective and prospective comparative trials should consider adherence to a set of reporting guidelines to improve the quality of evidence in the literature with respect to individual treatment-related outcomes. The need for prospective multi-institutional efforts cannot be overstated.

Keywords Malignant peripheral nerve sheath tumor · MPNST · Neurofibromatosis 1 · NF-1 · Publishing guidelines · Chemotherapy · Radiotherapy

Introduction

Malignant peripheral nerve sheath tumors (MPNST) are a rare, aggressive, and heterogenous group of tumors and represent a notable challenge to efficacious treatment [1]. Up to 50% of MPNSTs occur in association with neurofibromatosis type 1 (NF-1) and compared to sporadic MPNSTs; NF-1-associated MPNSTs have been associated with lower survival rates [1, 2]. One study by Vasconcelos et al. including 92 patients found that NF1 status was one of the most important predictors of survival in patients with MPNST [3]. Several other studies have reported similar results supporting the classical notion of NF-1 association as a main predictor of a poor clinical course [1, 2, 4–7]. In the context of this, it is critical to specifically examine NF-1-associated MPNSTs with respect to optimal treatment options, which at present remain controversial and unclear [2].

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Due to the relative rarity of MPNSTs, treatment decisions vary widely between institutions and depend upon the clinical decision making of individual practitioners [2, 3]. The treatment options for NF-1-associated MPNSTs broadly include surgery (SG), chemotherapy (CT), and adjuvant radiotherapy (RT). The main goal in management of MPNSTs should primarily be to achieve negative surgical margins as with any soft-tissue tumor [8, 9]. MPNSTs are generally considered chemoresistant and have even been reported to have worse outcomes following administration [2]. However, several studies have examined the use of specific neo-adjuvant chemotherapeutic regimens to examine responses in sporadic and NF-1-associated MPNSTs [10–12]. Despite radio-resistance and the risk of radiation-associated MPNST formation, at present RT, is still recommended for larger MPNSTs or those with particularly aggressive histologic findings [13]. The only curative known treatment is wide-negative surgical margins before distant metastases occur, which may or may not be feasible based on the tumor size and location [13]. Overall, the role and efficacy of CT and RT continue to be the subject of debate.

In the present systematic review, we sought to examine the existing literature for any studies that have reported outcomes with respect to specific treatments received by patients with NF-1-associated MPNSTs. Furthermore, we set out to highlight the need for consistent reporting guidelines to inform individual treatment-related outcomes.

Methods

The present systematic review was performed according to the PRISMA guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses). A systematic search was conducted in PubMed/Medline and Cochrane databases by two independent Investigators (PT, MT), search terms: "Malignant Peripheral Nerve Sheath Tumor," "MPNST," "Neurofibromatosis" "Neurofibromatosis-1," "Neurofibromatosis Type 1". Any discrepancies were resolved through consensus.

Selection criterion

Pre-determined criteria defined the following requirements for inclusion of a study: (i) an included study must be randomized controlled trial, prospective trial, observational trial, or case report, (ii) the study must have been published by December of 2018, (iii) the study must have explicitly reported the NF-1 status of the patients, and (iv) the study must have reported quantitative outcomes data of overall survival and respective treatment arms including surgery (SG), chemotherapy (CT), and radiotherapy (RT). These inclusion criteria were used to focus only on studies of NF-1-associated MPNSTs that report their findings in a way that may be informative regarding patient outcomes with respect to each individual treatment arm (SG + CT + RT, SG + CT, SG + RT, or SG alone).

Data abstraction and statistics

Independent and blinded reviewers (DX, MT) extracted data from eligible studies. Variables of abstraction included author, years of enrollment, location, study design, treatment arms, number of patients, sex, follow-up, age at presentation, reported histologic subtype, mitotic rate, time from NF1 diagnosis, tumor location, recurrence, time to recurrence, metastasis, time to metastasis, and any associated complications. The primary outcome was overall survival following treatment at the last reported follow-up. Primary outcomes and patient characteristics were presented using descriptive statistics.

Risk of bias assessment

Risk of bias was assessed by two investigators (PT, MT) with the Robins-I tool for non-randomized studies [14]. The following domains were evaluated: confounding, selection of participants, departure from intended interventions, missing data, measurement of outcomes, and selective reporting. Any discrepancies were resolved via consensus following discussion with senior authors.

Results

Literature search results

The literature search of Pubmed/Medline and Cochrane resulted in 444 records after removal of duplicates. After screening of titles and abstracts, 416 articles were found to be irrelevant and excluded from the study. The 28 remaining articles were eligible for full-text evaluation. Of these, 16 studies were excluded for the following reasons: No data on the NF1 status of patients in these studies ($n = 11$), MPNST not associated with NF-1 ($n = 1$), treatment not included surgery, chemotherapy, or radiation ($n = 1$), and outcomes were not delineated based on treatment arm ($n = 3$). Overall, 12 studies met the predetermined eligibility criterion and were included in the systematic review, outlined in the PRISMA flow diagram (Fig. 1) [15–25].

Included study characteristics

The present study included 50 patients from 1984 to 2017 across 12 observational studies. Only patients with NF-1-associated MPNSTs were included. The mean patient age at

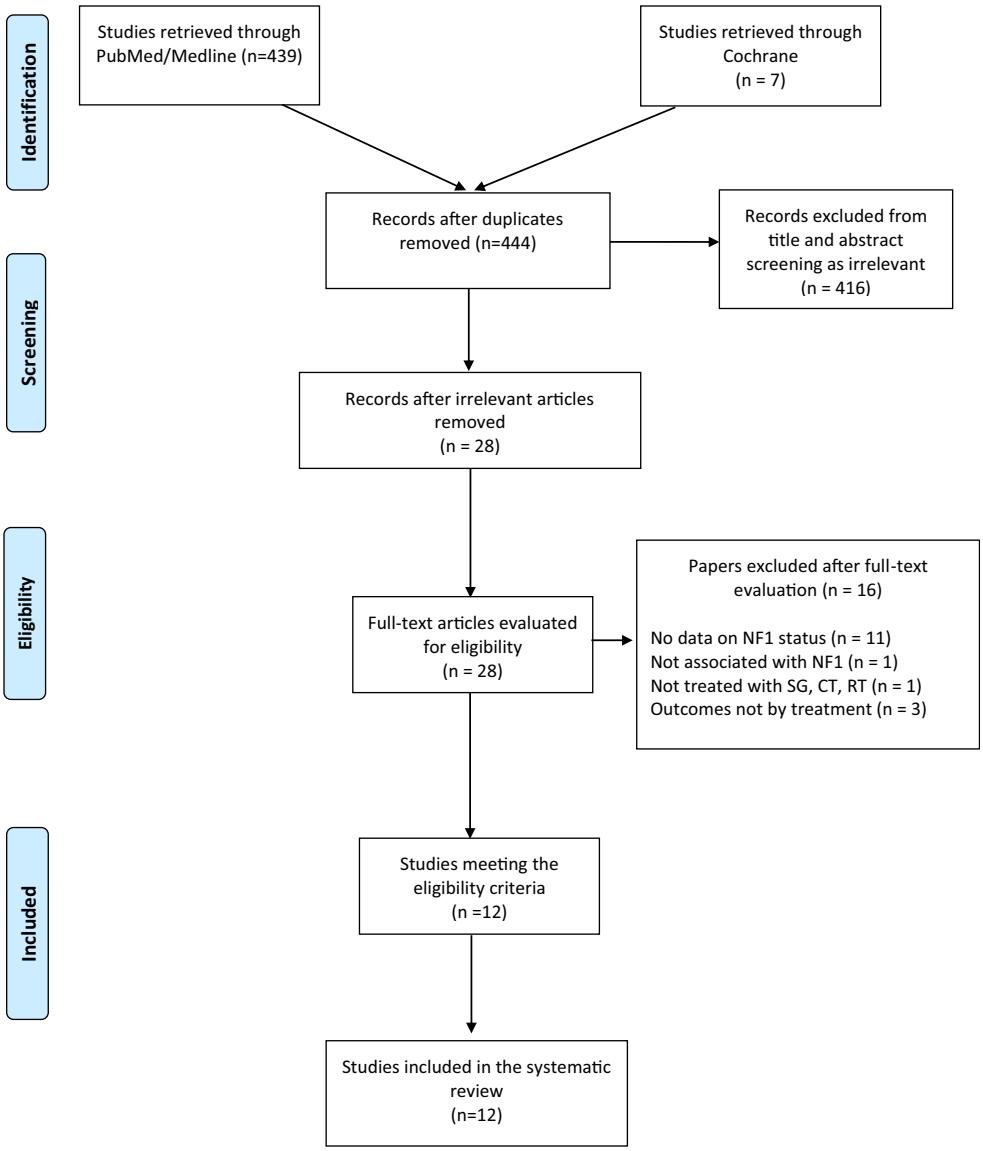

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow diagram

surgery varied between studies from 9.43 (SD, ± 12.7) to 43 (SD, ± 8.59) years of age. All of the included studies reported data on overall survival (OS 52%, $n = 26/50$) but mean follow-up in months among the studies and among patients varied widely, between 10.85 (SD, ± 10.38) and 192 (SD, ± 98.22). From the included studies, patients underwent either SG alone ($n = 21$), SG + CT ($n = 10$), SG + RT ($n = 7$), or SG + CT + RT ($n = 12$). Overall study characteristics are detailed in Table 1. A detailed assessment of risk of bias with the Robins-I tool for nonrandomized studies is available in Supplemental Table 1.

Few studies reported consistent quantitative information regarding details of histologic findings and tumor classification, though all studies categorized the lesions as MPNSTs. The most consistently reported histologic classification was the mitotic rate, reported in ten of 12 studies where all but four patients had a high mitotic rate [15–21, 23–26]. In the nine studies which reported the presence or of absence of necrosis, 14 patients were reported to have necrosis on histopathologic examination [15, 16, 18, 19, 21, 23–26]. However, one study reported that "most" patients had necrosis without a specified number [25], and the other remaining studies did not specify the presence or absence of necrosis [17, 20, 22, 25]. Ogose et al., Rekhi et al., and Alina et al. reported specifically on the malignant-triton-tumor subtype [16, 20, 26].

The studies inconsistently reported descriptive information regarding time from NF-1 diagnosis and tumor location. Five studies reported the time from NF-1 diagnosis which ranged from 16 years prior to MPNST diagnosis to at the same time of MPNST diagnosis [15, 16, 22, 23, 26]. All studies reported information on tumor location that could allow classification of MPNSTs as either extremity ($n = 16/50$) or non-extremity ($n = 34/50$) lesions. Ten studies reported information that allowed for classification of patient's MPNSTs as either deep ($n = 29/38$) or superficial

Table 1 Characteristics of included studies reporting treatment-specific outcomes for NF-1-associated MPNSTs

Study	Country	Number of patients	% Male	Age, years mean (SD)	Location ex/non-ex	Number of Patients Receiving Each Treatment				Follow-up, months mean (SD)
						SG	SG + CT	SG + RT	SG + CT + RT	
An 2017	Korea	8	50	12.63 (4.00)	2/6		6		2	46.0 (66.2)
Alina 2015	USA	1	0	36.0 (–)	0/2				1	48.0
Schaefer 2015	USA	5	60	42.8 (8.13)	2/3	5				72.8 (60.5)
Moretti 2011	USA	4	75	43 (8.48)	2/2		3		1	22.6 (6.9)
Baena-Ocampo 2009	Mexico	2	50	25.5 (9.19)	0/2	1		1		27.5 (12.0)
Rekhi 2008	India	4	67	29 (8.02)	4/2	1	1	2		9.7 (12.4)
Kim 2005	Korea	2	0	32 (1.41)	0/2				2	16.5 (6.4)
Coffin 2004	USA	3	50	9.33 (12.70)	0/3	1			2	192.0 (98.2)
Ogose 2001	Japan	2	50	17.5 (3.53)	0/2				2	30.5 (21.9)
Asavamongkolkul 2001	Thailand	2	0	33.5 (2.12)	0/2	1		1		11.5 (4.9)
Chang 1994	Taiwan	7	57	32 (17.8)	2/5	5		2		10.9 (10.4)
Ducatman 1984	USA	10	50	12.1 (2.6)	5/5	7		1	2	57.2 (87.5)

MPNST malignant peripheral nerve sheath tumor, *SD standard deviation*, *Ex extremity*, *Non-Ex non-extremity*

($n = 9/38$) [15–17, 19, 21–26]. The availability of quantitative information also differed between the included studies regarding further procedures, treatment related complications, treatment details, chemotherapy type, chemotherapy dose, radiation dose and schedule, and resection margins. These details are discussed further for each treatment group.

Outcomes with surgery, chemotherapy, and adjuvant radiotherapy

Seven of the included studies reported the treatment of patients with MPNST using SG, CT, and RT with a total of 12 patients [15, 16, 18, 21, 22, 25, 26]. The aggregate overall survival in this group was 58% ($n = 7/12$). Among the included studies, six of 12 patients experienced local recurrence at a mean time-to-recurrence of 8.31 months (SD, ± 7.8) and three of 12 patients experienced metastatic lesions at a mean time-to-metastasis after treatment at 101.6 months (SD, ± 144.9). The mean follow-up varied widely between studies ranging from 1.38 (SD, ± 0.5) years to 13.3 years (SD, ± 16.1).

Regarding the type of surgery, one study utilized limb amputation [25], two studies used subtotal-resection (STR) [15, 16], three studies used gross total-resection (GTR) [19, 21, 26], and one study did not specify the type of surgery used [22]. Regarding chemotherapy, six of the seven studies reported the type of chemotherapeutics used [15, 16, 18, 21, 22, 26]. Chemotherapy dose and treatment regimen were reported inconsistently among the studies. Only four of the seven studies reported details of radiotherapy [15, 16, 21, 26]. Overall chemotherapy and radiotherapy details are presented in Table 2.

Outcomes with surgery and adjuvant radiotherapy

Five studies reported treatment of patients with MPNST using SG and RT for a total of seven patients [19, 20, 23–25]. The overall survival in patients who received both SG and RT was 42% ($n = 3/7$). Four patients developed local tumor recurrence at a mean time-to-recurrence of 6 months (SD, ± 4.4) [19, 20, 23, 24]. Two patients developed distant metastases at a mean time-to-metastasis of 8 months [20, 24]. The mean follow-up of the included studies varied from 0.6 to 2.6 years. Two studies used GTR [20, 23]; two studies used STR [24, 25], and one study did not report the type of surgery used [19]. Regarding radiotherapy, only one study described details of radiation treatment [23] as outlined in Table 2.

Outcomes with surgery and chemotherapy

Three of the included studies reported on a total of ten patients who received both SG and CT [15, 18, 20]. The overall survival in these patients was 70% ($n = 7/10$). Seven of the ten patients developed local recurrence at a mean time-to-recurrence of 32.2 months (SD, ± 54.3) [15, 18, 19]. Three of the ten patients developed distant metastasis; however, data regarding time-to-metastasis was unavailable [19, 20]. The mean follow-up among the studies varied between a range of 0.5 and 3.0 years (SD, 7.0). Reported chemotherapeutic use and regimen are described in Table 2.

Outcomes with surgery alone

Seven studies treated patients with MPNSTs with SG alone on a total of 21 patients [17, 19, 20, 22–25]. The overall survival

Table 2 Summary of chemotherapy and radiotherapy details of included studies treating NF-1-associated MPNSTs

Treatment Arm	Study	Number of patients	Chemotherapy details	Radiation details
Surgery, chemotherapy, and radiotherapy	An 2017	2	Cyclophosphamide + mesna vincristine, dacarbazine adriamycin, carboplatin isofosfamide, etoposide	One patient: 54 Gy/30 fx One patient: 50.4 Gy/28 fx
	Alina 2015	1	Isofosfamide + mesna, 2 g/m^2 adriamycin, 75 g/m^2	65.4 Gy
	Moretti 2011	1	Doxorubicin, isofosfamide, etoposide	NR
	Kim 2005	2	All patients: 6 cycles of MAID therapy: 3 days of: Isofosfamide 2000 mg/m^2, doxorubicin 20 mg/m^2, dacarbazine 300 mg/m^2 One patient: 6 cycles of VIP therapy Etoposide, 75 mg/m^2, isofosfamide, 1000 mg/m^2, cisplatin, 20 mg/m^2	54 Gy
	Coffin 2004	2	Isofosfamide, adriamycin, vincristine	NS
	Ogose 2001	2	One patient: doxorubicin One patient: isofosfamide, VP-16, doxorubicin, cyclophosphamide	One patient: 46 Gy/23 fractions One patient: 70 Gy/35 fractions
	Ducatman 1984	2	NA	NR
Surgery, radiotherapy	Baena-Ocampo 2009	1	NA	NR
	Rekhi 2009	2	NA	NR
	Asavamongkolkul 2001	1	NA	21 Gy/7 fx
	Chang 1994	2	NA	NR
	Ducatman 1984	1	NA	NR
Surgery, chemotherapy	An 2017	6	All patients: Cyclophosphamide + mesna, dincristine, dacarbazine, adriamycin Two patients also received: isofosfamide, carboplatin, etoposide One patient also received: carboplatin	NA
	Moretti 2011	3	Patient 1: Doxorubicin, isofosfamide × 3 cycles, etoposide, isofosfamide × 2 cycles Doxorubicin, isofosfamide × 1 cycles, isofosfamide, etoposide × 2 cycles Patient 2: Doxorubicin, isofosfamide × 6 cycles Patient 3: Doxorubicin, isofosfamide × 2 cycles campotecan × 3 cycles	NA
	Rekhi 2008	1	NR	NA

Gy gray, *Fx* fractions, *NA* not applicable, *NR* not reported

following treatment with surgery alone was 42% ($n = 9/21$). Eight of the 21 patients developed local recurrence, with a mean time-to recurrence of 8.1 months (SD, ± 3.9) [17, 23–25]. Five of the 21 patients developed distant metastases, with a mean time-to metastasis of 18.25 months (SD, ± 4.6). Among these patients who received SG only, nine patients underwent GTR, five patients underwent STR, four patients underwent amputation, one patient underwent marginal excision, and two patients underwent "excision" not otherwise specified. The mean follow-up among studies ranged from 1 to 5.6 years (SD, ± 5.1).

Discussion and future perspectives

The present systematic review examined the existing literature for any studies which reported treatment-related outcomes with respect to the use of SG, CT, and/or RT. Few studies have specifically reported findings based upon individual treatment arms and NF-1-associated MPNSTs. Furthermore, the reporting of information regarding the type of surgical resection, chemotherapeutic details, and radiotherapy details was inconsistent. Most notably, the follow-up among the studies varied widely preventing

Table 3 Proposed Reporting Guidelines for NF-1 Associated MPNSTs (RG-MPNST) for Each Patient and Treatment Arm

Section	Item	Description
Baseline characteristics	1. Age at diagnosis	Indicate the age at diagnosis.
	2. Sex	Indicate the sex of the patient.
	3. NF-1 status	Indicate the NF-1 status and associated family history if applicable.
Histopathologic findings	4. Grade	Indicate the grade: high or low
	5. Mitotic index	Indicate the mitotic index in a quantitative fashion with number of mitoses per high-powered field.
	6. MPNST subtype	Specify the sub-type and other features if applicable. (e.g., "Malignant Triton Tumor" or "Perineural Differentiation")
	7. Presence or absence of necrosis	Specify the presence or absence of necrosis in a quantitative fashion per high-powered field.
	8. Molecular markers	If available, specify the presence of molecular tumor markers through qPCR or immunohistochemistry.[1,2] Consider tissue banking for future analysis by consultation with your institutional clinical or research pathology core with IRB approval.
Location	9. Specific tumor location	Describe the tumor location in detail (e.g., Thoracic Spine, Brachial Plexus, Superior Mediastinum, etc.). The location of the tumor will impact feasibility of resection and further treatment decisions.[3]
	10. Cutaneous or deep	Specify whether the MPNST is a cutaneous or deep tissue lesion.
	11. Prior mass	Detail if the patient's MPNST arose from a prior neurofibroma or other lesion.
Radiologic findings	12. Tumor dimensions	Specify the tumor dimensions in centimeters.
	13. Radiologic description	Provide a detailed radiologic description of the lesion and involvement of surrounding structures drawing from MRI and, if available, FDG-PET for diagnosis and treatment response.
Surgery	14. Type of surgery used	Describe the scope of surgical resection that was performed: gross total resection, sub-total resection, debulking
	15. Positive or negative surgical margins	Describe if the postoperative surgical margins appear positive or negative for residual tumor.
	16. R Classification of residual mass	Classify the surgical status using the R scale. [4] R0 – negative surgical margins, R1 – microscopic residual tumor, R2 – macroscopic residual tumor
	17. Associated surgical complications	Report any associated surgical complications.
Chemotherapy	18. Type of chemotherapeutic	Specify the type of chemotherapeutic used.
	19. Dose of chemotherapeutic	Specify the dose of each chemotherapeutic.
	20. Regimen and number of cycles	Specify the dosing regimen and number of cycles used.
	21. Route(s) of administration	Specify the route of administration of chemotherapeutics used.
	22. Associated complications	Report any complications associated with chemotherapeutic use.
Radiotherapy	23. Gy units per fraction	Specify the number of Gy administered per fraction.
	24. Number of fractions	Specify the total number of fractions.
	25. Total number of Gy units	Specify the total number of Gy units administered to each patient.
	26. Timing of radiation doses	Specify the timing of radiation doses.
	27. Associated complications	Report any complications associated with radiotherapy.
Outcomes	28. Local recurrence	Report all instances of local recurrence with respect to each patient or treatment arm.
	29. Time to local recurrence	Report the time to local recurrence with respect to each patient or treatment arm.
	30. Distant metastases	Report all instances of distant metastases with respect to each patient or treatment arm.
	31. Time to distant metastases	Report the time to distant metastases with respect to each patient or treatment arm.
	32. Disease-free survival	Report disease-free survival with respect to each patient or treatment arm.
	33. Overall survival	Report overall survival with respect to each patient or treatment arm.
	34. Follow-up	Report follow-up with respect to each patient or treatment arm in order to minimize the risk of follow-up bias.

NF-1 neurofibromatosis type 1, qP*CR* quantitative polymerase chain reaction, *IRB* Institutional Review Board, *MRI* magnetic resonance imaging, *FDG-PET* fluorodeoxyglucose positron emission tomography, *Gy* gray (SI unit of radiation dose)

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the ability to draw reasonable conclusions regarding therapeutic efficacy.

The outcomes for patients with NF-1-associated MPNSTs has largely remained unchanged since 2002 [27]. The current state of evidence has not identified a clear role for adjuvant CT or RT in NF-1-associated MPNSTs. Nonetheless, several chemotherapeutic treatment options have been or are under active investigation for MPNSTs and other soft tissue sarcomas including erlotinib, sorafenib [28], imatinib [29], dasatinib [30], bevacizumab/everolimus, and gantespib/sirolimus [13]. Various other chemotherapeutic agents have also been implemented for MPNSTs with the suggestion that many of these agents have been proven to be less efficacious in NF-1-associated MPNSTs [13, 27, 31]. Regarding radiotherapy, local control was improved in a study of 91 patients but with no impact on overall survival 13, 32. Adjuvant radiotherapy is still recommended in patients with large MPNSTs with difficult margins [27].

It should be emphasized, however, that many of these studies involving CT and RT group sporadic MPNSTs and NF-1 associated MPNSTs with other soft-tissue sarcomas. The importance of multi-institutional efforts and well-designed prospective trials specifically for MPNSTs and NF-1-associated MPNSTs cannot be overstated. While it is important to note that the practical feasibility of conducting appropriately designed trials is limited owing to the rarity of the disease and extensive associated follow-up, this does not remove the need for evidence-based evaluation of putative treatment options specifically in this disease entity. Some initiatives have recognized and made steps in the right direction, such as the Children's Tumor Foundation Neurofibromatosis Biobank and the Sarcoma Alliance for Research Through Collaboration and Neurofibromatosis Clinical Trials Consortium which are representatives of multi-institutional efforts for tissue banking and clinical trials for targeted therapy [27].

Until further collaborative, multi-institutional, and even international efforts are underway to address this rare disease process, the quality of published data from retrospective and prospective single-center institutions would benefit from adherence to a standard set of proposed reporting guidelines. Here we propose a simple set of guidelines to report patient-level data outlined in Table 3 that could improve the quality of reported evidence regarding treatment-specific outcomes in NF-1-associated MPNSTs.

Limitations

To our knowledge, this is the first systematic review to specifically examine treatment-related outcomes in NF-1-associated MPNSTs among observational trials. The results of the present study should be examined in the context of several limitations. First, inherent to the designs, all studies were retrospective, non-randomized, observational studies providing limited and variable patient-level data. Secondly, the data in each treatment arm regarding baseline characteristics of each MPNST's histologic classification, presence or absence of necrosis, specifics of tumor location, radiographic data and immunohistochemical classification, and time from NF-1 diagnosis was inconsistently reported. Critically, the included studies varied widely in terms of posttreatment follow-up and specifics of each treatment regimen (i.e., chemotherapy type, dose, route of administration, radiation dosing regimen) resulting in difficulty in comparing individual treatment arms. Future prospective and appropriately designed studies should be conducted in order to establish consistency of reporting and to compare NF-1-associated MPNSTs in a clinically relevant fashion in an effort to develop evidence-based treatment recommendations for this disease process.

Conclusion

The quality of evidence in the literature regarding optimal treatment options for NF-1-associated MPNSTs remains tenuous. Future retrospective and prospective trials should adhere to an agreed upon set of reporting guidelines to improve the quality of evidence in the literature with respect to individual treatment-related outcomes. The need for prospective multi-institutional efforts cannot be overstated.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not applicable for this systematic review.

Informed consent Not applicable for this systematic review.

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