

Local recurrence in malignant peripheral nerve sheath tumours: multicentre cohort study

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Abstract

Background: Malignant peripheral nerve sheath tumours (MPNSTs) have high local recurrence (LR) rates. Literature varies on LR risk factors and treatment. This study aimed to elucidate treatment options and risk factors for first and second LRs (LR1 and LR2) in a large multicentre cohort.

Method: Surgically treated primary MPNSTs between 1988 and 2019 in the MONACO multicentre cohort were included. Cox regression analysed LR1 and LR2 risk factors and overall survival (OS) after LR1. Treatment of LR1 and LR2 was evaluated.

Results: Among 507 patients, 28% developed LR1. Median follow-up was 66.9 months, and for survivors 111.1 months. Independent LR1 risk factors included high-grade tumours (HR 2.63; 95% c.i. 1.15 to 5.99), microscopically positive margins (HR 2.19; 95% c.i. 1.51 to 3.16) and large tumour size (HR 2.14; 95% c.i. 1.21 to 3.78). Perioperative radiotherapy (HR 0.62; 95% c.i. 0.43 to 0.89) reduced the risk. LR1 patients had poorer OS. Synchronous metastasis worsened OS (HR 1.79; 95% c.i. 1.02 to 3.14) post-LR1, while surgically treated LR was associated with better OS (HR 0.38; 95% c.i. 0.22 to 0.64) compared to non-surgical cases. Two-year survival after surgical treatment was 71% (95% c.i. 63 to 82%) versus 28% (95% c.i. 18 to 44%) for non-surgical LR1 patients. Most LR1 (75.4%) and LR2 (73.7%) patients received curative-intent treatment, often surgery alone (64.9% versus 47.4%). Radiotherapy combined with surgery was given to 11.3% of LR1 and 7.9% of LR2 patients.

Conclusion: Large, high-grade MPNSTs with R1 resections are at higher LR1 risk, potentially reduced by radiotherapy. Surgically treated recurrences may provide improved survival in highly selected cases.

Introduction

Malignant peripheral nerve sheath tumours (MPNSTs) are rare and aggressive malignant soft-tissue sarcomas (STS) and compromise 5–10% of all STS^{1–3}. Approximately 50% of MPNSTs arise sporadically, while about 25–50% of MPNST cases are associated with neurofibromatosis type 1 (NF1)^{4–10}. Patients with NF1 have an increased risk of developing an MPNST with a lifetime risk of 8–13%^{4,11–16}. MPNSTs can originate within a (plexiform) neurofibroma in patients with NF1 and can also be present with partial rhabdomyoblastic differentiation (Triton tumour)¹⁷. In addition, MPNSTs can also develop sporadically or be associated with prior exposure to radiation^{4,18}. Considering the various potential tumour locations, MPNSTs can exhibit a range of diverse clinical presentations. According to the European Society for Medical Oncology guidelines, the cornerstone of treatment for primary MPNST remains surgery with the aim of achieving clear surgical margins and therefore increasing survival¹⁹.

While there are no recommended adjuvant treatments for MPNSTs, perioperative radiotherapy (RT) is often used to improve local control^{1,6,20}. On the other hand, the role of perioperative chemotherapy (CT) has not yet been fully defined.

Conflicting results have been reported in the literature regarding survival benefits of CT. Despite complete resection and the use of RT, studies show that an estimated 40–70% of MPNST patients experience a first local recurrence (LR1)^{7,18,20–22}. With these numbers, MPNSTs harbour among the highest recurrence rates in STS²³. Due to its rarity, risk factors for the development of an LR1 vary in the current literature. In *Table S1*, an overview of previous larger cohort studies assessing predictors for LR has been depicted. The development of an LR1 in patients is associated with a morbid event that decreases functional outcomes²⁴. As many patients have already undergone multimodal treatment (that is, surgery and RT) before experiencing a recurrence, the management of the recurrence is consequently associated with higher morbidity²⁵. In certain cases, achieving local control after an LR1 may be more challenging than with primary tumours, primarily due to the distorted anatomy resulting from previous treatment²⁶. There is significant value in identifying risk factors and investigating the present treatment approaches and outcomes for recurrent cases.

Overall, a diagnosis of MPNST carries a poor prognosis, and in the current literature, the treatment of recurrences remains unclear and varied^{1,4,7,18,27,28}. The primary objective of treatment of recurrence is to prolong disease-free survival; nevertheless, second

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recurrences (LR2) do occur. Therefore, it is crucial to understand the impact of treatment options for an LR1 on the development of an LR2 and also on overall survival (OS) after an LR1.

The aim of this project was to identify risk factors associated with recurrence, and the treatment of recurrences, as well as their impact on OS in MPNST patients across nine sarcoma centres in the Netherlands and the Mayo Clinic, Rochester, Minnesota, USA; and additionally, to characterize the risk factors related to the development of an LR2 and treatment of an LR2.

Materials and methods

Patient population

A retrospective cohort study of the nine Dutch sarcoma centres and the Mayo Clinic, the MONACO study, was undertaken. All patients diagnosed with pathologically proven primary MPNST from 1988 to 2019 who were surgically treated for the primary tumour were included in this study. Follow-up was done according to nationwide guidelines. The diagnosis of all patients conformed to the World Health Organization's classification of soft tissue and bone tumours²⁹. Patients with uncertain pathological reports or diagnoses based on incomplete information during follow-up were excluded. Additionally, patients who presented with LR after previous resection at a different facility were excluded from the study.

Ethical approval

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Erasmus Medical Center (protocol code MEC-2018-1662, 29 October 2018). Informed consent was not required due to the retrospective nature of the study and because the data were pseudo-anonymized. The study was not preregistered in an independent, institutional registry.

Covariates

Covariates extracted from medical records for analysis were patient, tumour, and treatment characteristics and survival data. An LR1 was defined as the first radiological or pathological evidence of a recurrence at the site of the primary tumour bed. An LR2 was defined as the second radiological or pathological evidence of a recurrence at the site of the first recurrence. Age was determined as the patient's age at the time of diagnosis. The ASA classification system was employed to categorize patients' physical status³⁰. Tumour size was assessed as the maximum diameter of the tumour mass through imaging or pathology reports. Tumour grade was categorized as either low or high grade based on the

Fédération Nationale des Centres de Lutte Contre le Cancer grading system, with grade 1 corresponding to a low-grade tumour, while grades 2 or 3 indicate a high-grade tumour. Tumours originating below or within the deep fascia were classified as deep-seated. NF1 status was extracted from pathological reports and was established either when explicitly mentioned in the report or when there was a pathology report of previous plexiform neurofibroma resections or the presence of two or more neurofibromas.

Surgical margin was categorized as R0 (microscopically negative, no tumour cells found in surgical borders), R1 (microscopically positive) or R2 (macroscopically positive). Tumour site was divided into extremity, central (including thorax, abdomen, pelvis, retroperitoneal) and head and neck categories. Triton status was extracted from pathological reports and was confirmed either when explicitly mentioned or when the report indicated MPNST with rhabdomyoblastic differentiation. RT-associated MPNST was defined as having previously received radiation therapy at the same site as the primary tumour bed. Concurrent metastases were defined as having metastases within 3 months after the diagnosis of a LR.

The study's endpoints included LR1, LR2 and OS.

Statistical analysis

All statistical analyses were performed in R (version 4.2.2). Baseline characteristics as well as treatment modalities were compared between patients with and without an LR1 and LR2.

Overall survival was defined as the duration from definitive surgery to either the date of death or the date of the last follow-up. Time-to-LR was defined as the time interval between definitive surgery and date of first LR. Time-to-LR2 was defined as the time interval between LR1 and date of LR2. Estimated median survival was calculated using the Kaplan–Meier method for several covariates of interest.

Multivariable Cox proportional hazards (PH) models were used to estimate the effect of several covariates on the development of an LR1, OS after the LR1 and the development of an LR2. In the multivariate models with LR1 or LR2 as primary outcome, death was considered as a competing risk. The selection of candidate predictors for the various outcomes was based on clinical expertise and existing literature. Univariable and multivariable analyses with 95% confidence intervals were used to estimate the effects of the covariates on the different outcomes. Variables with $P < 0.25$ from the univariable analyses were included for further evaluation when constructing the multivariable model.

Proportional hazards were assessed visually with the Schoenfeld residuals. Missing values were imputed using multiple imputations

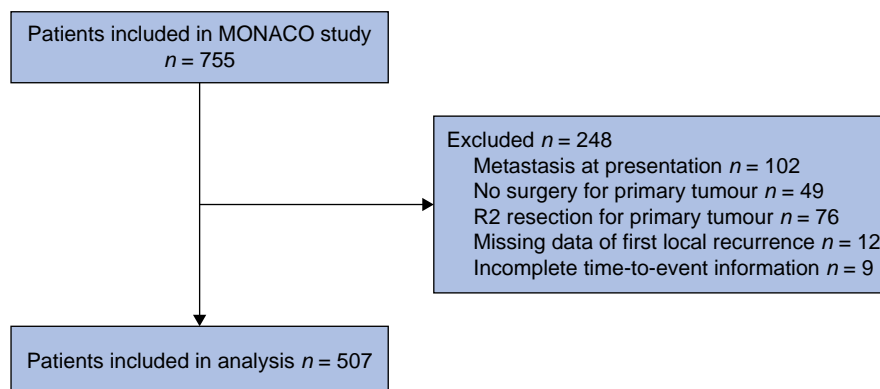


Fig. 1 Study flow chart

Table 1 Patient characteristics

Variable	Overall (n = 507)	No LR1 (n = 365)	LR1 (n = 142)
Age (years), mean(s.d.)		43.21(20.25)	43.44(17.58)
Male gender	270	197 (54.1)	73 (51.4)
NA	1	1	–
ASA			
I	160	120 (59.1)	40 (51.3)
II	107	73 (36.0)	34 (43.6)
III	14	10 (4.9)	4 (5.1)
NA	226	162	64
NF1			
No	322	241 (68.9)	81 (60.0)
Yes	163	109 (31.1)	54 (40.0)
NA	22	15	7
Tumour size			
<5 cm	130	113 (37.5)	17 (17.0)
5–10 cm	164	117 (38.9)	47 (47.0)
>10 cm	107	71 (23.6)	36 (36.0)
NA	106	64	42
Tumour depth			
Superficial	73	58 (25.4)	15 (17.4)
Deep	241	170 (74.6)	71 (82.6)
NA	193	137	56
Tumour grade			
High grade	284	201 (83.4)	83 (92.2)
Low grade	47	40 (16.6)	7 (7.8)
NA	176	124	52
Triton tumour			
No	303	219 (91.2)	84 (95.5)
Yes	25	21 (8.8)	4 (4.5)
NA	179	125	54
RT-associated			
No	444	325 (93.4)	119 (88.1)
Yes	39	23 (6.6)	16 (11.9)
NA	24	17	7
Site of primary tumour			
Head and neck	71	58 (15.9)	15 (10.6)
Extremities	255	184 (50.4)	71 (50.0)
Central	177	121 (33.2)	56 (39.4)
Unknown	21	21 (5.8)	–
Metastasis during LR1			
No	475	365 (100.0)	110 (77.5)
Yes	32	–	32 (22.5)
Surgical margin			
R0	328	257 (70.4)	71 (50.0)
R1	143	87 (23.8)	56 (39.4)
Unknown	36	21 (5.8)	15 (10.6)
Re-resection for primary tumour			
No	365	254 (69.6)	111 (78.2)
Yes	113	81 (22.2)	22 (15.5)
NA	39	30 (8.2)	9 (6.3)

Values are n (%) unless otherwise indicated. LR1, first local recurrence; NA, not available; NF1, neurofibromatosis type 1; RT, radiotherapy.

(MI; $m = 20$) and estimates were pooled using Rubin's rule³¹. $P \leq 0.05$ was considered statistically significant. Results from the Cox PH models were described in HRs with 95% confidence intervals. All statistical tests were two-sided. The packages 'mice' for MI, 'survival', 'rms' and 'survminer' were used for the survival and competing risk analyses.

Results

Patient population

A total of 755 patients were included in the MONACO database. Patients who presented with a metastasis at presentation ($n = 102$), who were not treated surgically for the primary tumour

Table 2 Initial treatment

Variable	Overall (n = 507)	No LR1 (n = 365)	LR1 (n = 142)
Total treatment			
Surgery	215	152 (41.6)	63 (44.4)
Surgery + RT	221	160 (43.8)	61 (43.0)
Surgery + CT	18	14 (3.8)	4 (2.8)
Surgery + RT + CT	53	39 (10.7)	14 (9.9)
Any type of radiotherapy			
No	210	151 (41.4)	59 (41.5)
Yes	280	203 (55.6)	77 (54.2)
Unknown	17	11 (3.0)	6 (4.2)
Pre- or postoperative radiotherapy			
No	215	154 (42.2)	61 (43.0)
nRT	74	61 (16.7)	13 (9.2)
aRT	200	138 (37.8)	62 (43.7)
Unknown	18	12 (3.3)	6 (4.2)
Any type of chemotherapy			
No	419	298 (81.6)	121 (85.2)
Yes	71	53 (14.5)	18 (12.7)
Unknown	17	14 (3.8)	3 (2.1)
Pre- or postoperative chemotherapy			
No	419	298 (81.6)	121 (85.2)
nCT	44	37 (10.1)	7 (4.9)
aCT	25	14 (3.8)	11 (7.7)
Both	2	2 (0.5)	–
Unknown	17	14 (3.8)	3 (2.1)
Primary wound closure			
No	41	35 (14.6)	6 (6.7)
Yes	287	204 (85.4)	83 (93.3)
Non-functional reconstruction			
No	386	277 (82.9)	109 (87.2)
Yes	73	57 (17.1)	16 (12.8)
NA	48	31	17
Functional reconstruction			
No	444	322 (95.3)	122 (97.6)
Yes	19	16 (4.7)	3 (2.4)
NA	44	27	17

Values are n (%). aCT, adjuvant chemotherapy; aRT, adjuvant radiotherapy; CT, chemotherapy; LR1, first local recurrence; nCT, neoadjuvant chemotherapy; nRT, neoadjuvant radiotherapy; NA, not available; RT, radiotherapy.

($n = 49$), who had an R2 resection ($n = 76$), with missing data on LR1 ($n = 12$) and patients with incomplete time-to-event information ($n = 9$) were excluded in this analysis (Fig. 1). Of the 507 patients included in this study, 142 developed an LR1 during the follow-up period. Of the 142 patients with an LR1, patients without treatment for their recurrence ($n = 50$), patients with a metastasis during their LR1 ($n = 13$), patients with an R2 margin ($n = 1$) and patients with missing data on their LR2 ($n = 7$) were excluded from further analysis.

Patient and tumour characteristics are summarized in Table 1. The median follow-up time for all patients was 66.9 months (i.q.r. 108.7). The median follow-up time for survivors was 111.1 months (i.q.r. 123.1). There was a trend for a higher incidence of NF1 in patients with an LR1 (40.0% versus 31.1%, $P = 0.026$). In LR1 patients, there was a slight male predilection (51.4%, $P = 0.850$). Tumours were usually large (>5 cm, 53.5%, $P < 0.005$) and most were located in the extremities (50.3%, $P = 0.140$). However, it is worth noting that the male predilection and tumour location were not statistically significant. Patients who develop an LR1 often have initial high-grade tumours (92.2% versus 83.4%, $P = 0.015$) and microscopically positive margins (R1) (39.4% versus 33.2%, $P < 0.005$). Patients with an LR1 were mostly treated with surgery only for their primary tumour (44.4%) or surgery and adjuvant RT (43.0%) (Table 2).

Table 3 Univariate and multivariate analysis of risk factors for the development of a first local recurrence

Variables	Univariate		Multivariate	
	HR (95% c.i.)	P	HR (95% c.i.)	P
Age (per 10 years)	1.01 (0.928,1.11)	0.767		
NF1				
No	1.00	–	1.00	–
Yes	1.49 (1.04,2.13)	0.030	1.14 (0.779,1.66)	0.507
Tumour grade				
Low grade	1.00	–	1.00	–
High grade	2.38 (1.10,5.16)	0.032	2.63 (1.15,5.99)	0.026
Tumour size				
<5 cm	1.00	–	1.00	–
>5 cm	2.45 (1.47,4.08)	0.001	2.14 (1.21,3.78)	0.011
Triton tumour				
No	1.00	–		
Yes	0.683 (0.271,1.73)	0.424		
Tumour depth				
Superficial	1.00	–	1.00	–
Deep	1.41 (0.841,2.37)	0.198	1.07 (0.607,1.90)	0.807
Site of primary tumour				
Head and neck	1.00	–	1.00	–
Extremities	1.26 (0.717,2.21)	0.425	1.10 (0.593,2.03)	0.768
Central	1.65 (0.934,2.93)	0.087	1.28 (0.682,2.38)	0.447
Margin primary tumour				
R0	1.00	–	1.00	–
R1	2.06 (1.45,2.93)	<0.001	2.19 (1.51,3.16)	<0.001
Radiotherapy primary tumour				
No	1.00	–	1.00	–
Yes	0.809 (0.544,1.14)	0.230	0.616 (0.426,0.892)	0.012
Chemotherapy primary tumour				
No	1.00	–		
Yes	0.897 (0.544,1.48)	0.669		

NF1, neurofibromatosis type 1.

Risk factors for the development of an LR1 in primary MPNST

One hundred and forty-two patients (28.0%) developed an LR1 after they underwent surgery for their primary tumour. The median time to an LR1 was 10.6 months (i.q.r. 16.7). On multivariate analysis, factors independently associated with the development of an LR1 were a high tumour grade (HR 2.63; 95% c.i. 1.15 to 5.99), microscopically positive margins (R1) (HR 2.19; 95% c.i. 1.51 to 3.16) and a tumour size >5 cm (HR 2.14; 95% c.i. 1.21 to 3.78) (Table 3). On the contrary, the use of RT (HR 0.62; 95% c.i. 0.43 to 0.89) reduced the risk for development of an LR1. Patients with extremity MPNSTs were more likely to receive RT ($P=0.004$). However, in multivariate analysis, there was no significant association between the tumour location and the use of RT.

Treatment of LR1

Of the patients developing an LR1, 92 (64.9%) were surgically treated for their recurrence (Table 4). R0 resections were achieved in 37 (37.8%) patients. R1 resections were achieved in 13 (13.3%) patients, and three patients had an R2 margin (3.1%) as final surgical margin. LR1s were mainly treated with surgery only (50.7%). In 29 (20.4%) patients with an LR1, no treatment was performed. Among these 29 patients, the absence of treatment was likely due to the unresectability of tumours caused by tumour location (62.1% centrally located) or tumour characteristics, with most tumours being large (>10 cm, 62.5%) and high grade (94.1%). Of the 59 (41.5%) LR1 patients without primary RT, 15 (25.4%) still underwent RT for their LR1. Of the patients treated with RT, 2.8% received neoadjuvant and 14.8%

adjuvant RT to surgery. In total, 5.6% of patients received only RT as treatment for their recurrence.

Risk factors for overall survival in MPNST patients with an LR1

The median survival from diagnosis of an LR1 until death or last follow-up date was 39.2 months (95% c.i. 22.3 to 60.0; Fig. 2). Of the 142 patients with an LR1, 32 (22.5%) also had a concurrent metastasis. On multivariate analysis, factors independently associated with OS in patients with an LR1 consisted of only a metastasis during the recurrence (HR 1.79; 95% c.i. 1.02 to 3.14). Surgically treated LR1s, on the other hand, were associated with better OS (HR 0.38; 95% c.i. 0.22 to 0.64; Table 5). The median survival in patients surgically treated for their LR was 56 months, compared to 43 months ($P>0.005$) in patients without surgery for their LR.

Risk factors for the development of an LR2 and treatment

A total of 71 patients were treated with curative intent for their LR1. Among these, 38 (53.5%) patients who underwent surgical treatment for their LR1 experienced an LR2 (Table 6). The median time from the surgical treatment of an LR1 to the development of an LR2 was 17.6 months (i.q.r. 16.1). Of the patients who developed an LR2, 32 (84.2%) were solely treated with surgery for their LR1. A total of 12 patients also received RT following their surgery for their LR1. Among these 12 patients, 8 (33.3%) developed an LR2. Various potential risk factors for the development of an LR2 were analysed univariately (Table 7). However, on univariate analysis, no statistically significant risk

factors contributing to the occurrence of an LR2 could be identified.

Of the patients developing an LR2, 23 (60.5%) were surgically treated for their recurrence (Table 4). R0 resections were achieved in eight (21.1%) patients. R1 resections were achieved in three (7.9%) patients, and one patient had an R2 margin (2.6%) as final surgical margin. Second local recurrences were mainly treated with surgery only (47.4%). In nine patients (23.7%) with an LR2, no treatment was performed. Radiotherapy

combined with surgery was administered in three (7.9%) patients and RT alone in four (10.5%). Of the patients treated with RT, all patients received adjuvant RT.

Table 4 Treatment of recurrences

Variable	LR1 (n = 142)	LR2 (n = 38)
Time to local recurrence, mean(s.d.)	23.29(34.98)	17.60(19.42)
Surgery for LR1/LR2		
No	44 (31.0)	14 (36.8)
Yes	92 (64.8)	23 (60.5)
Unknown	6 (4.2)	1 (2.6)
Surgical margin		
R0	37 (37.8)	8 (21.1)
R1	13 (13.3)	3 (7.9)
R2	3 (3.1)	1 (2.6)
Unknown	45 (45.9)	26 (68.4)
Treatment of LR1/LR2		
No treatment	29 (20.4)	9 (23.7)
Surgery	72 (50.7)	18 (47.4)
Surgery + RT	16 (11.3)	3 (7.9)
Surgery + CT	3 (2.1)	1 (2.6)
Surgery + RT + CT	1 (0.7)	1 (2.6)
RT	8 (5.6)	4 (10.5)
CT	7 (4.9)	1 (2.6)
Unknown	6 (4.2)	1 (2.6)
Radiotherapy		
No	65 (45.8)	13 (34.2)
nRT	4 (2.8)	–
aRT	21 (14.8)	8 (21.2)
Unknown	52 (36.6)	17 (44.7)
Chemotherapy		
No	80 (56.3)	21 (55.3)
nCT	3 (2.1)	1 (2.6)
aCT	7 (4.9)	–
Both	1 (0.7)	2 (5.3)
Unknown	51 (35.9)	14 (36.8)

Values are n (%) unless otherwise indicated. aCT, adjuvant chemotherapy; aRT, adjuvant radiotherapy; CT, chemotherapy; LR1, first local recurrence; LR2, second local recurrence; nCT, neoadjuvant chemotherapy; nRT, neoadjuvant radiotherapy; RT, radiotherapy.

Discussion

In patients with MPNSTs, independent risk factors for the development of an LR1 after resection are a high grade, large tumour size (>5 cm) and microscopically positive margins. The administration of radiotherapy for the primary tumour potentially reduces the risk of the development of a LR1. The treatment of LRs varied, and most patients were treated with surgery alone. Synchronous metastasis during a local recurrence had a negative impact on OS, while a surgically treated recurrence is expected to have a better OS.

According to the literature, a high tumour grade, microscopically positive margins and a large tumour size are important prognostic factors for the occurrence of an LR1 in MPNST patients, which is consistent with the findings of this study^{21,32,33}. The importance of surgical quality seems crucial in the development of a recurrence³⁴. While contradictory results have been reported in the literature regarding the use of RT in patients with MPNSTs, the current study demonstrates that RT reduces the risk of developing an LR1^{7,11,32,35–38}. In the current literature, there is still some discussion about the use of radiotherapy in patients with MPNSTs when an R0 resection is expected^{36,39,40}.

Significant factors that affect survival after an LR1 are still unknown for MPNSTs. The occurrence of concomitant metastasis during an LR1 was independently associated with worse OS following the LR1 diagnosis. Further investigation is needed to explore the relationship between histologic subtypes and LRs, as it is reasonable to assume that tumours with different subtypes may demonstrate distinct clinical behaviours and modified survival outcomes⁴¹.

In this cohort, a microscopically positive margin was not identified as an independent risk factor for OS after LR diagnosis. Also, tumour grade did not emerge as a significant prognostic factor influencing survival in MPNST patients after LR1. However, it should be acknowledged that the findings of this study may have been affected by a limited number of cases involving low-grade tumours (7 of 142). In contrast to other

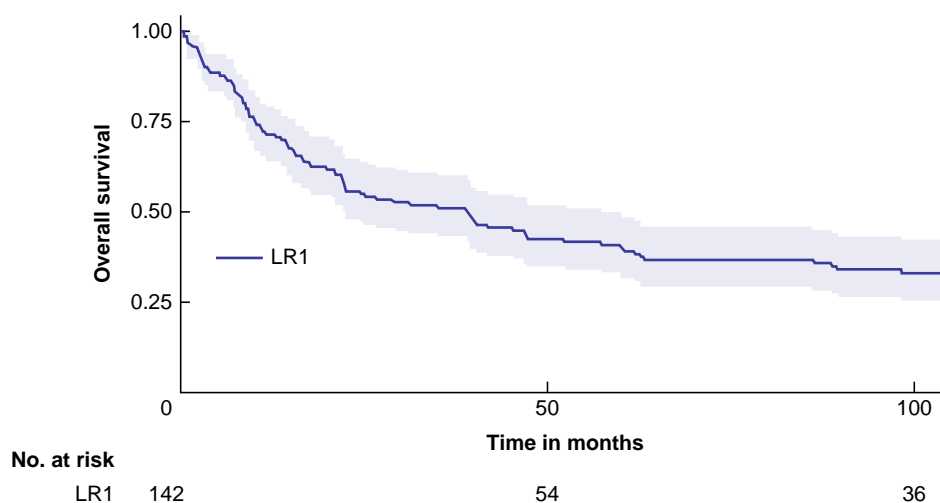


Fig. 2 Survival after first local recurrence (LR1)

Table 5 Univariate and multivariate analysis of risk factors for overall survival in patients with a first local recurrence

Variables	Univariate		Multivariate	
	HR (95% c.i.)	P	HR (95% c.i.)	P
Age (per 10 years)	1.05 (0.938,1.17)	0.415		
NF1				
No	1.00	–		
Yes	0.98 (0.614,1.53)	0.938		
Tumour grade				
Low grade	1.00	–	1.00	–
High grade	2.35 (1.42,3.88)	0.001	2.06 (0.846,5.00)	0.121
Tumour size				
<5 cm	1.00	–	1.00	–
>5 cm	1.66 (0.815,3.38)	0.170	1.24 (0.59,2.61)	0.573
Tumour depth				
Superficial	1.00	–	1.00	–
Deep	2.30 (1.42,3.71)	0.001	1.98 (0.985,3.96)	0.061
Site of primary tumour				
Head and neck	1.00	–		
Extremities	1.13 (0.570,2.25)	0.723		
Central	1.37 (0.681,2.74)	0.382		
Margin primary tumour				
R0	1.00	–	1.00	–
R1	1.35 (0.880,2.07)	0.174	1.08 (0.654,1.78)	0.769
Radiotherapy primary tumour				
No	1.00	–		
Yes	1.27 (0.830,1.94)	0.275		
Surgery LR1				
No	1.00	–	1.00	–
Yes	0.364 (0.238,0.557)	<0.001	0.375 (0.221,0.636)	<0.001
Margin LR1				
R0	1.00	–		
R1	1.39 (0.743,2.62)	0.307		
R2	0.777 (0.425,1.42)	0.418		
Radiotherapy LR1				
No	1.00	–	1.00	–
nRT	0.465 (0.275,0.784)	0.005	1.34 (0.526,3.40)	0.545
aRT	0.583 (0.325,1.05)	0.075	0.752 (0.388,1.46)	0.404
Metastasis during LR1				
No	1.00	–	1.00	–
Yes	2.532 (1.62,3.97)	<0.001	1.79 (1.02,3.14)	0.046

aRT, adjuvant radiotherapy; LR1, first local recurrence; NF1, neurofibromatosis type 1; nRT, neoadjuvant radiotherapy.

retrospective studies, tumour size was not identified as a significant factor^{12,13,32,39}. The variability in the chosen cut-offs observed in other published cohorts, ranging from 5 to 15 cm, could possibly explain this discrepancy. The use of RT did not have a significant influence on survival in the current study. The current literature on the use of RT still presents inconclusive results. Some studies demonstrate improved survival in patients receiving RT, while others do not show improved long-term survival^{6,12,35,39,42–45}.

A recurrence that has been treated surgically is expected to improve the 2-year survival in patients diagnosed with an LR1. This is in line with one other large cohort study ($n=477$) in which complete surgical resection of the tumour is a significant prognostic factor for patients with recurrent STS⁴¹. However, it is challenging to discern whether this association between surgical treatment and the expected better OS in patients with local recurrence is due to patient selection or a genuine improvement in quality of life.

The occurrence of an LR1 after prior resection, with or without RT, significantly impacts patients' well-being. Managing an LR1 becomes challenging due to the complexities of prior therapies and recurrence in a previously irradiated area. The treatment of recurrences depends on several factors, including the patient's physical condition, preferences and the feasibility of curative interventions. The feasibility of a curative treatment depends on

various tumour characteristics, one of which is the presence of concomitant metastasis, which is a poor prognostic factor as shown in this study. One study states that the occurrence of an LR1 is strongly influenced by the feasibility of surgical intervention for the primary tumour⁴⁶. However, these results could be hampered by indication bias, because patients were more likely to be selected for surgery based on tumour and patient characteristics.

For primary MPNSTs, surgical resection is the recommended treatment, aiming to achieve complete removal with clear margins as the primary objective²². Although adjuvant or neoadjuvant therapy is being increasingly considered, its effectiveness in improving survival in primary MPNSTs has not been consistently demonstrated⁴⁷.

Although MPNSTs generally exhibit more aggressive behaviour than most types of STS, risk factors for the development of an LR1 in other types of STS include high grade, microscopically positive margins and tumour size, consistent with findings in the current cohort^{41,48}. This suggests that the same treatment strategy for recurrences may be applicable for recurrent MPNSTs as well. The authors suggest surgery as the primary treatment modality for patients with recurrent MPNSTs, while a personalized approach may be most effective for adjuvant treatment. When considering the use of RT as adjuvant treatment, it is

Table 6 Characteristics of patients with a second local recurrence

Variable	Overall (n = 71)	No LR2 (n = 33)	LR2 (n = 38)	P
Age (years), mean(s.d.)		40.15(15.32)	44.29(15.77)	0.268
Male gender	34	19 (57.6)	15 (39.5)	0.199
ASA				
I	27	14 (70.0)	13 (68.4)	0.576
II	11	5 (25.0)	6 (31.6)	
III	1	1 (5.0)	–	
NA	32	13	19	
NF1				
No	44	22 (68.8)	22 (61.1)	0.686
Yes	24	10 (31.2)	14 (38.9)	
NA	3	1	2	
Tumour size				
<5 cm	11	5 (21.7)	6 (25.0)	0.966
5–10 cm	10	5 (21.7)	5 (20.8)	
>10 cm	26	13 (56.5)	13 (54.2)	
NA	24	10	14	
Tumour depth				
Superficial	10	4 (18.2)	6 (28.6)	0.656
Deep	33	18 (81.8)	15 (71.4)	
NA	28	11	17	
Tumour grade				
High grade	41	22 (95.7)	19 (82.6)	0.343
Low grade	5	1 (4.3)	4 (17.4)	
NA	25	10	15	
Triton tumour				
Yes	44	23 (69.7)	21 (55.3)	0.982
No	1	–	1 (2.6)	
NA	26	10 (30.3)	16 (42.1)	
Site of primary tumour				
Head and neck	6	1 (3.0)	5 (13.2)	0.241
Extremities	44	23 (69.7)	21 (55.3)	
Central	21	9 (27.3)	12 (31.6)	
Surgical margin LR1				
R0	29	18 (54.5)	11 (28.9)	0.089
R1	12	4 (12.1)	8 (21.1)	
Unknown	30	11 (33.3)	19 (50.0)	
Treatment of LR1				
Surgery	55	23 (69.7)	32 (84.2)	0.283
Surgery + RT	12	8 (24.2)	4 (10.5)	
Surgery + CT	3	1 (3.0)	2 (5.3)	
Surgery + RT + CT	1	1 (3.0)	–	
Radiotherapy for LR1				
No	33	14 (42.4)	19 (50.0)	0.296
nRT	2	1 (3.0)	1 (2.6)	
aRT	11	8 (24.2)	3 (7.9)	
Unknown	25	10 (30.3)	15 (39.5)	
Chemotherapy for LR1				
No	40	21 (63.6)	19 (50.0)	0.642
nCT	3	1 (3.0)	2 (5.3)	
Both	1	1 (3.0)	–	
Unknown	24	10 (30.3)	14 (36.8)	

Values are n (%) unless otherwise indicated. CT, chemotherapy; LR2, second local recurrence; NA, not available; NF1, neurofibromatosis type 1; RT, radiotherapy.

important to take into account the disadvantages, such as wound complications in preoperative RT and late radiation toxicities in postoperative RT. These factors should be considered in the decision-making process as they can have a negative impact on functional outcome scores in patients^{25,49}. Furthermore, it is important to consider that around 10% of MPNSTs can arise as a result of previous irradiation, particularly among NF1 patients⁵⁰. This should also be taken into account during the decision-making process.

Despite curative treatment in patients with an LR1, there is still a high risk of developing an LR2. However, there is no literature available on risk factors for the development of an LR2 in

Table 7 Univariate analysis of risk factors for the development of a second local recurrence

Variables	Univariate	
	HR (95% c.i.)	P
Tumour grade		
Low grade	1.00	–
High grade	0.627 (0.262,1.50)	0.308
Tumour size		
<5 cm	1.00	–
>5 cm	1.01 (0.376,2.69)	0.991
Site of primary tumour		
Head and neck	1.00	–
Extremities	0.404 (0.150,1.08)	0.081
Central	0.605 (0.213,1.72)	0.352
Margin LR1		
R0	1.00	–
R1	2.01 (0.832,4.87)	0.140
Radiotherapy LR1		
No	1.00	–
nRT	1.05 (0.376,2.92)	0.930
aRT	0.373 (0.111,1.25)	0.125
Chemotherapy LR1		
No	1.00	–
nCT	1.17 (0.389,3.49)	0.786
Both	1.10 (0.398,3.02)	0.861

CT, chemotherapy; LR1, first local recurrence; RT, radiotherapy.

MPNST patients, and only a small amount of papers have been published on LR2 in other types of STS^{51–53}. Approximately 54% of patients with an LR1 requiring surgical treatment develop an LR2. This is consistent with a study investigating LR2 in patients with STS who underwent surgical treatment for their LR1, which reported a second recurrence rate of 50%⁵¹. Two other studies reported a LR2 rate ranging from 24% to 37% in patients with STS. In the current study, no statistically significant predictors for the development of an LR2 in patients with an LR1 were found. Most patients with an LR2 in this study underwent surgical treatment, consistent with the literature^{52,53}.

This multicentre retrospective study is subject to inevitable limitations arising from its retrospective design, including potential selection bias due to selective loss of follow-up and missing data. However, over 90% of the included patients were followed until death, and a multiple imputation technique was used to reduce this risk of bias. Due to its retrospective nature, patients in this study underwent treatment over a span of nearly 30 years, potentially leading to variations in treatment standards that could impact the results. Additionally, it is important to acknowledge that a central review of pathology was not performed in this study, which could introduce limitations in accurately diagnosing MPNST due to the absence of specific histologic criteria. Also, due to the low number of patients treated for an LR1 and subsequently developing an LR2, it is likely that univariate analyses could not find any significant risk factors.

Nevertheless, due to the size of this large international and nationwide study on recurrent MPNST, new insights have been provided. Furthermore, as all included patients were treated in specialized centres, the review of pathology might be of lesser significance. This design enhances the generalizability of the data and models by minimizing the potential for selection or referral bias. As STS can present very heterogeneously, research on a single histological subtype level is necessary to improve our understanding of tumour behaviour to aid tailoring ideal treatment and outcomes. In contrast to most population-based

studies on (recurrent) MPNST, this study incorporated significant entity-specific details, including NF1 and Triton status, as well as important clinical and treatment information on LRs.

Almost 30% of the MPNST patients develop an LR. Consistent with the literature, this study demonstrated that risk factors associated with a higher risk of a recurrence were a high grade, microscopically positive margin and larger tumour size. The use of RT was associated with a reduced risk of development of a recurrence. The treatment of LRs varied, and most patients were treated with surgery only. Synchronous metastasis during an LR1 had a negative impact on survival, while surgically treated cases showed longer OS. Despite curative treatment of an LR1, 54% will develop an LR2.

Collaborators

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The authors declare no conflict of interest.

Supplementary material

[Supplementary material](#) is available at *BJS Open* online.

Data availability

The data that support the findings of this study are available on request from the corresponding author, upon reasonable request. The data are not publicly available due to information that could compromise the privacy of research participants.

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