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## Original Research

# A nationwide cohort study on treatment and survival in patients with malignant peripheral nerve sheath tumours



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## KEYWORDS

MPNST;  
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 Retroperitoneal space;  
 Combined modality

**Abstract Background:** Despite curative intents of treatment in localized malignant peripheral nerve sheath tumours (MPNSTs), 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. Paediatric cases (age  $\leq 18$  years) and synchronous metastases were excluded from analyses. Separate Cox proportional hazard models were made for retroperitoneal and non-retroperitoneal MPNSTs.

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treatment;  
Survival analysis

**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 MPNSTs, older age (60+), presence of NF1, size >5 cm, and deep-seated tumours were independently associated with worse survival. In retroperitoneal MPNSTs, male sex and age of 60+ years were independently associated with worse survival. Survival of R1 and that of R0 resections were similar for any location, whereas R2 resections were associated with worse outcomes. Radiotherapy and chemotherapy administrations were not associated with survival.

**Conclusion:** In localized MPNSTs, risk stratification for survival can be done using several patient- and tumour-specific characteristics. Resectability is the most important predictor for survival in MPNSTs. 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.

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## 1. Introduction

Malignant peripheral nerve sheath tumours (MPNSTs) are rare and aggressive soft tissue sarcomas (STS), accounting for 2% of all STS [1]. Although 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 tumours, which reportedly have been associated with poorer survival [8,9].

To date, surgery is the only proven therapy increasing survival in localized MPNSTs [3,10]. As in other STS, radiotherapy is commonly administered 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 MPNSTs, 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.

## 2. Methods

### 2.1. Patient population

Data of patients treated between 1989 and 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 an automated pathological archive (PALGA) and the National Registry of Hospital Discharge Diagnosis (LMR). Patient and tumour 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.

### 2.2. Covariates

Covariates extracted for analysis were: year of diagnosis (1989–2005/2006–2017), sex, age, established diagnosis of NF1, tumour site, tumour stage (presence of metastasis/no metastasis), tumour size ( $\leq 5$ / $> 5$  cm), tumour depth (superficial/deep of the fascia), tumour morphology (Triton tumour/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. Tumour sites were categorized as follows: head and neck, extremities, trunk (including thorax, abdomen, and pelvis), retroperitoneal, and not otherwise specified (NOS). Resection margins were regarded

as tumour-free (R0), microscopically positive (R1, <1 mm margin), and macroscopically positive (R2). Tumour 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. Paediatric and synchronous metastatic cases were excluded from all statistical analyses as they are treated differently.

### 2.3. 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 MPNSTs 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).

## 3. Results

### 3.1. 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 to 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:  $39.8 \pm 18.0$ ) compared to non-NF1 patients (mean:  $52.4 \pm 21.3$ , Fig. 1). Most tumours were large (>5 cm, 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 tumours made up 6.1% of all MPNSTs. In 11.5% of all cases, patients presented with synchronous metastases.

Table 1  
Clinicopathologic characteristics of all malignant peripheral nerve sheath tumours (MPNSTs).

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

MPNST: malignant peripheral nerve sheath tumour, NA: not available, NF1: neurofibromatosis type 1, NOS: not otherwise specified, SD: standard deviation.

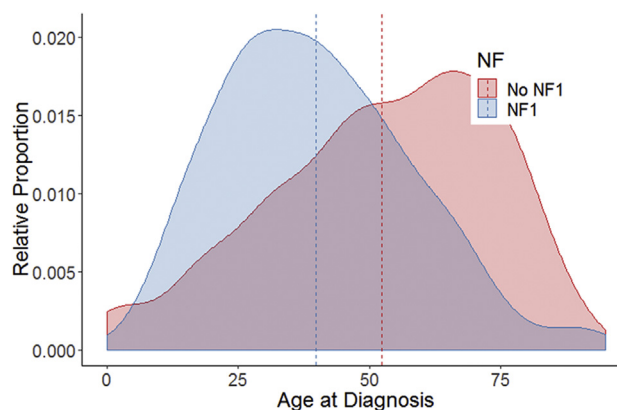


Fig. 1. Relative age distribution of malignant peripheral nerve sheath tumours (MPNSTs) between NF1 and non-NF1 patients.

### 3.2. Treatment of localized adult MPNSTs

Surgical resection was performed in 88% of localized MPNSTs (Table 2). Surgical margin involvement did not differ significantly between retroperitoneal and non-retroperitoneal tumours ( $p > 0.05$ ). Overall, a microscopically radical resection (R0) was achieved in 66.3%

Table 2  
Treatment of localized MPNSTs in adults.

	Variable	Overall	nRP MPNST	RP MPNST	p-value
<i>Surgically treated</i>	<b>Surgical margin</b>				
	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%)	
	<b>Radiotherapy sequence</b>				<b>0.044</b>
	No radiotherapy	313 (55.8%)	295 (55.0%)	19 (70.4%)	
Preoperative radiotherapy	28 (5.1%)	25 (4.7%)	3 (11.1%)		
	Postoperative radiotherapy	213 (39.2%)	208 (40.2%)	5 (18.5%)	
	<b>Chemotherapy</b>				<b>0.012</b>
	No	517 (93.3%)	495 (93.9%)	22 (81.5%)	
	Yes	37 (6.7%)	32 (6.1%)	5 (18.5%)	
<i>Biopsy only</i>	<b>Radiotherapy</b>				0.26
	No	50 (66.7%)	43 (64.2%)	7 (87.5%)	
	Yes	25 (33.3%)	24 (35.8%)	1 (12.5%)	
	<b>Chemotherapy</b>				0.39
	No	57 (76.0%)	52 (77.6%)	5 (62.5%)	
	Yes	18 (24.0%)	15 (22.4%)	3 (37.5%)	

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

of the patients, whereas 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 became 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 MPNSTs (18.5% versus 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 MPNSTs ( $p > 0.05$  for both).

### 3.3. Survival in localized non-retroperitoneal MPNSTs

The 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 ( $p < 0.05$ , Fig. 2). The median survival years of R0, R1, and R2 (and unresected patients) resections were, respectively, 14.7 years, 5.8 years, and less than a year ( $p < 0.05$ ). Although median survival of NF1 patients was shorter compared to non-NF1 patients (3.2 versus 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 ( $p < 0.05$ ). The 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 versus 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 ( $p < 0.05$ , Fig. 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 tumour depth was significantly associated with survival ( $p < 0.05$ ). In younger adults (<60 years), larger tumour size (>5 cm) was then the strongest predictor of poorer survival ( $p < 0.05$ ). However, when tumour sizes were smaller than 5 cm, only the patient's gender remained a critical factor significantly associated with survival; female patients had a worse prognosis ( $p < 0.05$ ).

### 3.4. Predictors for survival in localized non-retroperitoneal MPNSTs

On multivariate analysis, age of 60+ years, lesions in NF1 patients, large (>5 cm) and deep-seated tumours were significantly associated with a poor survival in localized non-retroperitoneal MPNSTs (all  $p < 0.05$ , Figs. 4 and 5). Tumour site, Triton tumours, 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

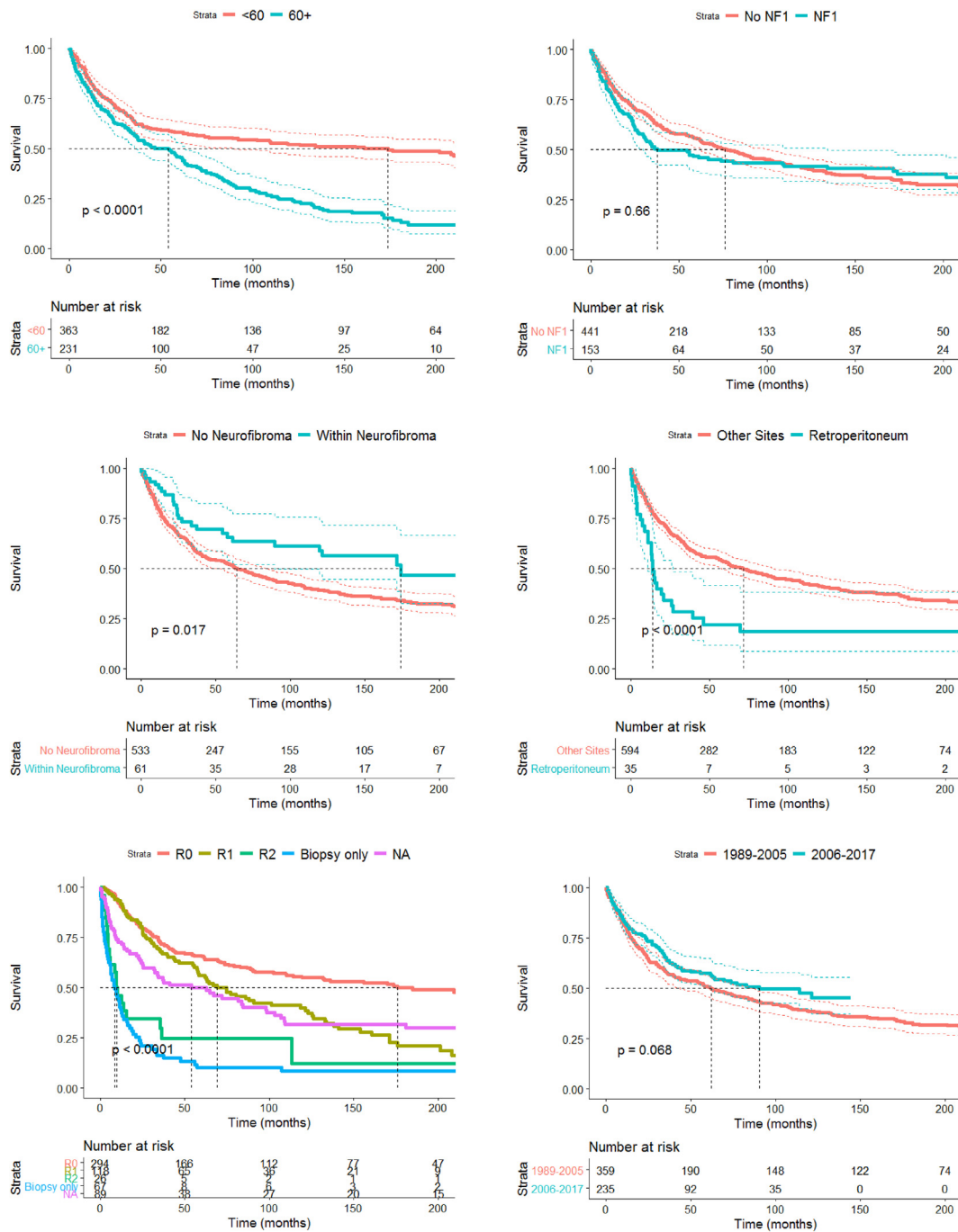


Fig. 2. Kaplan–Meier curves of overall survival in localized adult non-retroperitoneal MPNSTs. A) Older versus younger adults. B) NF1 versus non-NF1 patients. C) MPNSTs arising within a neurofibroma versus not arising within a neurofibroma. D) Retroperitoneal versus non-retroperitoneal sites. E) Resection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

with increased survival ( $p \approx 0.08$ ). Surgical margins were the only treatment related factor significantly associated with survival. Both R2 resections and biopsies 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 uses of radiotherapy and chemotherapy were not independently associated with survival (both  $p > 0.05$ ).

### 3.5. Survival and predictors for survival in localized retroperitoneal MPNSTs

Retroperitoneal MPNSTs had a significantly worse outcome: median survival of 1.1 years compared to 6.0 years in patients with MPNSTs in other tumour sites ( $p < 0.05$ , Fig. 2D). The multivariate model for retroperitoneal MPNSTs specifically showed that older age and R2 and no resections were also associated with

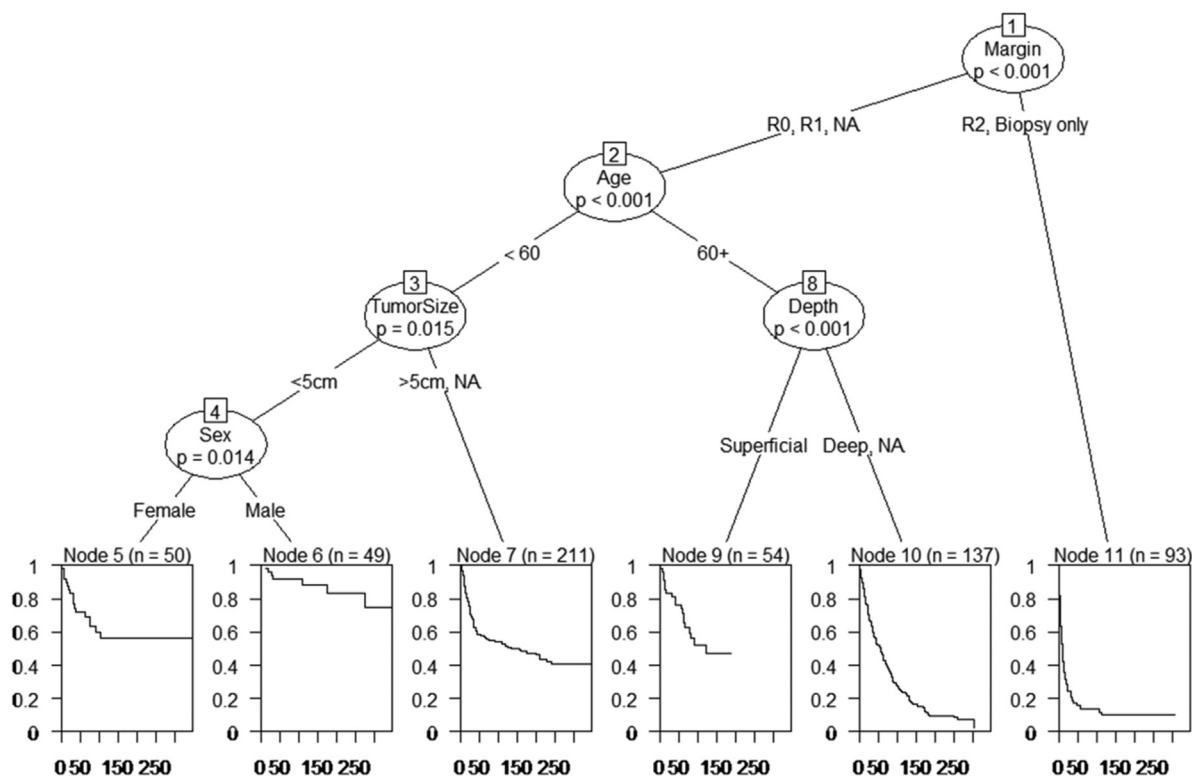


Fig. 3. Conditional inference tree of overall survival in localized non-retroperitoneal adult MPNSTs.

poorer survival in this subset of MPNSTs (both  $p < 0.05$ , Fig. 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 administrations were not significantly associated with survival ( $p > 0.05$ ).

#### 4. Discussion

Using a large nationwide unselected group of MPNSTs, several patient-, tumour-, and treatment-related prognostic factors were identified. In localized non-retroperitoneal MPNSTs, older age, presence of NF1, and large, deep-seated tumours are patient- and tumour-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.

##### 4.1. Tumor and patient-specific predictors of survival in MPNSTs

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. Although 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]. Tumour biology between NF1 and sporadic MPNSTs 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 paediatric cases had the best prognosis, while older patients did significantly worse [24]. Larger tumour size has repeatedly been reported to affect survival [2–5,21,22,25], whereas tumour depth has only been shown an independent predictor of survival in one study [10]. Tumour 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 tumours, despite the largest

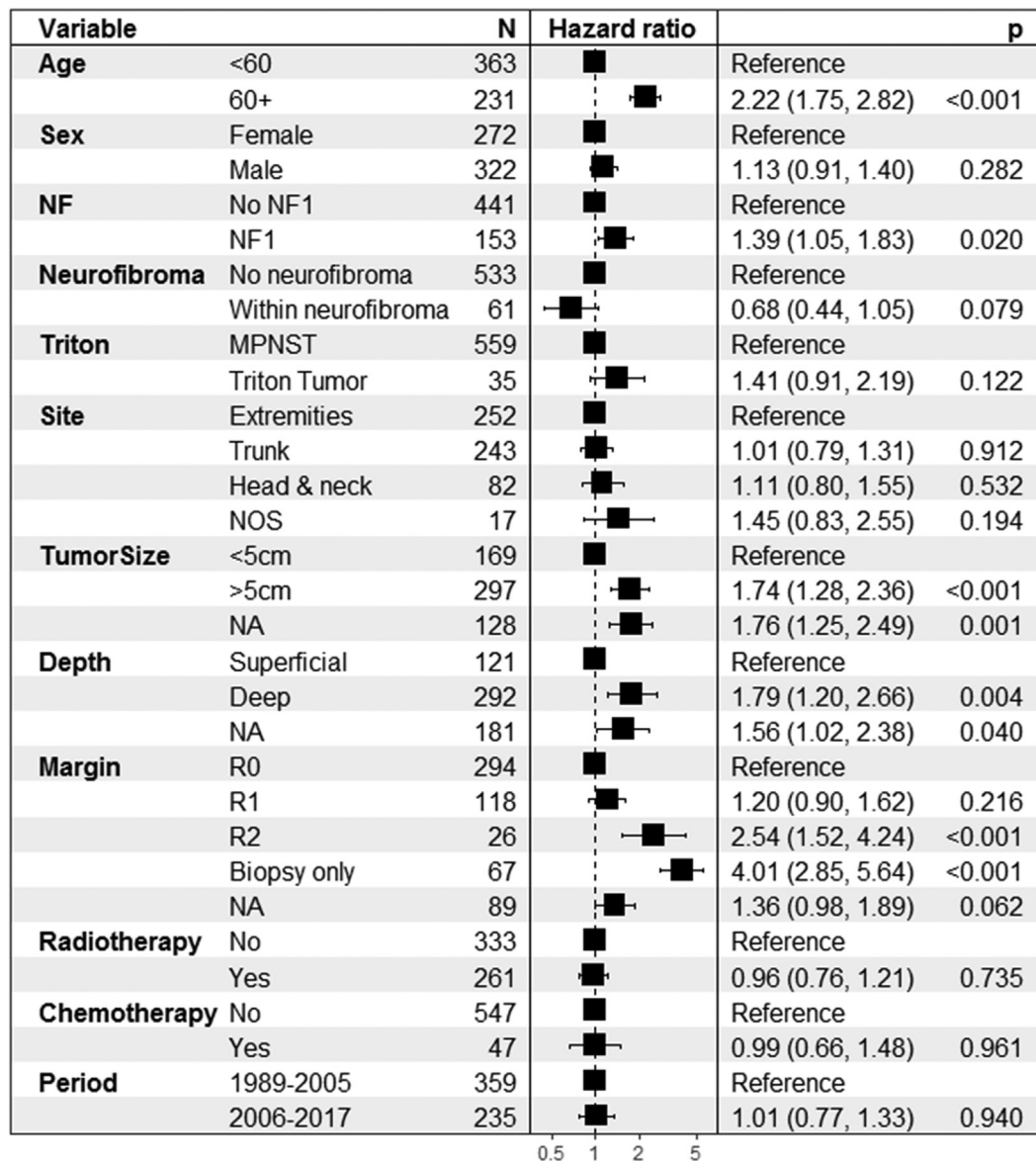


Fig. 4. Cox proportional hazard model for overall survival in localized non-retroperitoneal adult MPNSTs, C-statistic: 0.715, N = number of patients, NA = not available.

proportion being NF1 patients, may possibly be explained by tumour grade [27]. However, an exact explanation could not be found in this study and is therefore of interest in future studies.

#### 4.2. Treatment of localized MPNSTs

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. Although 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 decreased morbidity. This is of special interest for tumours 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 tumours 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



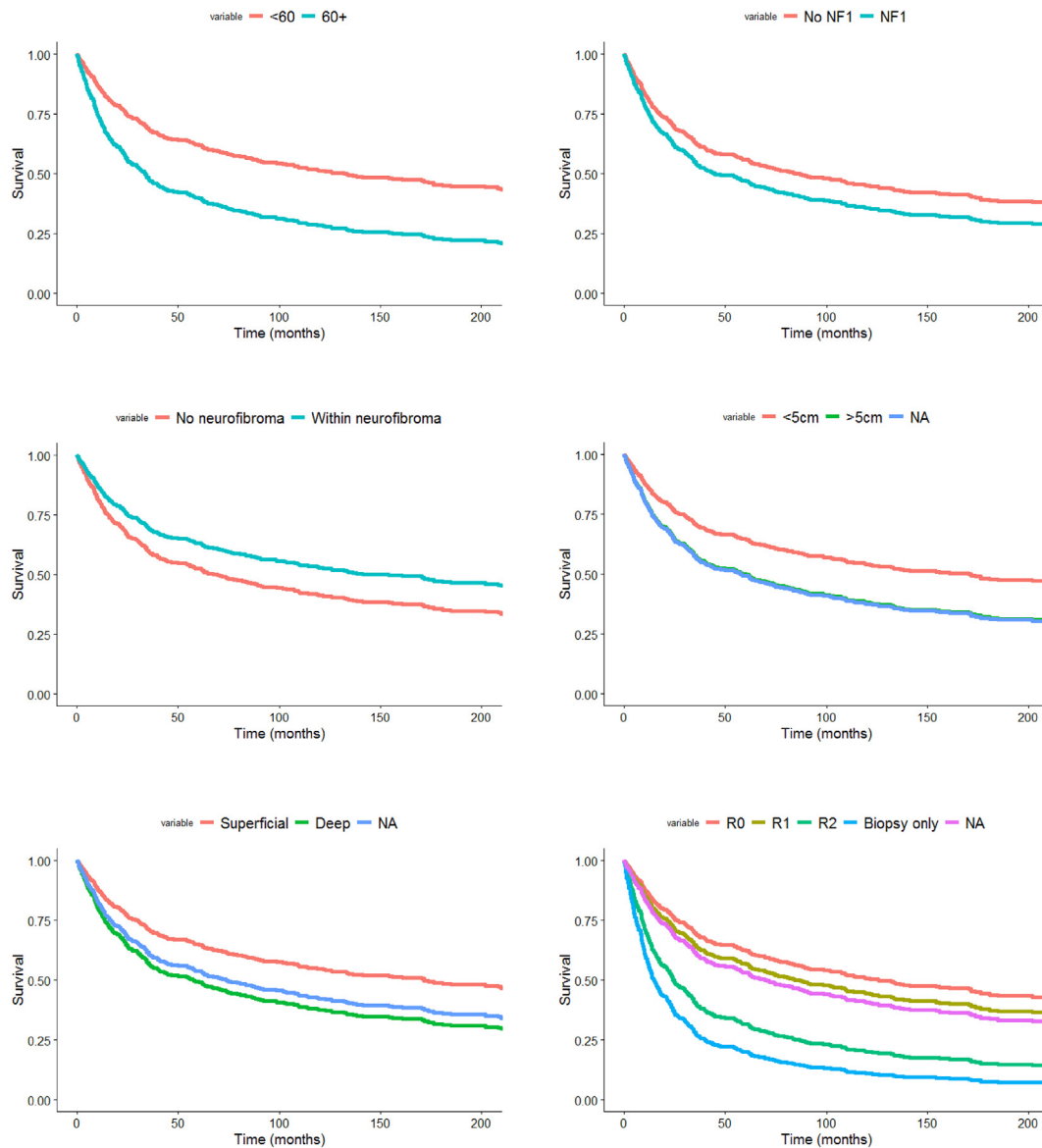


Fig. 5. Adjusted survival curves of prognostic factors in localized non-retroperitoneal MPNSTs. A) Older versus younger adults. B) NF1 versus non-NF1 patients. C) MPNSTs arising within a neurofibroma versus not arising within a neurofibroma. D) Larger (>5 cm) versus smaller ( $\leq 5$  cm) tumours. E)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

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].

#### 4.3. Strengths and limitations

Limitations are inevitable as in part only registry data were 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, tumour grade could not be analysed because of heterogeneity in reporting. However, the definition of low-grade tumours 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 MPNSTs. 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, tumours within neurofibromas, R0/R1/R2 resection

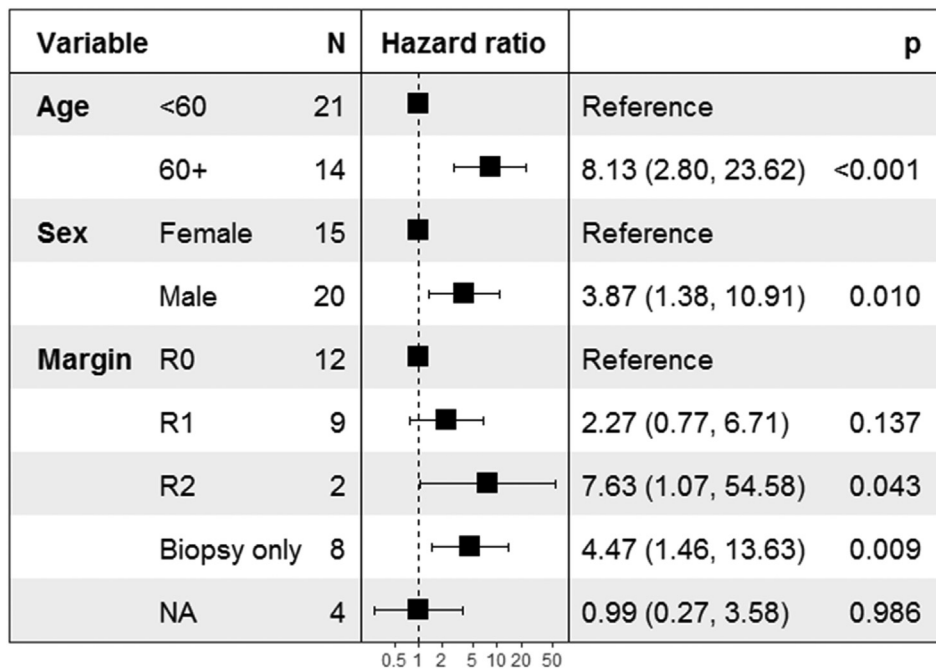


Fig. 6. Cox proportional hazard model for overall survival in localized retroperitoneal adult MPNSTs, C-statistic: 0.811, N = number of patients, NA = not available.

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 behaviour. Especially, there may be important clinical varieties within a single entity such as in

MPNSTs, like NF1 patients, malignant transformation within neurofibromas, or tumours 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 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 specialities involved in their multimodal treatment.

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

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

N: number of patients, NF1: neurofibromatosis type 1, OS: overall survival, Rx-I: radiation-induced.

<sup>a</sup> Significantly associated (+), not significantly associated (-), not evaluated (NA).

<sup>b</sup> Localized disease only.

<sup>c</sup> Analyses on disease-specific survival.

<sup>d</sup> Multivariate analyses on completely resected cases only.

<sup>e</sup> Includes paediatric cases only.

### 5. Conclusion

In localized MPNSTs, risk stratification for survival can be done using several patient- and tumour-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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### Conflict of interest statement

No author has any form of disclosure.

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