Neurofibromatosis-associated malignant peripheral nerve sheath tumors in children have a worse prognosis: A nationwide cohort study

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Abstract

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

Methods: Data were obtained from the Netherlands Cancer Registry (NCR) and the Dutch Pathology Database (PALGA) from 1989 to 2017. All primary MPNSTs were collected. Demographic differences were analyzed between adult and pediatric (age ≤18 years) MPNST. In children, demographic and treatment differences between neurofibromatosis type 1 (NF1) and non-NF1 were analyzed. A Cox proportional hazard model was constructed for localized pediatric MPNSTs.

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

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

KEYWORDS
epidemiology, MPNST, NRSTS, prognostic factors, survival

Abbreviations: HR, hazard ratio; IRS, Intergroup Rhabdomyosarcoma Study; MPNST, malignant peripheral nerve sheath tumor; NCR, National Cancer Registry; NF1, neurofibromatosis type 1; NRSTS, non-rhabdomyoblastic soft-tissue sarcoma; OS, overall survival; PALGA, Dutch Pathology Database; SE, standard error; STS, soft-tissue sarcoma.

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

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

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

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

2 | METHODS

2.1 Data source

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

2.2 Covariates

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

2.3 Statistical analysis

All pathological reports of a patient registered in the NCR were screened for the final diagnosis of MPNST; all cases with doubtful diagnoses were excluded. Demographic differences were compared between adult and pediatric MPNSTs and in pediatric patients between NF1 and non-NF1 MPNST. Treatment modalities were compared between NF1 and non-NF1 pediatric patients excluding those who presented with metastatic disease. Five-year survival rates were estimated using the Kaplan-Meier method to compare adult and pediatric MPNSTs, metstatic and nonmetastic pediatric MPNST, and in localized pediatric patients for NF1 status, tumor depth, tumor size, resection margin, and time period of diagnosis. Kaplan-Meier curves were made for all comparisons of localized pediatric patients only, except for the comparison of metastatic versus localized disease at presentation. Differences were assessed using the log-rank test. A multivariate Cox proportional hazard model was constructed by backward selection for localized pediatric MPNSTs only. P values of < 0.05 were considered statistically significant. In order to create a
### Table 1: Demographic differences of pediatric and adult MPNST

| Variable | Overall | Pediatric | Adult   | P value |
|----------|---------|-----------|---------|---------|
| N        | 784     | 70        | 714     |         |
| Male gender | 421 (53.7%) | 38 (54.3%) | 383 (53.6%) | 1.00   |
| NF1      | 210 (26.8%) | 26 (37.1%) | 184 (25.8%) | 0.06   |
| **Site** |         |           |         |         |
| Extremities | 303 (38.6%) | 24 (34.3%) | 279 (39.1%) | 0.78   |
| Trunk    | 312 (39.8%) | 29 (41.4%) | 282 (39.5%) |         |
| Retroperitoneum | 43 (5.5%) | 3 (4.3%) | 40 (5.6%) |         |
| Head and neck | 100 (12.8%) | 11 (15.7%) | 89 (12.5%) |         |
| NOS      | 26 (3.3%) | 3 (4.3%) | 24 (3.4%) |         |
| **Tumor size** |         |           |         |         |
| ≤5 cm   | 190 (32.1%) | 10 (28.6%) | 180 (32.3%) | 0.65   |
| >5 cm   | 402 (67.9%) | 25 (71.4%) | 377 (67.7%) |         |
| NA      | 192     | 35        | 157     |         |
| **Tumor depth** |         |           |         |         |
| Superficial | 139 (24.8%) | 6 (14.0%) | 133 (25.7%) | 0.10   |
| Deep    | 421 (75.2%) | 37 (86.0%) | 384 (74.3%) |         |
| NA      | 224     | 27        | 197     |         |
| Triton tumor | 48 (6.1%) | 3 (4.3%) | 45 (6.3%) | 0.68   |
| Metastatic disease at presentation | 90 (11.5%) | 6 (8.6%) | 84 (11.8%) | 0.56   |
| Time Period |         |           |         |         |
| 1989-2005 | 454 (57.9%) | 43 (61.4%) | 411 (57.6%) | 0.62   |
| 2006-2017 | 330 (42.1%) | 27 (38.6%) | 303 (42.4%) |         |

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

parsimonious model, a ratio of five events per degree of freedom was chosen. Additionally, adjusted survival curves were constructed for individual prognostic factors based on the final model.23 Statistical analyses and data visualization were conducted using R version 3.6.0 (R Core Team, 2019).

### 3 | RESULTS

#### 3.1 | Patient population

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

#### 3.2 | Treatment of localized pediatric MPNST

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

#### 3.3 | Survival and factors associated with survival in pediatric MPNST

In the complete nationwide cohort, the estimated five-year survival rate of any pediatric MPNST was 62.0% (SE: 5.9%) compared with...
TABLE 2  Demographic differences between NF1 and non-NF1 patients

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

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

46.2% (SE: 1.9%) in adult MPNST (P < 0.05). In localized disease only, five-year survival rates were 66.3% (SE: 6.0%) and 51.6% (SE: 2.1%), respectively (P < 0.05). Pediatric patients initially presenting with metastatic disease had a one-year survival rate of 33.3% (SE: 19.2%) compared with 82.8% (SE: 4.7%, P < 0.05) presenting with localized disease (Figure 1). In localized pediatric patients only, NF1 patients had lower five-year survival rates (52.4%, SE: 10.1%) compared with non-NF1 children (75.8%, SE: 7.1%, P < 0.05). Also, estimated five-year survival rates were higher in children diagnosed after 2005 (87.6% SE: 6.7% vs 53.9% SE: 8.0%, P < 0.05). On multivariate analysis of localized pediatric MPNST, NF1 status was the only patient- and tumor-specific variable independently associated with survival (HR: 2.98; 95% CI, 1.17-7.60, P < 0.05; Figures 2 and 3). Additionally, patients presenting after 2005 were significantly associated with increased survival (HR: 0.20; 95% CI, 0.06-0.69, P < 0.05), without demographic or overall treatment differences between these time periods. Surgical margins, the use of chemotherapy, radiotherapy, and any sequence of multimodal treatment were not significantly associated with survival in localized pediatric MPNST (all P > 0.05).

4.1 Survival in pediatric MPNST

Historically, pediatric MPNSTs have been associated with poor prognosis, with five-year survival rates ranging from 34.6% to 65%.6,24,25 Earlier series reported even worse survival rates.26–28 However, a trend toward increased survival in pediatric MPNST has been suggested in a study using data from the Surveillance, Epidemiology, and End Results Program (SEER) database.29 Anthracycline-based regimens with or without additional ifosfamide have shown superior results in a large cohort of pediatric patients in a study published in 2005.6 The European Pediatric Soft-Tissue Sarcoma Group (EpSSG) consequently published results of their 2005-2016 cohort in which doxorubicin and ifosfamide was used whenever chemotherapy was administered.15 The study by the EpSSG showed higher five-year survival rates compared with the earlier publication of the Italian and German Soft-Tissue Sarcoma Cooperative Group. This may explain at least in part the increasing survival rates observed in this study after 2005, as doxorubicin and ifosfamide use may have risen compared with adult MPNST (P < 0.05). In localized disease only, five-year survival rates were 66.3% (SE: 6.0%) and 51.6% (SE: 2.1%), respectively (P < 0.05). Pediatric patients initially presenting with metastatic disease had a one-year survival rate of 33.3% (SE: 19.2%) compared with 82.8% (SE: 4.7%, P < 0.05) presenting with localized disease (Figure 1). In localized pediatric patients only, NF1 patients had lower five-year survival rates (52.4%, SE: 10.1%) compared with non-NF1 children (75.8%, SE: 7.1%, P < 0.05). Also, estimated five-year survival rates were higher in children diagnosed after 2005 (87.6% SE: 6.7% vs 53.9% SE: 8.0%, P < 0.05). On multivariate analysis of localized pediatric MPNST, NF1 status was the only patient- and tumor-specific variable independently associated with survival (HR: 2.98; 95% CI, 1.17-7.60, P < 0.05; Figures 2 and 3). Additionally, patients presenting after 2005 were significantly associated with increased survival (HR: 0.20; 95% CI, 0.06-0.69, P < 0.05), without demographic or overall treatment differences between these time periods. Surgical margins, the use of chemotherapy, radiotherapy, and any sequence of multimodal treatment were not significantly associated with survival in localized pediatric MPNST (all P > 0.05).

4 | DISCUSSION

In this large, nationwide, unselected group of MPNST, pediatric patients presented similarly compared with adult MPNST. In children, NF1 patients more commonly had large tumors, but were treated similarly compared with non-NF1 patients. In localized pediatric MPNST, only NF1 status was independently associated with poor survival. No treatment-related factors were independently associated with survival. Also, patients presenting after 2005 were independently associated with increased survival.
TABLE 3  Treatment of localized pediatric MPNST

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

MPNST, malignant peripheral nerve sheath tumor; NF1, neurofibromatosis type 1.

with other regimens since the first publication in 2005. Furthermore, in other sarcoma trials, such as the EpSSG rhabdomyosarcoma 2005 trial also showed increase in survival in both study arms, indicating that survival of sarcomas in children generally may be improving over the years. This may in turn be due to centralization of their healthcare. Although survival rates in pediatric MPNST from previous studies show comparable results as in adult MPNST,2,30,31 another study using SEER data showed that children had a better prognosis when controlling for known confounders.4 Few other studies have found factors associated with survival in pediatric MPNST.6,15,27 NF1 status has previously been reported as well to be independently associated with worse survival in children.6,15,27 It is not yet completely clear what NF1-related factors cause this difference. Demographically, all but initial tumor size differed in this study between NF1 and non-NF1 patients and no differences in treatment modalities were observed, especially in final surgical margins. And although not independently associated with survival in this study, larger tumor size and nonextremity tumor site have also been associated with worse survival in pediatric MPNST.6,27 However, the model did not improve by adding any of the two factors, and the association of NF1 status with survival was independent of both factors. In part, it may be due to lower chemosensitivity, which has been suggested in NF1 patients.6,16,32,33 However, in the EpSSG study, similar response rates were seen between NF1 and non-NF1 children.15 The impact of NF1 status on survival in adults has been controversial as well. Although a meta-analysis suggests there is no influence seen in studies published after 2000,20 several large recent studies do find NF1 status to be independently associated with worse survival.21,34,35 Some immunohistochemical markers have been proposed predictors of poor survival as well as they may reflect more aggressive biology of the tumor, such as loss of p53,2,36 negative S100 staining,37 or loss of H3K27 trimethylation.38

4.2 Treatment of pediatric MPNST

Although this study did not find a significant difference in survival between R2 resections and biopsies only compared with complete resections, results from previous studies in adults have shown a strong benefit on survival if performed.11,30,31,34,39,40 In pediatric MPNST, Intergroup Rhabdomyosarcoma Study (IRS) groups III/IV (translating to R2 and metastatic cases, respectively) have been associated with worse survival as well,6,26 yet this effect may partially be due to the inclusion of metastatic patients in these analyses. Also, previous studies in pediatric MPNSTs showed higher rates of IRS III/R2 patients compared with this study, possibly indicating a selection bias in larger pediatric sarcoma centers.6,24–28,41 It may also imply that the subgroup was underpowered as only seven patients had R2 resections or biopsies only. As MPNSTs are aggressive in general and surgery is the only treatment proven effective, R0/R1 resections should still be strived after.42 Although R1 resections have been associated with increased risks for local recurrence, they have not been associated with worse survival in both adult and pediatric MPNST.3,6,17,21 This may provide an opportunity for the adoption of planned positive margins in MPNSTs.
FIGURE 1  Kaplan-Meier curves for overall survival in localized pediatric MPNST. (A) Tumor stage at presentation (metastatic vs localized); (B) NF1 status; (C) tumor size ($\leq 5$ cm vs $> 5$ cm); (D) tumor depth (superficial vs deep of the fascia); (E) resection margin (R0 vs R1 vs R2/biopsy); and (F) time period (1989-2005 vs 2006-2017)
FIGURE 2  Cox proportional hazard model in localized pediatric MPNST

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

as well, thus decreasing morbidity in some patients.43,44 The role of both chemotherapy and radiotherapy is controversial in MPNST, even more so in pediatric patients. Radiotherapy is generally administered for local control, either preoperatively or after R1 resection.3,17,18,42 Guidelines usually follow adult doses, which is generally equal to 50 Gy preoperatively and 60–66 Gy postoperatively.17,42,45,46 However, in children, keeping long-term radiation complications to a minimum is important and has resulted in lower radiation dose of 50.4–54 Gy in the EpSSG guidelines. Although R1 resections may decrease postoperative morbidity by avoiding resection of adjacent functional structures, close margin surgery will necessitate the use of radiotherapy, which in turn may also impair function. Careful preoperative planning including a reconstructive surgeon and shared decision-making are therefore crucial. The use of chemotherapy in unresectable cases may benefit patients as some may become resectable and thus downstage the tumor,6,32 and is therefore incorporated in both the EpSSG and the Children’s Oncology Group (COG) guidelines. The benefit of chemotherapy in an adjuvant setting is, however, less clear. Some studies have suggested its use in large, high-grade STS including MPNSTs.14,42,47 Ideal cytotoxic regimens include a combination of doxorubicin and ifosfamide as they have shown to give the best effect in both adult and pediatric MPNST.6,32,33,48 Yet response rates in MPNSTs are still very low, even more so in NF1 patients.6,16,32,33 Given the low chemosensitivity of MPNSTs, novel therapies are desperately warranted. Currently, multiple new therapies are under investigation, including targeted therapies, immunotherapy, and oncolytic viruses.49 However, to date no targeted therapy has been proven effective in MPNST patients.50–55

4.3 Strengths and limitations

This study is based on registry and pathological data only and subsequently resulting in some limitations. NF1 status is not routinely registered in the NCR, and all diagnoses were made based on pathological reports. This has possibly resulted in an underestimation of the total amount of NF1 patients. However, the incidence rate in this study is in concordance to other series.6,15,24,25 Tumor size was also commonly missing, which may have underestimated the effect of tumor size on survival in this study. Tumor grade could also not be analyzed because of its heterogeneity in reporting. Nonetheless, low-grade tumors have only recently been defined following a consensus meeting.56 Other clinical information such as the efficacy of chemotherapy or radiotherapy on disease-free survival was not available for this study. Nevertheless, using a nationwide cohort of patients, a model for

FIGURE 3 Adjusted survival curves for prognostic factors in localized pediatric MPNST. (A) NF1 status and (B) time period (1989-2005 vs 2006-2017)
localized pediatric MPNST could be constructed. The advantage of such data is that models may be more generalizable as there is no form of selection or referral bias. The SEER database also allows for analyses of large patient cohorts, but lacks data on NF1 status, tumor depth, R0/R1/R2 resection margins, and the use of chemotherapy.\textsuperscript{4,29} It becomes increasingly clear that STS can present very heterogeneously, and single histological subtypes may present differently, having additional risk factors that warrant attention. As MPNSTs carry a high risk for postoperative morbidity and oncological treatment failure, more knowledge needs to be gathered from their adult counterparts as well as other high-risk pediatric NRSTS. As such, ideal patient-tailored treatments may be elucidated balancing both oncological and functional outcomes.

5 | CONCLUSION

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

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available through the Netherlands Cancer Registry (NCR/IKNL) and the Dutch Pathology Database (PALGA).

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CONFLICTS OF INTEREST

No author has any form of disclosure.

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