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Malignant Peripheral Nerve Sheath Tumors (MPNST): A SEER Analysis of Incidence Across the Age Spectrum and Therapeutic Interventions in the Pediatric Population

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Background. Malignant peripheral nerve sheath tumors (MPNST) are very rare in the general population and challenging to treat. A paucity of data exists regarding the incidence of MPNST across all age groups and treatment outcomes in the pediatric population. We aimed to characterize both using the Survival, Epidemiology, and End Results (SEER) database. ***Procedure.*** The SEER-18 database with information on the United States population from 1973 to 2009 was queried for cases of MPNST. For incidence data, 1,182 cases were found among the general population. Of those, 165 cases were in individuals aged 0–19. After exclusions, 139 cases from the SEER-18 database met study criteria for outcomes analysis. For each patient, variables including gender, age, race, stage (localized, regional, or distant), surgical treatment, and radiotherapy were obtained. ***Results.*** The overall incidence of MPNST was 1.46 per million person-years, with increased incidence among the elderly. In the pediatric population, the incidence was 0.56 per million person-years, and was higher among post-pubertal children aged 10–19. Median overall survival in the pediatric population was 30 months, with only localized disease and treatment with surgery being positive prognostic factors on multivariate analysis. ***Conclusions.*** MPNST is a rare disease and, among children, is most frequent seen in adolescents. Surgery is crucial as first-line treatment for MPNST, especially if the tumor is localized at diagnosis. In patients with non-localized MPNST, the disease remains extremely difficult to manage, and both surgery and radiotherapy are interventions that should be considered. Pediatr Blood Cancer 2014;61:1955–1960.

Key words: incidence; malignant peripheral nerve sheath tumors; radiation therapy; SEER; survival

INTRODUCTION

Malignant peripheral nerve sheath tumors (MPNST) are spindle cell sarcomas that are also known as malignant schwannomas, neurofibrosarcomas, and neurogenic sarcomas. They represent all malignant tumors arising from the nerve sheath of peripheral nerves. MPNST can arise from any peripheral nerve, but the larger nerve trunks, including the brachial plexus, the sacral plexus, and the sciatic nerve, are the most common sites [1–3].

MPNST is a very rare disease; there exists a paucity of data regarding the demographics or treatment of these malignancies, especially in a pediatric population. In the overall population, including adults, the incidence of MPNST is suggested to be 0.001% [4]. Only 10–20% of MPNST arise in the first two decades of life [5]. There are currently no large population-based analyses to explore incidence trends in children with MPNST.

In a recent multi-institution study of 167 pediatric patients with MPNST, the overall 5-year survival was 43–59% and the 5-year progression-free survival was 29–45% [6]. Gross total resection with wide margins is the preferred primary definitive treatment and has been shown to be the leading prognostic factor in overall survival (OS). In many patients, this operation may not be possible or associated with significant post-operative functional loss due to the resection of adjacent major vessels and/or nerves [3]. Other prognostic indicators are tumor size and the presence of neurofibromatosis [4].

Given the importance of establishing local control and the difficulty in obtaining wide negative surgical margins, radiation therapy (RT) has been used as an adjuvant. Results have been conflicting. The only retrospective studies of pediatric patients with MPNST demonstrated a trend toward improved local control with the use of adjuvant RT [5–10]. For this reason, and extrapolating from the experience in treating other soft-tissue sarcomas, adjuvant radiotherapy is often used in cases of MPNST that cannot be fully resected [3,11].

The present report represents one of the largest pediatric MPNST populations to date. We collected and analyzed data from the SEER database published by the National Cancer Institute in order to better understand the demographics of this malignancy in children. We also compared outcomes in patients receiving non-pharmaceutical therapeutic interventions to contribute additional information regarding frequency and efficacy of surgery and external beam radiotherapy in patients with MPNST.

METHODS

The Surveillance, Epidemiology, and End Results 18 (SEER-18) database from the National Cancer Institute was used to identify patients with MPNST from 1973 to 2009. The SEER-18 database covers 28% of the United States population from a wide variety of geographic areas including all or part of Alaska, California, Connecticut, Georgia, Hawaii, Iowa, Kentucky, Louisiana, Michigan, New Jersey, New Mexico, Utah, and Washington [12]. The lack of any identifying information in the data collected from the SEER-18 database made this study exempt from Institutional Review Board approval at the University of Rochester.

In patients aged 0–19, a total of 165 cases were found in the SEER-18 database. For the analysis of therapy-associated outcomes data, four cases were excluded due to incomplete data, one case was excluded due to the use of brachytherapy rather than beam radiation, and 24 further cases were excluded due to lack of tumor staging information, leaving 139 cases. For each patient, gender,

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age, race, stage (localized, regional, or distant), surgical treatment, and radiotherapy were obtained. Whether or not individual patients had neurofibromatosis type 1 could not be ascertained from the SEER database. Staging was defined per SEER Summary Staging; localized describes tumors confined to the organ of tumor origin, regional describes tumors extending to regional lymph nodes or directly to adjacent organs, and distant implies metastasis to distant organs or lymph nodes [13]. OS was obtained from the SEER database for this study. No patients in this grouping were noted as lost to follow-up, thus no censoring of the data was required.

In order to determine the incidence of MPNST in the population at large and specifically in the pediatric population, the SEER-18 database reporting from 1973 to 2009 was again used. In total, there were 1,182 cases of MPNST across the entire spectrum of ages. No pediatric or adult cases were excluded from the incidence analysis. The effect of age, gender, race, and region on incidence was analyzed separately for the overall population as well as the pediatric-only population. Age-adjusted incidence rates were calculated using the SEER*Stat software and expressed as MPNST cases per 1,000,000 person years. Incidence rate ratios (IRRs) were also calculated with SEER*Stat.

Median OS was calculated and presented with an interquartile range (IQR). Hazard ratios were determined through the Cox proportional hazards model. Comparisons between OS in the presence or absence of surgery and radiotherapy were made using the Kaplan–Meier method within two subgroups, patients with localized tumor and patients with non-localized tumor. Association of survival with radiotherapy and surgery were compared using the log-rank test. Associations between therapeutic intervention and age, race, gender, and stage were determined via chi-squared analysis. Multivariate analysis was performed using the Cox proportional hazards model adjusting for age, gender, race, stage, presence of surgical intervention, and presence of radiotherapeutic intervention. All statistical analysis was performed and figures made using STATA ver. 11 (StataCorp., College Station, TX).

RESULTS

Overall MPNST Incidence Data

The overall incidence of MPNST among the entire population (of all ages) was 1.46 per million person-years (1.38–1.54). Females (1.26, 1.16–1.37) had a lower incidence rate than males (1.69, 1.56–1.83) with an IRR of 0.74 (0.66–0.84, $P < 0.001$). Overall, MPNST is a disease with a greater incidence in the elderly population, with the incidence peaking at 3.75 per million person-years in those aged 75–79. Figure 1 shows incidence rates across the spectrum of life. Among racial groups, compared to Caucasians, there was decreased incidence of MPNST in Asian or Pacific Islanders (IRR = 0.61, 0.47–0.79, $P < 0.001$) and a trend toward increased incidence in African Americans (IRR = 1.18, 0.99–1.40, $P = 0.06$).

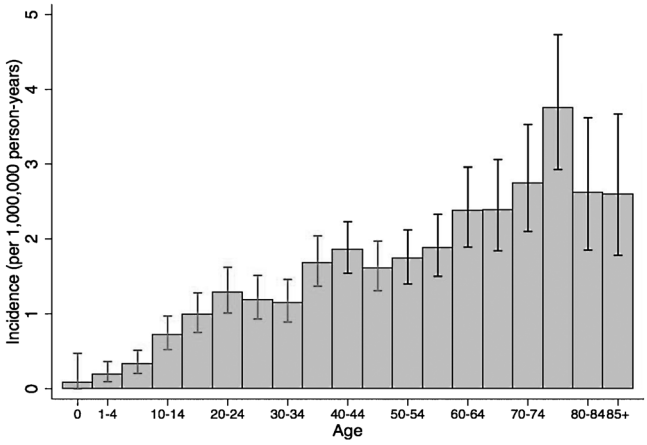

Fig. 1. Incidence of MPNST across the spectrum of age. Brackets represent the 95% confidence interval for each age group. Those age groups with a gray bracket have a statistically significant difference in IRR compared to the 85+ age group.

Pediatric MPNST Incidence Data

The overall incidence of MPNST in children under 19 years old was found to be 0.56 per million person-years (95% CI: 0.46–0.66). Male children (0.53, 0.41–0.68) and female children (0.58, 0.45–0.74) had similar incidence rates. Among children, those in the first year of life, those aged 1–4, and those aged 5–9 had a statistically significant lower incidence of MPNST compared to those aged 15–19 as shown in Table I. There were no statistically significant differences in incidence rate between Caucasians (0.56, 0.45–0.68), African Americans (0.66, 0.42–0.99), Asian or Pacific Islanders (0.36, 0.14–0.74), or American Indian/Alaska Natives (0.00, 0.00–0.96).

Patient and Tumor Characteristics

A total of 139 pediatric patients in the SEER database met study criteria for outcomes analysis. An overview of the patient population is presented in Table II. The median survival time for all patients in the study was 30 months. Of those patients, 53% of patients were male, and 72% were white. Of the 139 patients, 71 had only localized tumor, 44 had regional disease, and 24 had distant disease. In total, 90% of patients were treated with surgery and 42% of patients were treated with EBRT.

TABLE I. Incidence of Malignant Peripheral Nerve Sheath Tumor in the United States, 1973–2009

Age	Incidence rate (per million person-years)	Incidence rate confidence interval	Incidence rate ratio	Incidence rate ratio confidence interval	*P*-value
0	0.08	0–0.47	0.08	0.01–0.49	<0.001
1–4	0.19	0.09–0.36	0.19	0.08–0.40	<0.001
5–9	0.33	0.20–0.51	0.33	0.19–0.56	<0.001
10–14	0.72	0.52–0.97	0.73	0.48–1.10	0.14
15–19	0.99	0.75–1.28	n/a	n/a	n/a

TABLE II. Clinical Characteristics, Malignant Peripheral Nerve Sheath Tumor in Children, 1973–2009

Variable	Number (n = 139)	Median survival (mo, IQR)
Age		
0	1 (0.7%)	124
1–4	5 (3.6%)	20 (11–70)
5–9	21 (15.1%)	38 (15–56)
10–14	48 (34.5%)	40 (17–72)
15–19	64 (46.0%)	23 (12–80)
Gender		
Male	74 (53.2%)	37 (16–87)
Female	65 (46.8%)	22 (15–65)
Race		
Caucasian	100 (71.9%)	31 (15–73)
African American	32 (23.0%)	22 (10–62)
Other	7 (5.0%)	51 (24–93)
Surgery		
Yes	125 (89.9%)	33 (16–73)
No	14 (10.1%)	14 (7–18)
Radiotherapy		
Yes	59 (42.4%)	22 (17–84)
No	80 (57.6%)	42 (12–51)

A significant difference in survival was noted in patients that had localized versus patients with "non-localized" tumors, defined as patients with either regional or distant disease (HR = 0.53, $P < 0.001$). Analysis was performed regarding the efficacy of radiotherapy and surgery in these two groups separately. For patients with localized tumors (n = 71): median survival time was 49 months (IQR = 22–86 months), 61% of patients were male, 72% of patients were white, 96% had surgery, and 35% were treated with EBRT. For patients with non-localized tumor (n = 89): median survival time was 18 months (IQR = 10–50 months), 46% were male, 72% were white, 84% had surgery, and 50% of patients received EBRT.

Surgery and Radiotherapy in Patients With Localized Tumors

Among patients with localized tumor, nearly all (95.8%) patients underwent surgical intervention. Surgery improved OS with a median OS of 50 months (IQR = 22–86 months) versus 15 months (IQR = 3–49 months) in those not undergoing surgery, as shown in Figure 2a. However, due to the small sample size of patients not having surgery (n = 3) a statistical comparison cannot be reasonably performed.

EBRT was used less commonly in these patients (35.2%). A statistically significant decrease in OS is noted among patients who were treated with EBRT (HR = 3.57, $P = 0.04$) as shown in Figure 2b. Those treated with EBRT had a median OS of 23 months (IQR = 16–53 months) versus 58 months (IQR = 37–95 months) for those not irradiated.

Surgery and Radiotherapy in Patients With Non-Localized Tumors

Of patients with non-localized tumor, 83.8% underwent surgery. Surgery is shown to have little effect on OS. Those who underwent surgery had a median OS of 20 months (IQR = 11–51 months) versus 14 months (IQR = 7–18 months) in the absence of surgery. No statistically significant association between the use of surgery and OS was found in patients with non-localized MPNST (HR = 0.79, $P = 0.49$) as shown in Figure 3a.

External beam RT was used in 50.0% of patients with non-localized tumors. Those who received EBRT had a median OS of 17 months (IQR = 11–50 months) and those who did not had a median OS of 19 months (95% CI = 10–54 months). There is no statistically significant association between OS and the use of EBRT in patients with non-localized MPNST (HR = 1.08, $P = 0.76$) as shown in Figure 3b.

Multivariate Analysis

Cox proportional hazards analysis was performed on the entire population of cases used in this analysis in a multivariate fashion including age, sex, race, use of surgery, use of radiation, and localization of tumor (Table III). The only statistically significant positive prognostic factors were the presence of localized disease ($P = 0.011$) and the receipt of surgery ($P = 0.026$). Of particular note, neither the use of surgery nor EBRT were positive or negative prognostic factors on multivariate analysis.

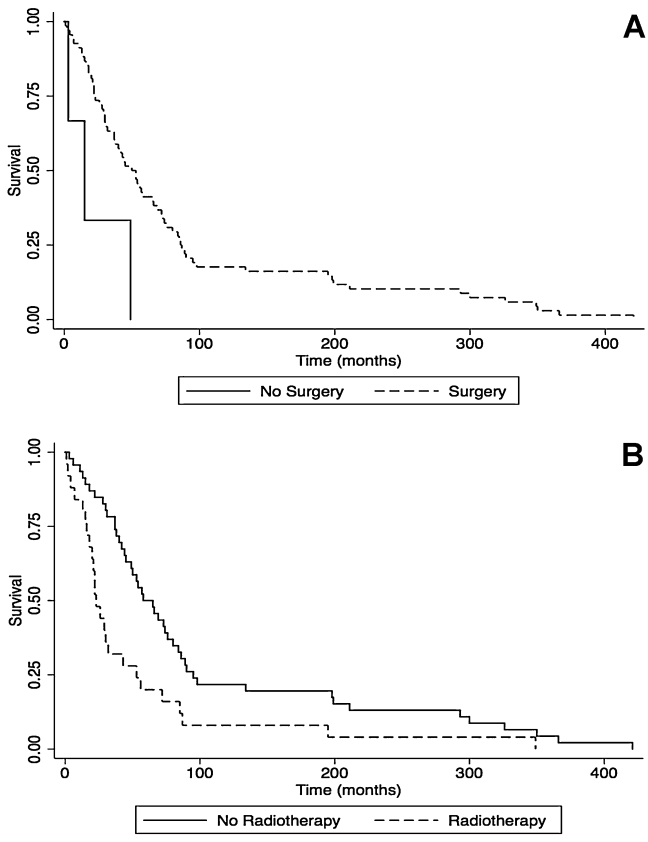

Fig. 2. (**A**) Kaplan–Meier curve depicting overall survival of pediatric patients with localized MPNST stratified by the receipt of surgery ($P = 0.08$). (**B**) Kaplan–Meier curve depicting overall survival of pediatric patients with localized MPNST stratified by the receipt of radiotherapy ($P = 0.04$).

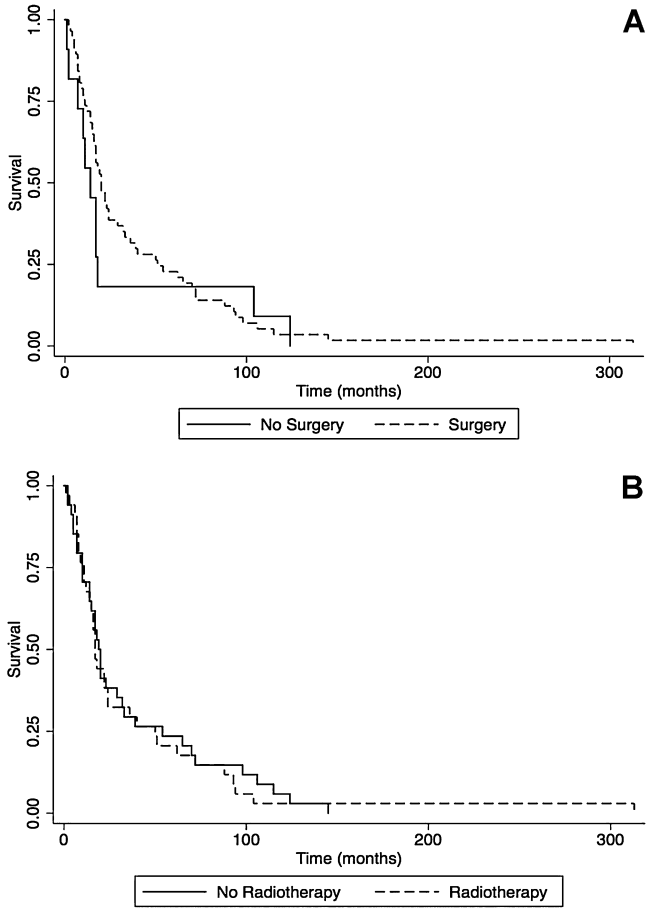

Fig. 3. (**A**) Kaplan–Meier curve depicting overall survival of pediatric patients with non-localized MPNST stratified by the receipt of surgery ($P = 0.49$). (**B**) Kaplan–Meier curve depicting overall survival of pediatric patients with non-localized MPNST stratified by the receipt of radiotherapy ($P = 0.76$).

DISCUSSION

MPNST is an extremely rare malignancy classified as a non-rhabdomyosarcoma soft tissue sarcoma (NRSTS). About 500–550 cases of NRSTS are diagnosed each year in children under the age of 20 in the United States [14]. MPNST represents the sixth most common NRSTS in children, accounting for 5.8% of NRSTS and 3.4% of all soft tissue sarcomas [15]. It is most frequently localized at presentation. Regional lymph node involvement is seen in 9% of patients and distant metastases in 6% of patients [6]. Of note, our series reports a much higher incidence of regional disease (31.7%). This is likely the result of the SEER definition of regional disease, which includes spread to anatomically adjacent organs. With a study population of 139 children, this study represents one of the largest series assessing demographics and therapeutic interventions in children with MPNST to date.

Neurofibromatosis type 1 (NF1) is a significant risk factor for the development of MPNST. Unfortunately, data regarding NF1 status in patients is not present in the SEER database, which could potentially be a confounding variable in any survival analysis. Positive NF1 status in MPNST patients has been shown to be associated with a poorer prognosis and an earlier diagnosis in adult populations [4,16,17]. Of particular note to our study, the use of EBRT in mice heterozygous for a mutation in *Nf1* was associated with an increased incidence for second malignancies [18]. In human clinical experience there has been concern for the development of occlusive vasculopathy after the use of EBRT for optic gliomas in NF1 patients [19,20]. Despite these concerns, a retrospective study from Wake Forest showed that EBRT was both efficacious and safe in the treatment of a variety of tumors in patients with NF1 [21].

The incidence data presented in this study is unique to the literature. The only previous report of incidence is from the Mayo Clinic experience with a finding of 0.001%, or one per 100,000 person-years [4]. We show an overall incidence rate for MPNST of 1.46 per million person-years, an order of magnitude lower than previously reported. This discrepancy is likely due to the fact that the Mayo Clinic paper used the population that visited the clinic rather than the population of the entire catchment area of the clinic to calculate incidence [4]. We also show that males have a higher incidence rate of MPNST than females, the incidence rate peaks at ages 75–79, and the incidence rate is lower in Asian/Pacific Islanders compared to Caucasians. This contrasts a recent series from the Mayo Clinic that had equal populations of male and female patients with MPNST [10]. These trends in incidence rates have not been previously well described and yield insight into those in the general population who are most at risk for MPNST.

Among children, the incidence rate was lower than the general population at 0.56 per million person-years. Within the pediatric population the disease predominately affects post-pubertal children, which is particularly intriguing in light of recent research that human MPNST stem cell-enriched cultures xenografted onto the sciatic nerve of ovariectomized *scid/Nf1*$^{-/+}$ mice showed increased proliferation and gross size when exposed to estrogen [22]. No differences in incidence rates were noted in the pediatric population according to gender or race. Supporting the validity of the incidence data presented here is the strong overlap in patient population characteristics between this study and the previously reported studies on pediatric MPNST [5–9].

Several previous studies of children with MPNST have been inconclusive regarding the benefit of radiation in the definitive management of pediatric patients with MPNST [5–9]. Recent SEER analyses of patients with NRSTS and with MPNST have both shown radiation to be associated with decreased OS [23,24]. Multivariate analysis of the entire cohort showed no statistically significant relationship between EBRT and OS in pediatric MPNST patients. This population-based review suggests that RT is associated with a decrease in OS only in those patients listed as having localized disease. It is possible that those treated with EBRT had more advanced disease than those treated with surgery alone. In

TABLE III. Cox Proportional Hazard Analysis of Variables and Risk of Death for Pediatric Patients With Malignant Peripheral Nerve Sheath Tumors

Variable	Hazard ratio	*P*-value
Age	0.95	0.552
Gender	1.08	0.687
Race	0.97	0.883
Surgery	0.70	0.026
Radiation	1.42	0.062
Localized tumor	0.61	0.011

a previous SEER analysis of NRSTS patients, those who received radiation were more likely to have high-risk disease per the COG risk stratification guidelines. Further, in the same paper, higher COG risk group stratification was a poor prognostic factor for OS in multivariate analysis [23].

Several previous retrospective studies have been performed in attempts to describe optimal therapy for children with MPNST. The earliest study was of 24 children treated between 1958 and 1984 at the Children's Hospital of Philadelphia. Complete surgical resection was found to be a positive predictor of OS and enhanced mitotic rate was found to be a negative predictor [9]. A study of 28 children treated from 1964 to 1993 at St. Jude Children's Research Hospital found gross surgical respectability to be a positive prognostic factor. RT was recommended for patients with positive surgical margins [7]. An Italian study performed at the Instituto Nazionale Tumori in Milan from 1976 to 1996 with 24 children diagnosed with MPNST showed that a non-statistically significant enhancement of local tumor control was noted in patients who received radiotherapy [5]. The Italian and German Soft Tissue Sarcoma Cooperative Group performed a multi-institution study of 167 consecutive children diagnosed with MPNST from 1975 to 1998. Complete surgical removal was reaffirmed as the preferred therapy if possible. Adjuvant chemotherapy was found to have minimal benefit. Radiotherapy was found to offer an improved control of local relapse rate after microscopically incomplete surgery; however no data was reported regarding OS [6]. A small study from Turkey of 13 children from 1988 to 2009 again showed that total surgical resection was associated with improved OS. The use of radiotherapy and chemotherapy were both shown in this cohort to have no effect on OS [8].

More recently, a SEER analysis was performed on a mixed cohort of pediatric patients under age 20 diagnosed with NRSTS, which includes MPNST. Patients with MPNST had worse OS on univariate and multivariate analysis. RT was associated with significantly worse OS in the entire population of NRSTS patients [23]. In concordance with strong evidence shown in previous retrospective series, surgery is shown in this series to be an important aspect of MPNST management, especially if the tumor is localized at diagnosis. The efficacy of chemotherapy was not analyzed here.

Given that the presence of localized disease is associated with increased OS, improved early detection of MPNST could be one target to improve overall outcomes in children with this malignancy. Quantitative F18-fluorodeoxyglucose positron emission tomography (FDG-PET) can be used to distinguish MPNST from benign neurofibromas with moderate accuracy [25–27]. Research is ongoing using FDG-PET to determine which neurofibromas are most likely to undergo malignant transformation [28,29]. A variety of serum and cellular markers for prognosis are also being developed [30–33]. Newer techniques in RT may also be beneficial to increasing the efficacy and tolerability of EBRT in pediatric patients with MPNST. A prospective single-arm trial is underway regarding the safety and efficacy of limited margin radiotherapy in children with high-grade NRSTS, including MPNST. Preliminary results have shown improved local control [34]. Proton therapy may also be useful in the control of pediatric MPNST [35].

Limitations of this study include those inherent to any investigation using the SEER database. As noted previously, the database limits our ability to investigate patient histories for further confounding variables. Furthermore, the methods of data entry and characterization change over time, resulting in the fragmentation of the data in some cases. The SEER database also lacks data on radiotherapy dosing and only has limited data on type of radiotherapy provided, inhibiting the analysis of specialized types of radiotherapy and the decision making process therein. The SEER database may also underreport the use of radiotherapy, which could confound results regarding the efficacy of radiotherapy [36].

MPNST is a rare malignancy in the general population, and even more rare in children. It has a very poor prognosis, as demonstrated in several series, and a paucity of treatment options [37]. We have shown that localized disease on diagnosis is correlated with increased OS, emphasizing the need for early detection of the malignant transformation of benign neurofibromas. We have also shown that surgery should remain a crucial component of first-line treatment for MPNST, especially if the tumor has not metastasized at diagnosis. In patients with non-localized MPNST, we have reinforced that the disease remains extremely difficult to manage and that both surgery and radiotherapy are safe interventions that should be considered in these patients.

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