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ARTICLE

Malignant peripheral nerve sheath tumor with and without neurofibromatosis type 1

Tumor maligno da bainha de nervo periférico com e sem Neurofibromatose tipo 1

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ABSTRACT

Objective: In this study, we review the institution's experience in treating malignant peripheral nerve sheath tumors (MPNSTs). A secondary aim was to compare outcomes between MPNSTs with and without neurofibromatosis type 1 (NF1). **Methods:** Ninety-two patients with MPNSTs, over a period of 20 years, were reviewed. A retrospective chart review was performed. The median age was 43.5 years (range, 3–84 years) and 55.4% were female; 41 patients (44.6%) had NF1-associated tumors. **Results:** Mean tumor sizes were 15.8 ± 8.2 cm and 10.8 ± 6.3 cm for patients with and without NF1, respectively. Combined two- and five-year overall survival was 48.5% and 29%. Multivariate analysis confirmed the association of tumor size greater than 10 cm (hazard ratio (HR) 2.99; 95% confidence interval (CI) 1.14–7.85; p = 0.0258) and presence of NF1 (HR 3.41; 95%CI 1.88–6.19; p < 0.001) with a decreased overall survival. **Conclusion:** Tumor size and NF1 status were the most important predictors of overall survival in our population.

Keywords: nerve sheath tumors; neurofibromatosis 1; survival.

RESUMO

Objetivo: Relatamos a experiência institucional no tratamento de tumores malignos da bainha de nervo periférico (TMBNP) e comparamos o prognóstico entre pacientes com e sem neurofibromatose tipo 1 (NF1). **Métodos:** Foram incluídos neste estudo 92 pacientes num período de 20 anos. Foi realizada uma análise retrospectiva dos prontuários, das características do tumor e do tratamento. A idade mediana era 43,5 anos (variação 3–84 anos) e 55,4% dos pacientes eram mulheres; 41 pacientes (44,6%) tinham tumores associados à NF1. **Resultados:** O diâmetro médio dos tumores era 15,8 ± 8,2cm e 10,8 ± 6,3cm para pacientes com e sem NF1, respectivamente. A sobrevida combinada em 2 e 5 anos foi de 48,5% e 29%. A análise multivariada confirmou que o tamanho do tumor acima de 10cm (hazard ratio (HR) 2.99; 95% intervalo de confiança (IC) 1.14–7.85; p = 0.0258) e a presença de NF1 (HR 3.41; 95%IC 1.88–6.19; p < 0.001) estão associados a uma pior sobrevida. **Conclusões:** O tamanho do tumor e a associação com NF1 foram os preditores mais importantes de sobrevida na nossa população.

Palavras-chave: neoplasias de bainha neural; neurofibromatose tipo 1; sobrevivência.

Malignant peripheral nerve sheath tumors (MPNSTs) correspond to 5–10% of all soft tissue sarcomas[1,2]. The MPNST originates from Schwann cells or Schwann cell precursors and was previously known as neurofibrosarcoma, neurogenic sarcoma, malignant schwannoma, and malignant neurilemmoma[3]. The MPNSTs occur mainly in adults with a median age of 35 to 44 years[2,4,5,6], and occasionally affect children[2]. These are aggressive tumors with a significant susceptibility to metastasize early in their course[4,5,6].

Malignant peripheral nerve sheath tumor pathogenesis is yet to be fully understood, but human and experimental studies have indicated the combination of cell transformation (skin-derived precursor cell) through loss of tumor suppressors (PTEN, p53 and $p16^{INK4A}$) and hyper-activation of growth factor receptor signaling, such as EGFR and PDGFR, together with extracellular matrix-mediated interactions, particularly mast cell pro-inflammatory signaling[7].

Malignant peripheral nerve sheath tumors have a widely-recognized association with neurofibromatosis type 1 (NF1) in up to half of all cases[2,4,5,6,7,8]. This association is extremely significant for tumor biology, since two major etiologies are recognized, namely NF1-associated and sporadic

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MPNST[5,7]. A third group has recently been included as a consequence of radiation therapy (RT-induced MPNST), which accounts for approximately 10% of the patients reported[2,5].

It is still unclear, however, how outcomes are influenced by different etiologies[5]. Radiation therapy-induced MPNST, for instance, seems to trend towards a worse disease specific survival compared with NF1-associated and sporadic tumors[5]. However, the classical association with a worse prognosis has been the NF1-associated group. Several studies have addressed this issue[2,4,5,6,8], which remains controversial. A recent meta-analysis done by Kolberg et al.[8] collected more than 1,800 non-overlapping MPNST patients with a specific question: whether NF1 status had any effect on survival. Interestingly, their results demonstrated a significantly worse outcome in NF1 patients, but with a recent trend in the last decade towards similar results in the sporadic group. In addition, they found no difference in survival when analyzing their own MPNST patients[8].

Due to their rarity and difficulty in diagnosis, MPNST series are rarely reported in the literature, mainly coming from US, Europe and Asian populations. In this study, we sought to report the first Latin American series of MPNST patients, who were treated consecutively over 20 years, in order to investigate patient and treatment characteristics, as well as prognostic factors in our population. A secondary aim was to compare outcomes between MPNSTs with and without NF1.

METHODS

All patients with a MPNST, treated from January 2, 1990 to December 30, 2010, were included in the study population. The institutional review board approved the terms and conditions of the present study. The histological diagnosis was confirmed by experienced institutional pathologists, but not re-reviewed for this study. Both NF1-associated and sporadic MPNSTs were included. Tumors were considered NF1-associated if the patient had the clinical diagnosis of NF1, based on two or more of the National Institutes of Health (NIH) criteria[9].

Based on this initial selection, 92 consecutive patients were treated at our institution and composed our study population. A retrospective chart review of patient, tumor and treatment characteristics was performed. Clinical data included age, gender, ethnicity, time of disease, NF1 status, tumor location (head and neck, trunk, and extremities), tumor size (main diameter), disease stage (American Joint Committee on Cancer [AJCC] staging system)[10], surgical resection, treatment goal (whether curative or palliative), and the use of chemotherapy and/or radiation therapy.

The median age at our study population was 43.5 years (range, 3–84 years) and 55.4% were female. Forty-one patients (44.6%) had NF1-associated MPNSTs.

Statistical analysis

Categorical variables were compared by using chi-square analyses, while continuous variables were compared using the Student t-test and Mann-Whitney non-parametric test, when necessary. The estimated overall and disease-free survivals were derived from the Kaplan-Meier method and Mantel-Haenszel log-rank test: survdiff. The Cox proportional-hazard model was used to investigate significant prognostic factors. We used Epi Info™ (version 7; available at www.cdc.gov/epiinfo/index.html) and the R software (version 2.15.2; available at www.r-project.org). The level of significance was set at $p < 0.05$.

RESULTS

Patient characteristics and treatment modality

In the NF-1 associated group, patients were commonly male ($p = 0.046$), younger ($p = 0.001$) and had larger tumors ($p = 0.003$). Mean time to presentation was 9.6 months (range, 2-48 months) in the NF1-associated group and 16.7 months (range, 1-96 months) in the sporadic group ($p = 0.6$). Mean tumor sizes were 15.8 ± 8.2 cm (range, 3–47 cm) and 10.8 ± 6.3 cm (range, 2–25 cm) for patients with and without NF1, respectively. Tumor distribution was similar between groups in the way that tumors were located in the extremities for most of the cases, followed by trunk, and head and neck lesions. Six patients (6.5%) presented with distant metastases, all of whom were affected by NF1. Patient demographics and treatment characteristics of the 92 patients are detailed in Table 1.

Curative treatment was commonly implemented in the sporadic group (78% vs 39% in the NF1-associated group, $p = 0.01$). Twenty-two patients (23.9%) were treated with neoadjuvant radiation therapy, 15 (16.3%) were treated with adjuvant radiation therapy and one patient (1.08%) was treated with brachytherapy. Palliative radiation therapy was given in the other 16 patients (17.4%). Overall, radiation therapy was given in 48.8% of NF1-associated and 66.7% of sporadic tumors. External beam therapy was given to these patients with doses in the range from 8-30 Gy for palliative means and 50-66 Gy for adjuvant purposes. Chemotherapy was used in 14 patients (15.2%; doxorubicin in seven, doxorubicin/ifosfamide in six; rescue regimens in one), mostly with a palliative intention (13 of 14 patients). Overall, chemotherapy was a component of treatment in 35.7% and 64.3% of NF1-associated and sporadic MPNST patients, respectively.

Local recurrence and survival analysis

At a mean follow-up of 24.8 months (range, 2–252 months) in the NF1-associated group and of 46.5 months (range, 3–208 months) in the sporadic group, 27 of 92 patients were alive. At the time of the last follow-up in the NF1-associated group, five patients (12.2%) had no evidence of disease, one (2.4%) was alive with disease, 31 (75.6%) were dead from the disease, and four (9.7%) were lost to further evaluation; while

in the sporadic group, 20 patients (39.2%) had no evidence of disease, one (2%) was alive with disease, 21 (41.2%) were dead from the disease, one (2%) died of other causes, and eight (15.7%) were lost to the follow-up.

The analysis of local recurrence was confined to the 56 patients with localized disease. In this group, 15 patients (26.8%) developed a local recurrence 1-192 months after surgery. Eight patients were re-operated upon after recurrence, four in each MPNST group. After a mean follow-up of 40 months, two patients (25%) were alive without evidence of disease, two (25%) were alive with disease, and four (50%) died from the disease.

The two- and five-year overall survival was 21% and 18% for NF1-associated and 76% and 40% for sporadic MPNST, respectively. Overall survival was significantly lower in the NF1-associated group ($p < 0.0001$), while disease-free survival was not statistically different between the groups ($p = 0.17$) (Figures 1 and 2). Age, gender and tumor location had no impact on the MPNST outcome (Table 2). On the other hand, tumor size and the treatment goal exerted a significant impact on the course of disease (Figures 3 and 4).

Table 1. Patient characteristics.

Characteristics	NF1-associated	Sporadic	p-value
Gender			
Male	23 (56.1%)	18 (35.3%)	0.046
Female	18 (43.9%)	33 (64.7%)	NS
Age at diagnosis, yr, (median)	6–68 (36.2)	3– 84 (48.9)	0.001
Presentation			
Mass	29 (70.8%)	37 (72.5%)	
Pain	11 (26.8%)	8 (15.7%)	
Ulceration	1 (2.4%)	3 (5.9%)	NS
Hemorrhage	-	2 (3.9%)	
Skin macula	-	1 (2%)	
Tumor size			
< 5 cm	3 (7.3%)	11 (21.6%)	
5–10 cm	7 (17.1%)	16 (31.4%)	0.003
> 10 cm	30 (73.2%)	18 (35.3%)	
Missing	1 (2.4%)	6 (11.8%)	
Tumor location			
Extremity	24 (58.5%)	33 (64.7%)	
Trunk	13 (31.7%)	11 (21.6%)	NS
Head and neck	4 (9.8%)	7 (13.7%)	
AJCC grade			
IA	1 (2.4%)	3 (5.9%)	
IB	1 (2.4%)	4 (7.8%)	
IIA	2 (5%)	6 (11.8%)	NS
IIB	1 (2.4%)	3 (5.9%)	
III	30 (73.2%)	35 (68.6%)	
IV	6 (14.6%)	-	
Treatment goal			
Curative	16 (39.1%)	40 (78.4%)	0.01
Palliative	25 (60.9%)	11 (21.6%)	
Follow-up, mo, mean	24.8	46.5	0.0001

NF1: neurofibromatosis type 1; yr: year; AJCC: American Joint Committee on Cancer; Mo: months; NS: not significant.

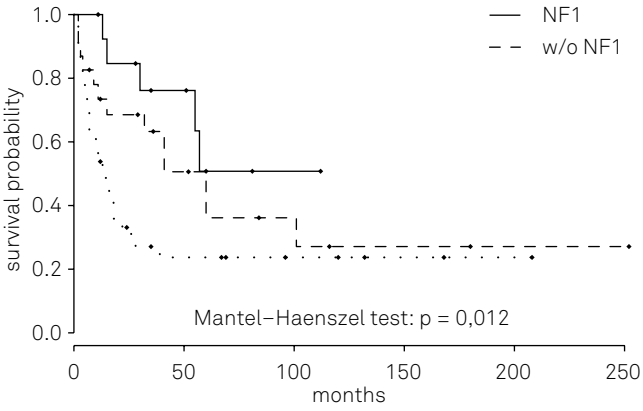

Figure 1. Kaplan-Meier curves for cumulative overall survival from MPNST patients with and without neurofibromatosis type 1 (NF1).

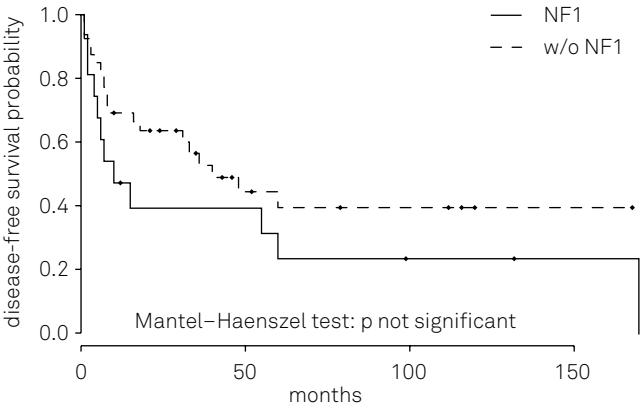

Figure 2. Kaplan-Meier curves for cumulative disease-free survival from malignant peripheral nerve sheath tumor (MPNST) patients with and without neurofibromatosis type 1 (NF1).

Table 2. Prognostic factors for overall survival and disease-free survival in the univariate analysis.

Prognostic factor	OS (mean) (mo)	p-value	DFS (mean) (mo)	p-value
NF1-status				
With	47.4	<0.0001	52.5	0.17
Without	104.6		76.5	
Age				
< 45 yr	90.2	0.42	78.4	0.54
> 45 yr	82.8		60.7	
Gender				
Male	69.6	0.12	53.2	0.11
Female	91.6		81.6	
Tumor location				
Trunk	66.4		68.7	
Extremity	107	0.16	51.5	0.53
Head and neck	37.1		36.2	
Tumor size				
< 5 cm	75.8		75.1	
5–10 cm	94.5	0.005	75.5	0.041
> 10 cm	56.2		60.8	
Treatment goal				
Palliative	13.8	0.0001	-	-
Curative	134.3		-	

NF1: neurofibromatosis type 1; OS: overall survival; DFS: disease-free survival; yr: year; mo: months; NS: not significant.

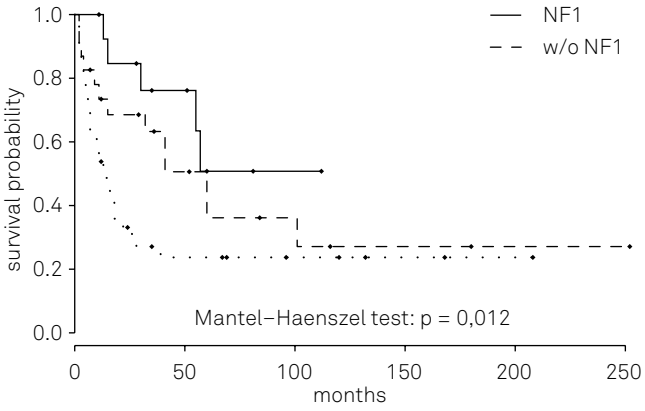

Figure 3. This graph illustrates the overall survival from malignant peripheral nerve sheath tumor (MPNST) patients according to tumor size.

Table 3. Multivariate analysis of prognostic factors associated with MPNST overall survival.

Variable	HR	95%CI	p-value
Model 1			
NF1	3.33	1.91–5.8	0.0000214
Model 2			
NF1	3.41	1.88–6.19	0.0000547
Tumor size > 10 cm	2.99	1.14–7.85	0.0258
Model 3			
NF1	2.4	1.25–4.6	0.0084
Tumor size > 10 cm	2.21	0.82–5.92	0.12
Curative treatment	0.21	0.11–0.42	0.00000523

HR: hazard ratio; CI: confidence interval; NF 1: neurofibromatosis type 1.

In the univariate analysis, increasing tumor size (greater than 10 cm) and the presence of NF1 were associated with a worse overall survival (Table 2). Multivariate analysis confirmed that a tumor size greater than 10 cm (HR 2.99; 95%CI 1.14–7.85; p = 0.0258) and the presence of NF1 (HR 3.41; 95%CI 1.88–6.19; p < 0.001) were associated with a decreased overall survival (Table 3).

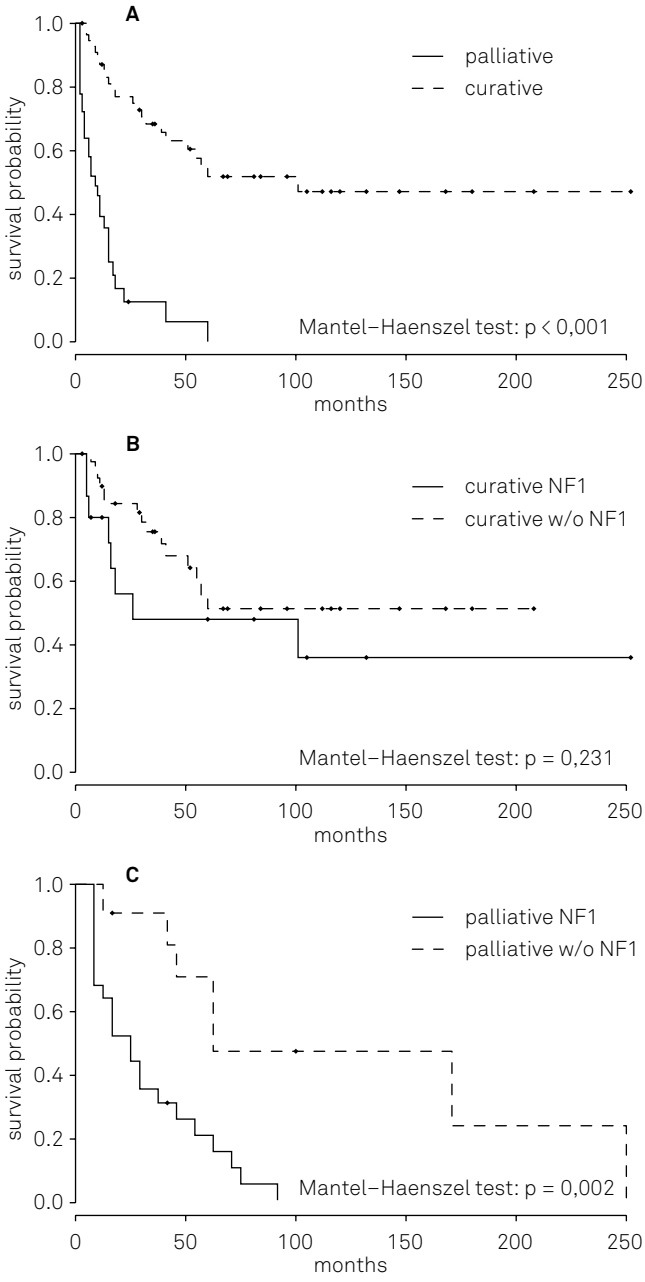

Figure 4. Kaplan-Meier curves for cumulative overall survival from malignant peripheral nerve sheath tumor (MPNST) patients according to treatment goal (A). In B, the graph demonstrates the overall survival for curative treatment according to tumor etiology (patients with and without neurofibromatosis type 1 [NF1]). In C, the graph illustrates the overall survival for palliative treatment according to tumor etiology.

DISCUSSION

To the best of our knowledge the current study represents the first Latin American MPNST series reported in the literature. Here, we report on a population of 92 patients who underwent treatment at our institution during a 20-year period. From an epidemiological standpoint, our patients were mostly female, which is similar to that observed by Stucky et al.[2], but most of the published series indicate at least a slight male predominance[4,5,6,8]. This is especially true for NF1-associated tumors, in which patients are generally male, younger, and have larger tumors at presentation[4,5,6,8]. Our results also corroborated previous reports concerning the occurrence of NF1 in approximately 45% of the patients and tumor distribution affecting mostly the extremities[2,4,5,6,7,8].

In our series, the presence of NF1 and tumor size had a significant negative impact on overall survival. The higher risk of mortality among NF1 patients has been a very conflicting issue in the literature. As mentioned, Kolberg et al.[8] found inconsistent results between their own series and the results of their seminal meta-analyses, which pointed towards similar survival in the last decade. They described at least four possibilities for which NF1 patients may carry a worse prognosis,

namely: 1) NF1-associated MPNSTs are inherently aggressive, 2) tumoral defense systems are less fit to control tumor growth, 3) delayed diagnosis resulting in advanced tumors, and (4) different treatment strategies in sporadic MPNST patients. The first two assumptions represent biological characteristics, which do not find any support in the molecular data known today[8]. The latter two represent clinical characteristics.

Interestingly, NF1 patients presented within 9.6 months from the onset of symptoms, while non-NF1 patients sought medical attention with a mean time of 16.7 months (p = 0.6). According to our results, neither delayed diagnosis nor different treatment strategies could burden the responsibility for a worse outcome in the NF1-associated group, converse to their assumptions. Our NF1 patients presented earlier with larger tumors and advanced disease suggesting other pathogenetic mechanisms for such an aggressive behavior.

In addition, we found a combined five-year overall survival of 29%. Considering only sporadic MPNST patients, the five-year overall survival was 40%, which is very similar to other large series[4,6,8]. Of note, however, is the observation that 73.2% of the NF1-associated tumors and 35.3% of the sporadic tumors in our series had lesions greater than 10 cm, making it the largest MPNST cohort of giant tumors reported to date. As previous authors, and we, have demonstrated, tumor size is one of the most important prognosticators of survival in patients with MPNST[4,5,6,8]. This could have contributed to our dismal results in the NF1 population. Moreover, it is worth mentioning that six patients (14.6%) of the NF1-associated tumor group presented with distant metastasis, which ***per se*** bore a fourfold increased risk of mortality[6].

Finally, as a soft tissue sarcoma, MPNSTs have been generally stratified by the AJCC staging system, which is considered the standard[11]. Tumor size, regional lymph node status, occurrence of distant metastasis and histological grade are collected in order to stage tumors and direct treatment[10,11]. Since it is used for stratifying all soft tissue sarcomas, which comprise a wide variety of histological subtypes with different biological behavior, several limitations of the current staging system have been addressed[11].

For categorizing tumor size (T-stage), for instance, the dichotomous division into less than, and greater than, 5 cm is usually effective in capturing the impact on outcome only for truncal sarcoma[11]. Our current analysis demonstrated that tumors greater than 10 cm, regardless of the NF1 status, carry a significantly worse prognosis in comparison with patients having intermediate-sized tumors (between 5–10 cm). This is in line with previous findings[4,8], suggesting that the AJCC staging system has significant limitations for the subset of MPNSTs, at least in the T-stage, and can reflect inaccurate prognostic information.

Even though MPNST survival is still dismal, it has consistently improved over time[8], which has raised an increasing interest in knowing and improving survivor experience. In this regard, there is a recent recommendation by the Center for Medical Technology Policy to include patient reported outcomes and measures of health-related quality of life into prospective clinical studies in the oncologic population[12]. This is extremely important in order to incorporate the patients' perspectives into treatment decision-making, thereby permitting a better understanding of the impact of disease and treatment on the patients' quality of life (QOL)[13].

There is a paucity of data in literature regarding QOL in patients suffering from MPNSTs. A recent national survey done in England included only two patients affected by MPSNTs, from their responders[14]. Their results were analyzed together with bone sarcomas and other soft tissue tumors. Interestingly, patient QOL was not related to amputation level or to histological diagnosis. Pain, on the other hand, affected approximately 90% of the patients in different levels, having a significant negative impact on QOL and physical function. Davidson et al.[13] found similar results, in things that concern the patient, to the impact of type of resection and radiation therapy among patients suffering from soft tissue sarcomas. Even though there was a high level of health-related quality of life one year after treatment, the anxiety/depression domain was associated with a significant change in the long-term, indicating that clinicians should be aware of the emotional impact of treatment[13]. Finally, half of the MPNST patients have NF1-associated tumors, which ***per se*** determine a decreased QOL in comparison to the general population[15].

There are limitations to this study. This is a retrospective investigation, in which methods of data entry and characterization change over time, thereby resulting in fragmentation of data in some cases.

In conclusion, MPNSTs are rare, aggressive tumors, which demonstrate a propensity to recur locally and disseminate early in their course, in spite of combined multimodality therapy. From the epidemiological standpoint, we observed a similar distribution of gender, tumor location and NF1 status, compared to previous reports in the literature using a more homogeneous population. Tumor size was considerably larger in the current study, suggesting that more effective screening programs should be developed in order to detect these tumors at an early stage, even for patients not affected by NF1. The presence of NF1 and tumor size had a significant negative impact on overall survival.

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