RAPID COMMUNICATION

Malignant peripheral nerve sheath tumors: clinicopathological aspects, expression of p53 and survival

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INTRODUCTION

Malignant peripheral nerve sheath tumors (MPNSTs) are rare and highly aggressive neoplasms, representing only 5% of soft tissue sarcomas (1,2). Approximately half of MPNST cases occur in association with neurofibromatosis type 1 (NF1) (3). MPNSTs may appear de novo or develop from the malignant transformation of a benign neural neoplasm, generally a plexiform neurofibroma (1). Solitary (unassociated with NF1) and localized (or discrete; multiple in NF1) neurofibromas do not have malignant transformation potential (1,3). NF1 loss of heterozygosity (LOH) has been demonstrated in NF1-associated and sporadic MPNSTs. Although NF1 LOH is believed to be sufficient for neurofibroma development, MPNST pathogenesis has been suggested to be a multistage process that includes other molecular alterations (4,5). TP53 mutations have been found in a subgroup of MPNSTs, indicating that a p53-mediated pathway is involved in their development (5,6).

Some clinicopathological features (e.g., the presence of NF1, high histological grade, necrosis, and rhabdomyoblastic differentiation) have been indicated to be important factors for lower survival in MPNST cases in some studies but not in others (2,7–10). The clinical significance of p53 expression in MPNSTs is also a controversial issue. We aimed to study p53 expression in MPNSTs and investigate its impact, as well as the impacts of the clinicopathological features of MPNSTs, on the survival rates. We also compared p53 expression in MPNSTs with their clinicopathological features and with p53 expression in neurofibromas.

MATERIALS AND METHODS

The Ethical Committee of the National Institute of Cancer (INCA), RJ, Brazil, approved this study.

Case Selection

MPNSTs diagnosed from 1996-2005 were obtained from the pathology files of INCA. The following inclusion criteria were used: available medical records and preserved paraffin blocks from the resected primary tumor with a sufficient quantity of material (in patients submitted to radiotherapy and/or chemotherapy prior to primary tumor resection, the biopsy material was used if it had the same histological grade as the resected material). Tumors with one of the following features were included: arose within a peripheral nerve; arose during the transition from a benign neural tumor; developed in a NF1 patient and exhibited the same histological features of most MPNSTs originating from a nerve; and developed in a non-NF1 patient, exhibited the same histological features as most MPNSTs and expressed S-100 (Dako Corp., Carpinteria, CA, USA, 1:4,000) and/or CD57 (clone TB01; Dako, 1:50). All samples were immunoreactive for anti-vimentin (clone V9; Dako, 1:800) and negative for anti-cytokeratin (clone AE1/ AE3; Dako, 1:400), anti-melanosome, (clone HMB-45, 1:200), anti-actin (smooth muscle; clone 1A4; Dako, 1:250), anti-actin/muscle (clone HHA35; Dako, 1:1,000), and anti-desmin (clone D33; Dako, 1:100) antibodies, except the malignant triton tumors, which exhibited anti-actin/muscle and desmin immunopositive areas. The immunohistochemistry (IHC) was performed after reviewing the H&E sections.

Plexiform neurofibromas diagnosed from 1996-2005 were obtained from the pathology files of INCA. The following inclusion criteria were used: available medical records, preserved paraffin blocks with sufficient quantity of material and presence of heterogeneous and diffuse expression of S-100 protein. The other selected neurofibromas had been used in two previous studies (11,12).

The diagnoses of all the MPNSTs and neurofibromas were confirmed by two pathologists.

Histological Analysis of Malignant Peripheral Nerve Sheath Tumors

Tables 1 and 2 show the clinical and pathological features, respectively, of the MPNSTs analyzed in this research. The tumors were classified as low- or high-grade according to the Armed Forces Institutes of Pathology criteria (1).
Table 1 - Clinical data of the patients with malignant peripheral nerve sheath tumors.

| Patient | Age at diagnosis | Gender | Race | NF1 | Site | Free surgical margins | Treatment | Local recurrence | Metastasis | Site of metastasis | Death | Overall survival (months) | Disease-free survival (months) |
|---------|------------------|--------|------|-----|------|-----------------------|-----------|-------------------|------------|---------------------|-------|--------------------------|-------------------------------|
| 1       | 27               | F      | —    | Yes | Lumbar | No | Resection | Yes | No | No | 21.60 | 18.23 |
| 2       | 44               | F      | W    | No  | Left elbow | No | Resection + Rxt | No | No | No | 13.60 | 13.60 |
| 3       | 29               | F      | —    | Yes | Right flank | No | Resection + Rxt | No | No | Yes | 12.47 | 12.47 |
| 4       | 23               | F      | B    | Yes | Pelvis | No | Resection | No | No | Yes | 4.87  | 4.87 |
| 5       | 28               | F      | W    | Yes | Right flank | Yes | Resection | No | No | No | 76.13 | 76.13 |
| 6       | 32               | F      | W    | No  | Left lower limb | Yes | Resection | No | Yes | Lung | 12.10 | .00* |
| 7       | 34               | F      | W    | No  | Right lower limb | Yes | Resection | No | No | No | 44.77 | 44.77 |
| 8       | 40               | F      | W    | No  | Breast | No | Resection + Rxt | No | No | No | 96.90 | 96.90 |
| 9       | 20               | F      | —    | Yes | Lumbar | — | Rxt | No | No | Yes | 1.83  | 1.83 |
| 10      | 53               | F      | B    | Yes | Left shoulder | Yes | Resection | No | No | Yes | 10.87 | 10.87 |
| 11      | 21               | F      | W    | Yes | Left lower limb | Yes | Resection | No | No | No | 67.50 | 67.50 |
| 12      | 23               | M      | W    | Yes | Left lower limb | — | Ct | No | Yes | Lung | 2.73  | .00* |
| 13      | 42               | F      | W    | No  | Pelvis | No | Resection + Rxt | No | Yes | Liver and pancreas | 11.30 | 9.60 |
| 14      | 68               | M      | W    | No  | Right upper limb | — | Resection + Rxt | Yes | No | No | 9.50  | 7.00 |
| 15      | 19               | M      | W    | No  | Right upper limb | — | Rxt | No | Yes | Lung | 16.10 | .00* |
| 16      | 23               | F      | W    | Yes | Sacrum and spine | — | Rxt | No | Yes | Lung | 7.73  | 7.67 |
| 17      | 34               | F      | B    | Yes | Abdomen | No | Resection | Yes | No | No | 10.10 | 5.43 |
| 18      | 60               | F      | B    | Yes | Right lower limb | Yes | Resection | No | Yes | Lung | 40.80 | 22.83 |
| 19      | 40               | F      | B    | No  | Thorax | Yes | Resection + Rxt | No | No | No | 61.10 | 61.10 |
| 20      | 78               | F      | W    | No  | Face sinus | No | Resection + Rxt | Yes | No | Yes | 77.90 | 50.20 |
| 21      | 24               | M      | W    | Yes | Right upper limb | — | Biopsy + Ct | No | Yes | Lung | 12.80 | 6.60 |
| 22      | 45               | M      | B    | Yes | Abdomen | — | Resection | Yes | Yes | Lung | 14.70 | 13.07 |
| 23      | 63               | M      | B    | Yes | Supraclavicular | Yes | Resection | No | No | Yes | 60.30 | 60.30 |
| 24      | 85               | M      | W    | No  | Head (temporal) | Yes | Resection | No | No | Yes | 20.20 | 20.20 |
| 25      | 72               | F      | W    | No  | Left lower limb | Yes | Resection + Rxt | No | Yes | Lung | 42.00 | 39.93 |
| 26      | 80               | F      | W    | No  | Right foot | Yes | Resection | No | Yes | No | 13.40 | 8.10 |
| 27      | 30               | F      | B    | No  | Thorax | Yes | Resection + Rxt | No | Yes | Bone | 35.70 | 4.67 |
| 28      | 41               | M      | B    | Yes | Right lower limb | — | Rxt | No | Yes | Cervical region | 7.20  | 6.97 |
The epithelioid MPNSTs included in this study were composed predominantly of epithelioid cells and exhibited spindle cells identical to those of conventional MPNSTs. The malignant triton tumors had areas of cells with rhabdomyoblast morphology, which expressed desmin and/or actin/muscle.

Construction of Tissue Microarray Paraffin Blocks

Two tissue microarray (TMA) paraffin blocks containing samples from all tumors were constructed. Five morphologically representative regions of each tumor were marked with a colored pen on the glass slides of H&E sections. Areas of necrosis and severe inflammatory infiltration were avoided. From each corresponding original paraffin block, five tissue cores (1.1 mm in diameter) were sampled from the marked areas in the donor block and mounted onto a recipient paraffin block, using the alternative method for the manual construction of TMAs (13).

Immunohistochemistry

Sections of 3 μm in thickness were cut and collected on silane-coated slides. After dewaxing, the p53 protein expression was assessed by IHC (anti-p53 antibody; clone DO-7; Dako Corporation, 1:100) using a protocol described elsewhere (14). A metastatic carcinoma was used as the positive control, and the omission of the primary antibody was used to establish the negative control.

The quantification of the p53 staining was performed with computerized digital image analysis (Image-Pro Plus software v4.5; Media Cybernetics), as previously described (14). The quantification was expressed as the positivity index (PI), which was defined as the p53-positive area divided by the tissue area. The tumors were classified as having low or high PIs (cut-off value = 0.0020). The intensity of the p53 expression (weak, moderate, or intense) was also evaluated.

Statistical Analysis

Clinicopathological and immunohistochemical variables were compared using the chi-squared, Fisher's exact, Student's t-, and Mann-Whitney U tests. The Kaplan-Meier method was used to evaluate the survival curves. The statistical significance of the clinicopathological variables was determined with the log-rank test. Multivariate analysis was performed using the Cox regression model. SPSS software v.11 was used for the statistical analyses. Differences were considered significant if p<0.05.

RESULTS

Twenty-eight MPNSTs and thirty-eight neurofibromas were included in this study.

Figures 1A–1C show some examples of MPNST included in the study (malignant triton tumor and MPNST with chondrosarcoma differentiation).

The overall and disease-free five-year survival rates of the MPNST patients were 46 and 39%, respectively. The data regarding the p53 expression in the MPNSTs and neurofibromas are described in Tables 2 and 3. p53 expression was more common in the MPNSTs than in the other lesions.
neurofibromas (χ² p<0.001). The only p53-positive neurofibroma (plexiform neurofibroma) presented weak nuclear immunoreactivity. In the MPNSTs, the nuclear p53 expression varied from weak to intense.

Figures 1D–1F show the expression of p53 in the plexiform neurofibroma and in two MPNSTs.

The p53 expression was not correlated with any of the following clinicopathological features of MPNSTs (Fisher’s exact test): NF1 (p = 0.433), local recurrence (p = 0.642), metastasis (p = 0.125), high grade (p = 0.364), high mitotic index (p = 0.278), and necrosis (p = 0.249).

In the p53-positive MPNSTs, there was no correlation of high PI with the clinicopathological variables (Mann-Whitney test): NF1 (p = 0.179), local recurrence (p = 0.643), metastasis (p = 0.353), high grade (p = 0.208), high mitotic index (p = 0.156), and necrosis (p = 0.387).

The epithelioid variant (p = 0.036) was the only significant variable in the log-rank analysis of disease-free survival (Table 4). The Cox regression analysis showed that necrosis (p = 0.024) was an independent prognostic factor for lower overall survival (p = 0.007) (Table 5).

**DISCUSSION**

The five-year overall survival rate of patients with MPNSTs has been reported to range from 23% to approximately 50% (2,15–17), similar to the rate of 46% found in this study. In our study, seven patients censored in the overall survival calculation had recurrence or metastasis, and three patients were lost to follow-up when the disease became terminal. Their deaths most likely went unobserved; therefore, their overall survival time may have been overestimated. This issue is usually a bias inherent in retrospective studies that intend to measure overall survival.

Although some authors have demonstrated the correlation of various clinicopathological parameters with the biological behavior of the MPNSTs, there is no consensus with regard to the importance of these factors in the prognosis of MPNST (2,7–10). In our study, the presence of necrosis was an independent predictor of mortality.

In the present work, only one (2.6%) neurofibroma (plexiform neurofibroma) expressed p53. Other studies have also demonstrated that p53 expression is rare or absent in neurofibromas (18–21). In contrast, the majority (64.3%) of MPNSTs expressed p53. Our results are similar to those of previous studies that used the same anti-p53 antibody clone, and the results of these studies showed that p53 expression in the MPNSTs varies from 42 to 100% (6,9,16,18–20,22). To our knowledge, there are only two previous studies that used TMA technology to investigate p53 expression in MPNSTs (16,22).

In some studies (9,20,21), an association between p53 expression and histological grade was observed, which differs from our research and that of others (18,19). One explanation for these divergent results could be the different criteria adopted for histological gradation. Although the United States National Institutes of Cancer and Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading systems are the most commonly used systems for sarcomas, the histological grading systems for sarcomas have no prognostic value for some histological subtypes, including MPNSTs (23). Therefore, we preferred to use a
simple system in which MPNSTs are classified into two grades: low and high (1).

We could not observe any influence of p53 expression on survival rates, similar to the results of a previous study (24). In contrast, other researchers showed that p53 expression was an important predictive factor for lower survival rate (16,19). In some studies (16,22), p53 expression was more common in neurofibromas associated with NF1 than in those not associated with NF1, but other studies (20) did not observe this association, similar to our results. There are a few possible explanations for these divergent results. First, some authors considered all cases that had any immunopositive cells as being positive, whereas others established cut-off points, varying from 3 to 10% of positive cells (9,20–22,24). Another important factor is that all previous studies used conventional pathologist-based manual scoring to quantify the p53 staining, which increases the inter-observer and intra-observer variabilities. Our study was the first to use computerized image analysis to calculate the p53 expression. Moreover, technical considerations, such as the storage time of the tissue sections on glass slides, can influence p53 immunoreactivity.

### Table 4 - Results of the influence of the clinicopathological variables on the overall and disease-free survival in patients with malignant peripheral nerve sheath tumors.

| Variables                        | Total SV (months) | Total SV (p log-rank) | Disease-free SV (months) | Disease-free SV (p log-rank) |
|----------------------------------|-------------------|-----------------------|--------------------------|----------------------------|
| **Gender**                       |                   |                       |                          |                            |
| Female                           | 54.3              | 0.109                 | 47.3                     | 0.118                      |
| Male                             | 23.5              |                       | 19.3                     |                            |
| **NF1**                          |                   |                       |                          |                            |
| Yes                              | 31.6              | **0.044**             | 31.4                     | 0.959                      |
| No                               | 59.9              |                       | 41.6                     |                            |
| **Location**                     |                   |                       |                          |                            |
| Trunk (yes/no)                   | 49.4/42.2         | 0.955                 | 47.3/27.4                | 0.390                      |
| Limbs (yes/no)                   | 37.9/47.0         | 0.937                 | 25.0/50.5                | 0.199                      |
| Lower limb (yes/no)              | 37.7/46.4         | 0.980                 | 21.9/50.8                | 0.108                      |
| Upper limb (yes/no)              | 12.2/46.1         | 0.912                 | 11.4/40.1                | 0.679                      |
| Head and neck (yes/no)           | 49.0/48.9         | 0.977                 | 50.2/39.7                | 0.531                      |
| **Treatment performed**          |                   |                       |                          |                            |
| Surgical resection + radiotherapy| 35.9              | 0.184                 | 35.886                   | 0.282                      |
| Other type of treatment          | 60.0              |                       | 55.629                   |                            |
| **Size of the tumor**            |                   |                       |                          |                            |
| ≤5 cm                            | 44.7              | 0.716                 | 28.9                     | 0.610                      |
| >5 cm                            | 57.6              |                       | 55.4                     |                            |
| **Free surgical margins**        |                   |                       |                          |                            |
| Yes                              | 49.7              | 0.925                 | 48.57                    | 0.516                      |
| No                               | 55.1              |                       | 41.5                     |                            |
| **Local Recurrence**             |                   |                       |                          |                            |
| Yes                              | 46.0              | 0.606                 | —                        | —                          |
| No                               | 60.6              |                       | —                        | —                          |
| **Metastases**                   |                   |                       |                          |                            |
| Yes                              | 54.4              | 0.135                 | —                        | —                          |
| No                               | 23.4              |                       | —                        | —                          |
| **Histological Grade**           |                   |                       |                          |                            |
| High                             | 31.7              | **0.045**             | 23.94                    | 0.095                      |
| Low                              | 68.6              |                       | 65.28                    |                            |
| **Mitotic index**                |                   |                       |                          |                            |
| ≥ 10 mitoses/10 high-power fields| 24.0              | 0.051                 | 21.54                    | 0.386                      |
| < 10 mitoses/10 high-power fields| 53.7              |                       | 44.77                    |                            |
| **Necrosis**                     |                   |                       |                          |                            |
| Yes                              | 19.1              | **0.003**             | 23.95                    | 0.138                      |
| No                               | 62.4              |                       | 50.23                    |                            |
| **Epithelioid Variant**          |                   |                       |                          |                            |
| Yes                              | *                 | *                     | 6.21                     | 0.036                      |
| No                               | 44.49             |                       | 43.98                    |                            |
| **Malignant Triton Tumor**       |                   |                       |                          |                            |
| Yes                              | 9.2               | 0.566                 | 18.42                    | 0.958                      |
| No                               | 46.3              |                       | 42.26                    |                            |
| **Chondrosarcoma differentiation**|                   |                       |                          |                            |
| Yes                              | 54.5              | 0.511                 | 46.17                    | 0.356                      |
| No                               | 43.8              |                       | 37.89                    |                            |
| **P53 protein expression**       |                   |                       |                          |                            |
| Positive                         | 43.8              | 0.942                 | 49.1                     | 0.418                      |
| Negative                         | 50.9              | 429                   | 42.6                     | 0.502                      |
| Low Pl                           | 38.9              |                       | 46.9                     |                            |
| High Pl                          | 43.5              |                       | 49.4                     |                            |

SV, survival; PI, positive index; *, the value could not be calculated because all cases were censored.
Necrosis was an important prognostic factor for lower overall survival, and the epithelioid variant was an important prognostic factor for shorter disease-free survival.
p53 expression was not associated with any clinicopathological features and did not have an impact on the survival rates of the MPNST patients. p53 expression was rare in the neurofibromas and common in the MPNSTs, showing that the p53 pathway most likely plays an important role in the tumorigenesis of MPNSTs.

AUTHOR CONTRIBUTIONS

Cunha KSG designed and conducted the research, analyzed the data, wrote the paper and had primary responsibility for the final content. Faria PA, Geller M and Moura-Neto RS designed the research and wrote the paper. Lopes VS designed and conducted the research. Caruso AC and Cunha KSG conducted the research. Silva LE analyzed the data. All authors read and approved the final version of the manuscript.

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Table 5 - Results of the Cox regression model for significant variables in the univariate analysis of overall survival.

| Steps | Co-variables | p-value | Exp (B) | 95% CI for Exp (B) |
|-------|--------------|---------|---------|-------------------|
|       |              |         |         | lower | upper          |
| 1     | Presence of NF1 | 0.497   | 0.627   | 0.163 | 2.413          |
|       | Histological  | 0.846   | 1.233   | 0.161 | 9.283          |
|       | Grade         | 0.276   | 0.426   | 0.092 | 1.975          |
|       | Necrosis      | 0.370   | 1.076   | 0.917 | 1.262          |
|       | Mitotic Index | 0.199   | 0.062   | 0.639 |
| 2     | Presence of NF1 | 0.465   | 0.609   | 0.161 | 2.301          |
|       | Necrosis      | 0.255   | 0.413   | 0.090 | 1.897          |
|       | Mitotic Index | 0.289   | 1.083   | 0.935 | 1.254          |
| 3     | Necrosis      | 0.143   | 0.343   | 0.082 | 1.434          |
|       | Mitotic Index | 0.226   | 1.093   | 0.947 | 1.261          |
| 4     | Necrosis      | 0.007   | 0.199   | 0.062 | 0.639          |