Abstract. Background: Malignant peripheral nerve sheath tumors (MPNST) account for up to 10% of all malignant soft tissue tumors in adults. Insufficient data are available on diagnosis, differential diagnosis and treatment modalities as well as prognosis. Patients and Methods: Examining our sarcoma database from 1991 to 2004, we evaluated 65 patients with histologically-proven MPNST in terms of clinical, histopathological as well as prognostic factors. Results: The median age was 54 years, the gender ratio was equal, the follow-up 36 months. Extremities were involved in 75% of cases, the trunk in 15% and the head in 9% respectively. A total of 9% of our patients presented with disease-positive lymph nodes, in 28%, distant metastases (primarily lung) occurred. A primary closure was performed in 60%; in 22%, a tendon transfer and flap coverage was necessary. In 11% of cases, the final treatment was amputation. The initial diagnoses which had to be revised during re-evaluation was 32.3%. The 5-year disease-free survival rate was 49%. Overall, 27% of patients first operated on at our Institution experienced local recurrence. The only significant negative prognostic factor for survival was occurrence of metastases. Conclusion: Our data indicate, that MPNST are tumor entities with a high rate of initial diagnoses that subsequently need to be adjusted (32%). Therefore, reference pathology should be requested. Tumor localization close to major nerves often results in functional restrictions after tumor resection. Because of the low mean life expectancy, early functional reconstructions by tendon transfer should be performed instead of nerve repair. Despite less radical tumor excision with often marginal resections, the survival rate is comparable to that of the literature where patients were treated with more radical procedures.

The terms for sarcoma arising within peripheral nerves are neurofibrosarcoma, neurogenic sarcoma, malignant schwannoma and malignant neurilemmoma (22). The most commonly used term is malignant peripheral nerve sheath tumor (MPNST) (13). MPNSTs are a rare variety of soft tissue sarcoma of ectomesenchymal origin, with an incidence of one per million per year (33). They account for 3-10% of soft tissue sarcomas (10, 18, 32, 34). By definition, any malignant tumor arising from or differentiating toward cells of the peripheral nerve sheath, in most cases probably from Schwann cells, is a MPNST (13, 20).

Histopathological diagnosis of MPNST may be difficult, since there is a variety of differential diagnoses. As the tumor is rare, re-classification may be necessary in terms of special tertiary reference centers.

Therapy consists mainly of surgery. Irradiation and chemotherapy are only used for selected patients (13).

The aim of this study was to analyze the clinical and histopathological progression of patients with MPNST and compare the survival rates to those of other studies, since in the past decades, our surgical treatment was less radical compared to other sarcoma centers. This policy could improve the quality of life for the patient but, on the other
hand, could be a risk factor for recurrence and reduced time of survival. Another key issue was the collection of data about inaccurate initial histological diagnoses. In our experience, diagnosis changed frequently during the course of treatment.

Patients and Methods

Patients. From 1991 to 2004, 65 patients underwent surgery for MPNST in our Department and the data were recorded in a prospective database.

The tumors were analyzed retrospectively with regard to prognostic factors such as localization, size, grading, surgical margins (R0/R1) and neo-/adjuvant therapies.

The tumors were prospectively diagnosed and classified by the Institute of Pathology at the Ruhr University Bochum, Germany. In uncertain cases a second opinion was obtained, mainly from Professor Katenkamp, Jena, Germany.

Definition of the terms used. The excised tumor was classified as ‘R0’ by the pathologist when the excised tumor was microscopically-covered by healthy tissue. In that situation we assumed, that the tumor had been removed completely. When the pathologist wrote “R1” this meant he had found microscopically positive resection margins. T1 tumor denotes a tumor diameter under 5 cm, T2 tumor a diameter over 5 cm. The grading increases with the lack of cellular differentiation compared to normal tissue. We chose the three-tier scale, where grade 1 (G1) means well-differentiated (low grade), G2 intermediate, and G3 poorly differentiated (high grade) tumor.

Statistical analysis. Data are presented using median and mean values, including the standard deviation (SD). Disease-specific survival (DSS) and local recurrence were constructed by the Kaplan-Meier method and by log-rank test (14). Significant differences in the factors were analyzed for independent prognostic importance by Cox proportional hazards regression. A value of p<0.05 was considered statistically significant. Twenty-two patients could not be traced to the end of the study and were censored at their last follow-up.

Results

The median age of 65 patients was 54 years (mean=52 years; range=14-88 years). The gender ratio was equal, with 32 males and 33 females. The median follow-up was 32 months (mean=36 months, range=1-126 months). Altogether, 7.7% (n=5) suffered from NF1. The median age at diagnosis of MPNST of patients with NF1 was 45.8 years.

The extremities were involved in 49 patients (n=29 lower extremity, n=20 upper extremity) followed by the trunk (n=10) and the head in (n=6; Table I).

T2 Tumors occurred in 48 of patients. A total of 53 of the MPNSTs were G2- or G3-differentiated. The 5-year disease-free survival rate was 49%. In 54% of patients local recurrence occurred. Only metastasis was found to be a significant prognostic factor for survival.

Symptoms at presentation. A total of 43 of the patients had discovered a swelling, which was the reason for consulting a physician. Symptoms at presentation were in 25 cases mild pain. Eight patients complained of dysesthesia; in nine patients, motor dysfunctions were observed, while 41 had no restrictions of movement. In 15 patients, no symptoms were recorded.

Surgical procedure. The primary goal of our surgical procedure was R0–resection, with as much healthy tissue as possible covering the tumor. On the other hand, in nearly all cases, mutilation was avoided as far as possible. A primary closure after tumor resection was achieved in 39 cases; in 14, a tendon transfer and flap coverage was necessary. Seven patients ultimately underwent amputation because of tumor expansion and patient condition, where a procedure with microvascular free soft tissue or bone transfer was no longer indicated (Table II).

Twenty-two patients were operated on at our hospital, 13 at other University hospitals and 21 at Community hospitals or by physicians as out-patients. In nine cases we were unable to determine where the first operation had taken place. The referrals were made because of R1 resections or unknown resection margins in 39 cases and R2 status in four cases.

Histology/grading. Biopsies prior to surgery were documented in 21 patients. In most cases, the first procedure was performed by an independent physician expecting a benign tumor-like lipoma and no biopsies prior to surgery were obtained. In some cases, we had no access to the result of biopsy.

In 31 cases the tumor was diagnosed as MPNST by the primary pathologists. Initial diagnoses which were rejected during re-evaluation (n=21, 32.3%) were monophasic fibrotic synovial cell sarcoma (n=4), benign neurofibroma (n=4), malignant melanoma (n=1), dermatofibrosarcoma protuberans (n=3), ganglial neuroblastoma (n=1), synovial cell sarcoma (n=3), liposarcoma (n=1), leiomyosarcoma/Non-Hodgkin lymphoma/malignant histiocytoma (n=1), leiomyosarcoma (n=2), spindle cell myxoid pleomorphic sarcoma (not otherwise specified, NOS, n=3). In 13 cases the initial diagnosis was unknown.

Six tumors were graded as G1, 29 as G2 and 24 as G3. In six patients, no grading of the tumor was recorded or was possible to assess because the patients had received neoadjuvant chemotherapy or irradiation.

Tumor size. A total of 48 of patients were operated on for T2 tumors, 12 for T1, in five patients, no classification was possible (the patients were referred with R1-status without recorded tumor dimensions).

Status of resection. In 24 patients, a negative resection margin was documented (R0), in 14 the resection margin was positive (R1: n=10, R2: n=4). All patients with R2 resection
were referred from other hospitals. In 27 cases (all patients transferred for re-resection), no exact resection status was documented and the former tumor area was re-resected. All patients with positive or unclear resection margins were re-resected at our hospital with the aim of R0 resection.

Adjuvant therapy. A total of 23 patients received adjuvant irradiation, 5 chemotherapy and 6 combined radio-chemotherapy. One patient had no adjuvant therapy and in 13 patients, administration of an adjuvant therapy was unknown.

Local recurrence. Altogether, 35 patients suffered from local recurrence; 22 did not and in 8 cases, the status was unknown.

Of the patients initially operated on at our hospital, six out of 22 (27%) and 29 out of 34 (85%) of the patients were originally operated elsewhere. Twenty patients suffered one local recurrence; 15 had two or more local recurrences. The time to the first recurrence (n=23) was a mean of 18 months, a median of eight months, ranging from one to 93 months after surgery.

The highest local recurrence rate was for tumor localized on the upper arm and trunk (Table I). The lowest rates were found for those on the lower leg and head (about 15%), followed by the forearm (20%) and thigh (37%).

Local recurrence occurred mainly in higher-grade MPNST (G1: n=1, G2: n=13 and G3: n=12). Patients with T1 tumors had local recurrence in seven cases, those with T2 in 21.

Metastasis. Six patients had already presented with disease-positive lymph nodes at the time of diagnosis. Eighteen patients had distant metastases at the time of presentation or developed them in the course of follow-up. In 14 cases only distant metastases were found; in two only positive lymph nodes and in four both local and distant metastases.

The distant metastases were located mainly in the lung (n=16), in combination with bones (n=2) or the mediastinum (n=2). One patient suffered metastases in the lungs, brain and liver, which were proven by biopsies. Only two patients had metastases without lung involvement: in one case osseous and in another peritoneal/intra-abdominal metastases were found.

All metastases were resected if the patient was in acceptable condition.

Overall survival. At the time of investigation, 25 patients had died, 18 were still alive; in 22 cases, the status was unknown.

The overall median survival rate was 55 months (Figure 1). The 5-year overall survival was 49%.

Of the patients with T1 tumors 60% were still alive five years with the disease, in the case of those with T2 tumors this was only 44%; however, no significant differences were found (p=0.54).

By histological grading again calculated by the Kaplan-Meier method showed the shortest survival time to be for patients with G3 tumors, followed by those with G2 and G1, but no significant differences were recorded (p=0.21). The 5-year survival was 63% for those with G1, 58% for G2 and 33% for those with G3-tumors (Figure 2).

There was a clear tendency of better survival chance for patients whose MPNST was resected with histologically tumor-negative margins, even when no significant difference was found (p=0.12; Figure 3). The calculated 5-year survival was 61% for patients with negative (R0) resection margins; they survived longer compared to 32% of those with positive resection margins.

Existing metastasis had a considerable influence on the survival of patients (Figure 4). Without verified metastases, the overall survival was 126 months; with metastasis, it was only 36 months; the 5-year survival was 74% versus 18% (p<0.01).

Discussion

With an incidence of about one per million MPNSTs are a very rare entity of soft tissue sarcoma (33). This may lead to an inadequate treatment rationale, beginning with resection under local anesthesia as an outpatient without prior biopsy and followed by histological misclassification. A prognostic nomogram for mortality shows the highest risk of all sarcomas for MPNST (15).

Diagnosis. The symptoms are non-specific, but a relatively high percentage of patients suffered from nerve-related
symptoms, which could be explained by tumor compression or infiltration.

The diagnosis should begin with a complete medical and family history and a physical examination, focusing on the skin and neurology (13). The most important known risk factor for MPNST development is NF1, in which 10% of patients develop an MPNST during their lifetime. About 50% of MPNSTs occur in patients with NF1, in our patient population only about 8% suffered from NF1 (10, 23). One reason for the low number of patients with NF1 could be that such patients are often connected to a hospital where parts of their neurofibroma were resected and where a relationship of trust develops. This explanation is highly speculative. Whether it has an impact on the outcome of our patients remains unclear. We should be aware that only deep plexiform neurofibromas are at-risk for malignant transformation and not superficial dermal lumps (30). The second known risk factor for developing an MPNST is radiation exposure decades prior to occurrence of MPNST, recorded for 10% of patients (8, 9, 12).

Studies have shown that patients with NF1 developed MPNST 10 years earlier than the normal population; we found a difference of eight years (5). The most common age at-diagnosis is between 20 and 50 years (4, 8, 10). The mean age at the time of first diagnosis for our patients was 52 years, which might be explained by a selection bias, as most children are treated by pediatric surgeons. In addition, many patients presented with long-existing T2 tumors and the rate of patients with NF1, who developed MPNST earlier, was very low. The observed equal incidence of MPNST in males and females corresponds to that of the literature (5).

The frequency of the involved areas was in accordance with the literature, where the proximal upper and lower extremities were the most common sites (2, 5, 23).

After imaging (magnetic resonance imaging or computer tomography with contrast medium) a biopsy should be performed. In our experience, open biopsies result in superior histological evaluation because more tissue is gathered which is more representative especially for inhomogeneous tumors.

After receiving the diagnosis of the biopsy, a chest x-ray and if necessary a chest CT (non-contrast) should be performed to evaluate for pulmonary metastases (13). Surgical procedure. The goal of surgery at our Department is tumor removal with microscopically clear margins of resection (8, 13). Our frequencies of negative resection margins are comparable with those of other studies (1, 29). The low number of patients first operated on at our Institution and the high number of patients treated first at other hospitals and referred with R1 or R2 status to our
hospital may have led to a selection bias (74% T2-tumors). One problem of resection of MPNSTs and soft tissue sarcomas in general starts with the considerable lack of uniform recommendations for the resection margin (27). Strong evidence-based data are lacking. The experience of over 2,000 sarcoma resections in the last 20 years and follow-up examinations led us to aim for R0 resection. Even resection margins of not more than 1 mm were tolerated. Follow-up examinations every three months after surgery for the first two years with MRI of the local area and x-ray of the chest are done. The second problem is the neglect of the resection margins by pathologists, which makes the comparison of different data difficult.

Nerve reconstructions by grafting were not performed. Instead of nerve reconstruction by grafting, tendon transfers were performed to enable for rapid mobility. If a nerve reconstruction is planned, a tendon transfer should be considered in addition, in order to allow rapid mobility because of the altogether short course of disease (13, 26). We were able to re-examine only three patients with tendon transfer after MPNST resection, a number, which allows no statement about the results, especially regarding the heterogeneous patient population. In the past, we investigated the long-term results after tendon transfers for drop foot corrections (n=53), with good functional results and improvement of the quality of life (28). Intended irradiation should be neo-adjuvant in the case of nerve reconstruction in order to allow better nerve regeneration.

Amputation was necessary in 11% of the patients, which represents a low value compared to other studies (10, 32). Amputation should be the last resort, because it was shown that patients with large ‘totally-excised’ tumors had no difference in survival from patients with incompletely-excised lesions, whether large or small (10). Because of better results in the treatment of soft-tissue sarcomas, patients with MPNST should be treated in specialized tumor Centers (17).

Despite using less radical procedures with focus on limb salvage and complete (R0) tumor resection, we achieved comparable survival rates. This treatment underlines a general tendency in tumor therapy. Whereas in the past resections of sarcomas were radical, including compartment resection and amputation in many cases (11), current opinion favors a limb-saving approach by performing specimen resection, which are covered only by 1-2 cm layer of healthy tissue – survival rates are practically the same (19, 21, 27). In combination with irradiation even R1 resection leads to results with analogous local recurrence rates and overall survival. Nevertheless, R0 resection should be the aim of surgical treatment and even few millimeters of healthy tissue covering the tumor are acceptable in our opinion (7, 24, 31). According to the literature available for MPNSTs, the level of evidence is currently low. Further studies with higher patient numbers are needed to corroborate the tendency revealed for soft tissue sarcoma in general, where resection with small margins does not impair the outcome for the patients but improves their quality of life.
Adjuvant therapy. The data collected here did not have strong statistical power because of selection bias, different adjuvant therapies and a low number of patients. Looking at the literature and from our own patients, the benefit from chemotherapy regarding local recurrence, metastasis or overall survival seems to be low (8, 10, 16). Other studies found that irradiation could improve local control (4, 22).

The role of systemic chemotherapy has never been adequately studied and is, therefore, still being controversially discussed (13, 16).

Local recurrence. Local tumor recurrence in the present study was comparable to other studies, where values between 20% to 40% are described (2, 23, 29, 32). Our results underline former findings that most local recurrences occurred within two years after resection (3, 23). Key parameters for local tumor recurrence are positive resection margins, site and recurrence at presentation (2, 13). The highest local recurrence rate was found for tumors of the trunk and arm, and occurred mainly in high grade MPNST and for larger tumors. The high incidence after foot tumors cannot be critically considered because of the low number of patients (n=3). The high number of local recurrences after primary tumor resection in peripheral hospitals may be due to difficult tumor sites (near large nerves or blood vessels) or tumor biology; it was shown for sarcoma that if a local recurrence occurs, the likelihood of further recurrence is much higher than if no recurrence had occurred before (6).

Metastasis. Nearly one third of patients presented with metastases or developed distant metastases, mainly in the lung. These results concur with former findings (2, 10, 32). Other sites affected are – as in our study – the liver, lymph nodes and brain (2). In addition, we found osseous and intra-abdominal metastases. Tumor-size, grading and local recurrences were described as independent risk factors for metastasis (2).

The survival rate of patients with pulmonary metastasis is poor, but the literature shows that selected patients could benefit from a resection of pulmonary metastases in particular (25).

Survival. The 5-year overall survival of 49% is comparable to that of other studies (1, 2, 4, 8, 23, 29, 32). In our study, only metastasis was found to be a significant independent prognostic factor for survival.

An obvious tendency for poorer survival was found for tumor size, site, grading and margins of resection, but no significant differences were recorded. Ducatman et al. also found no significant correlation between tumor grading and survival (8). Stucky et al. found that high tumor grade and tumor size over 5 cm were poor prognostic indicators for DSS (29). These findings stand in contrast to those of other studies (2, 8, 23). In one study, tumor size over 10 cm was found to be a significantly adverse parameter (23), we merely compared sizes over and under 5 cm.

Conclusion

We present one of the largest numbers of patients with MPNST treated at a single institution. MPNSTs are a rare tumor entity with a high rate of vague diagnoses. Pathohistological investigations by a reference pathologist are advisable.

According to the literature available, the less radical tumor excision carried out at our Institution leads to a survival rate comparable to treatment with more radical procedures plus it involves less mutilation of the patient. Amputation should be the last resort because wide surgical resection shows no benefit in overall survival in soft tissue sarcoma and leads to extremely mutilating operations. Because of the low life expectancy of patients with MPNSTs functional reconstruction should be performed early by tendon transfer and not by nerve transplantation, in order to improve quality of life.

Large retrospective studies are necessary to improve the poor evidence for treatment regimes of MPNSTs.

References

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