

International Consensus Statement on Malignant Peripheral Nerve Sheath Tumors in Neurofibromatosis 1¹

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Abstract

Neurofibromatosis 1 (NF1) is an autosomal dominant tumor predisposition syndrome in which affected individuals have a greatly increased risk of developing malignant peripheral nerve sheath tumors (MPNSTs). These cancers are difficult to detect and have a poor prognosis. Because patients may present to specialists from widely differing disciplines, the association with NF1 is often not appreciated, and there is no cohesive pattern of care. A multidisciplinary group of 33 clinicians and scientists with specialist knowledge in MPNST and NF1 reviewed the current published and unpublished data in this field, and distilled their collective experience to produce a consensus summary on MPNST in NF1. The known clinical, pathological, and genetic information on MPNST in NF1 was collated, and a database was established to record information in a uniform manner. Subgroups with a higher risk of developing MPNST were identified within the NF1 population. The consortium formulated proposals and guidelines for clinical and pathological diagnosis, surgical management, and medical treatment of MPNST in individuals with NF1. A multidisciplinary team approach to the management of this complex disorder is advocated. Progress can be made by adopting the guidelines proposed by this consortium and by widespread dissemination of standardized information. Collaborative research should be promoted with the aim of harnessing advances in molecular genetics to develop targeted therapies for MPNST in people with NF1.

Introduction

NF1⁴ is an autosomal dominant neurocutaneous disorder, with an estimated birth incidence of 1 in 2500 (1). The *NF1* gene on chromosome 17q 11.2 was identified by positional cloning, and its protein product, neurofibromin, functions as a tumor suppressor (2–4). One of the functions of neurofibromin is to reduce cell proliferation by accelerating the inactivation of the proto-oncogene *p21-ras*, which has a pivotal role in mitogenic intracellular signaling pathways (4). The cardinal and defining features of NF1 are café au lait macules, neurofibromas, skinfold freckling, iris Lisch nodules, and characteristic osseous dysplasia (5). The complications of the disorder are legion and may involve any of the body systems (6).

Individuals affected with NF1 harbor an increased risk of developing both benign and malignant tumors, supporting the classification of NF1 as a tumor predisposition syndrome. The most common tumor in

individuals with NF1 is the neurofibroma, a heterogeneous benign peripheral nerve sheath tumor (7, 8). Neurofibromas may appear as discrete, dermal neurofibromas, focal cutaneous or s.c. growths, dumbbell-shaped intraforaminal spinal tumors, or nodular or diffuse plexiform neurofibromas. Plexiform neurofibromas are composed of the same cell types as dermal neurofibromas but have an expanded extracellular matrix and often have a rich vascular supply. They develop along a nerve and may involve multiple branches, nerve roots, and plexi. Impingement on surrounding structures may cause functional compromise, and soft tissue and bone hypertrophy may occur (9).

Plexiform neurofibromas were clinically visible in 30% of 125 NF1 patients in a South Wales population study (10). Forty four percent of plexiform neurofibromas (32 of 72 patients) were diagnosed before 5 years of age in one clinic-based study (11) suggesting that many plexiform neurofibromas are congenital lesions. Multiple plexiform neurofibromas occur in 9–21% of cases (10–12). Although MPNST can develop in individuals in the general population, individuals with NF1 have a significantly increased risk. These tumors arise frequently in preexisting plexiform neurofibromas, which are very uncommon in people who do not have NF1. MPNSTs are often difficult to detect, metastasize to the lung, liver, brain, soft tissue, bone, regional lymph nodes, skin, and retroperitoneum, and have a poor prognosis (13). Because patients with MPNSTs may present to specialists from widely differing disciplines, the association with NF1 is often not appreciated, and there is no consistent or widely accepted pattern of care.

Aims. In this unique meeting, the aim was to establish an international, multidisciplinary consortium of experts on MPNST and NF1. The purpose was to collate the known clinical and genetic information about these tumors and to set up a standardized database to record information in a uniform manner. In addition, the goal was to formulate guidelines for clinical and pathological diagnosis, surgical management, and medical treatment. Moreover, strategies were proposed for developing targeted therapies for NF1-associated MPNSTs, taking into account the recent advances in molecular biology.

Materials and Methods

An international, multidisciplinary group of clinicians and scientists with a specialist interest in soft tissue sarcomas (MPNST) and NF1 was invited. Invitations were sent to clinicians working in specialist soft tissue sarcoma centers or large neurofibromatosis clinics and to individuals with research publications in these fields. The current knowledge in this field was reviewed based on personal expertise and the medical literature. Subsequently, the specialists pooled their collective experience to produce a consensus group summary on MPNST in NF1.

Results

Clinical Consensus Group. It is generally accepted that MPNSTs occur in about 2–5% of NF1 patients compared with an incidence of 0.001% in the general population (13). However, there may be differences in cross-sectional *versus* longitudinal determinations of risk

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³ D. H. G. was the leader of the following working groups: Medical Consensus Group, Surgery Consensus Group, Pathology Consensus Group, Oncology Consensus Group, and Molecular Biology Consensus Group. Members of the groups are listed in the Appendix.

⁴ The abbreviations used are: NF1, neurofibromatosis 1; MPNST, malignant peripheral nerve sheath tumor; MRI, magnetic resonance imaging; ¹⁸FDG, ¹⁸F-fluorodeoxyglucose; PET, positron emission tomography.

for MPNST, and the lifetime risk for MPNST could be as high as 10% (14). The majority of patients present in the second and third decades of life, and tend to be younger than their counterparts with MPNSTs in the general population (13). We have also identified MPNSTs in NF1 patients as young as 7 years and as old as 63 years of age. Clinicians should be alerted to the possible diagnosis of MPNST when a patient with NF1 develops unremitting pain not otherwise explained, rapid increase in size of a plexiform neurofibroma, change in consistency from soft to hard, or a neurological deficit.

Most NF1-associated MPNSTs appear to arise within preexisting plexiform neurofibromas. This observation suggests that individuals with NF1 and plexiform neurofibromas warrant increased surveillance for development of MPNST, and those with many or very extensive plexiform neurofibromas may have the highest risk. However, the natural history of plexiform neurofibromas has not been clearly defined, and these tumors may undergo periods of rapid growth followed by periods of relative quiescence. As such, rapid growth is not always a prelude to malignancy. This issue is currently being addressed by an international study using clinical assessment and volumetric MRI (Clinical Coordinator, Bruce Korf, Boston, MA).

There is no evidence that dermal neurofibromas or flat superficial plexiform neurofibromas undergo malignant transformation, and they do not require close monitoring. Nodular plexiform tumors associated with large peripheral nerve sheaths and extensive tumors involving the brachial, lumbar, or sacral plexus may give rise to MPNSTs and, therefore, merit heightened awareness. Plexiform neurofibromas, which are more centrally located and are more extensive, appear to have a higher likelihood of undergoing malignant change. Individuals with a "neurofibromatous" neuropathy might also have an increased risk of developing MPNST, because they develop dermal neurofibromas in early childhood and have diffuse plexiform involvement of the spinal nerve roots and peripheral nerves (15).

Patients in whom a microdeletion of the *NF1* locus is detected tend to have higher numbers of discrete dermal neurofibromas at earlier ages and might have a higher incidence of MPNST than the overall NF1 population (16). The increased risk of MPNST in this group could be readily tested by comparing the frequency of *NF1* microdeletions detected by fluorescence *in situ* hybridization of peripheral blood lymphocytes in NF1 patients with and without MPNST.

MPNSTs are often difficult to detect, because the clinical indicators of malignancy may also be features of active, benign plexiform neurofibromas. A MRI should be performed to locate the site, extent, and change in size of the plexiform neurofibroma, but it does not reliably determine malignant transformation. The diffuse nature of the plexiform neurofibroma may preclude total removal because of impingement on surrounding structures and neurological deficit.

PET with the glucose analogue ^{18}F FDG is a dynamic imaging technique, which permits the visualization and quantification of glucose metabolism in cells and reflects the increase in metabolism in malignant tumors (17, 18). A retrospective study of 18 NF1 patients demonstrated that ^{18}F FDG PET is a potentially useful, noninvasive method for detecting malignant change in plexiform neurofibromas (19). However, the distinction between low-grade MPNSTs and benign plexiform neurofibromas was not clear in all of the cases. It is recommended that a prospective study with clinical, radiological, and pathological correlation be undertaken to evaluate the value of ^{18}F FDG PET in the detection of malignant change in NF1. The new tracer ^{18}F -thymidine, which detects DNA turnover, might be helpful in distinguishing low-grade MPNSTs from active, benign plexiform neurofibromas in future PET-based studies.

Scrupulous documentation of information on NF1 patients with MPNST will play a vital part in optimizing the management of this condition. Data should be recorded in a standardized database, which

should be circulated to sarcoma units and to specialists in neurology, genetics, surgery, and oncology, who are likely to encounter these patients. Demographic details, confirmation of the diagnosis of NF1, history of cancer in the individual and family, clinical and radiological features of the MPNST, and pathological description of the tumor need to be included. Documentation of treatment modalities and outcome is essential. It is anticipated that molecular analysis of constitutional DNA and tumor material may play a pivotal role in determining therapeutic protocols.

Pathology Consensus Group. The options for diagnosis include fine needle aspiration, Tru-Cut needle biopsy, open incisional biopsy, and excisional biopsy. Fine needle aspiration is inadequate for the assessment of tumor type and grade, because dissociated tumor cells are obtained and architectural relationships lost. Tru-Cut needle biopsy is the method of choice when undertaken in a multidisciplinary team setting using expert radiological, surgical, and pathological advice. If sufficient tissue cores are taken and the specimen is sent fresh, techniques can be used such as imprint cytology to ensure that tumor tissue is present. Representative fresh tissue cores can be snap frozen in liquid nitrogen for molecular biological studies and research.

An open incisional biopsy provides more tissue for diagnosis and ancillary studies, but the sample is limited to one site. For this reason, it is necessary to ensure that the sample is representative and includes the areas suspected of malignancy. The combination of open incisional biopsy with multiple Tru-Cut needle biopsies from different areas may overcome this difficulty. This technique should be carefully planned so that future surgical resection margins are not compromised. An excisional biopsy should be reserved for small, superficially located tumors, which can be resected with a clear margin. This provides the most material for diagnosis and research. The technique of targeted biopsy using ^{18}F FDG PET and magnetic resonance registration is being developed in specialist centers and may be of potential benefit in the management of this group of heterogeneous tumors.

The minimum histological examination should comprise sections stained with conventional tinctorial stains including H&E and reticulin. In addition, immunohistochemical stains for S100 protein, the skeletal muscle markers desmin and myogenin, and a proliferation marker (MIB1) are required. Other spindle cell tumors may be excluded with appropriate immunohistochemical markers. In the future, there might be a place for the routine application of stains for known tumor suppressor genes or oncogenes (*p53*, *erbB2*, *p16*, and *p27*), for molecular analysis of NF1 and NF2 expression, and for determination of RAS activity (see "Molecular Biology Consensus Group").

The pathological features of MPNST reveal a fusiform or globoid mass associated with a nerve. Necrosis, pseudocystic change, or hemorrhage may be found. Histologically, the tumor is composed of spindle cells arranged in cellular fascicles (20). Divergent differentiation may occur, including rhabdomyoblastic change encountered in the malignant triton tumor variant (20, 21).

The pathological criteria for malignancy include invasion of surrounding tissues by tumor cells, vascular invasion, marked nuclear pleomorphism, necrosis, and the presence of mitoses (20). Even a single mitotic figure may be significant, particularly in a tumor with hypercellularity and nuclear atypia. The significance of the mitoses depends on the prognostic value of increased cell proliferation. Therefore, the most clinically relevant question is how best to determine malignant transformation in these tumors. The methods available for assessing growth rate include direct counting of observed mitotic figures, the estimation of proliferation index using immunostains, flow cytometry, other molecular techniques, or the detection of an imbalance between apoptosis and proliferation. The accurate prediction of biological behavior may depend on the interpretation of a combination of histological and immunohistochemical features.

There is a histological spectrum of peripheral nerve sheath tumors ranging from the clearly benign to the clearly malignant, and it is often possible to distinguish between high-grade and low-grade tumors. However, a significant number of tumors, the so-called “atypical neurofibromas” do not fit into any defined grading system (20, 22, 23). These may be locally aggressive but are less likely to metastasize. In addition, there are a few histologically low-grade tumors that behave aggressively. The application of molecular techniques to determine the gene expression profiles of gene expression in these tumors may help pathologists to predict biological behavior and outcome more accurately. The correlation with new imaging techniques may also help to resolve this issue.

Surgery Consensus Group. The aim of surgery is complete removal of the lesion with tumor-free margins (13). Biopsy of the lesion is essential before surgery is undertaken (see “Pathology Group” statement). Small lesions should be widely resected, and larger tumors should be as widely excised as possible (≥ 10 cm) to avoid centripetal spread. Reconstruction of the nerve after surgery for brachial and lumbosacral plexus lesions is not advocated, because it does not restore useful function and may compromise the adequacy of the surgical excision. Amputation may be indicated for extensive tumors and for MPNST, which recur after apparently adequate excision.

Patients should have baseline MRI 2–3 months after surgery. Additional imaging studies and their timing will depend on the patient symptoms and the nature of the primary tumor. ^{18}F FDG PET might be a useful screening investigation in the future, because it provides both a local and a body-wide scan within a single investigation for this group of “at-risk” patients.

Oncology Consensus Group. It is not clear whether patients with NF1 and MPNST have a different clinical course or response to treatment compared with their counterparts in the general population. The current management of MPNST should be identical to that of any other soft tissue tumor in that successful treatment depends on complete surgical excision. Radiotherapy provides local control and may delay the onset of recurrence but has little effect on long-term survival. Adjuvant radiotherapy should be given wherever possible for intermediate- to high-grade lesions and for low-grade tumors after a marginal excision.

Chemotherapy for adult soft tissue sarcomas is usually confined to the treatment of metastatic disease. Few drugs have been shown to be effective, and treatment comprises single agent doxorubicin or a combination of doxorubicin and ifosfamide (24). Although such treatment is not curative, it may achieve useful palliation for many patients, and complete, long-lasting remissions are observed in rare instances. Moreover, it may be useful in the preoperative setting to downstage patients with unresectable primaries.

MPNST appears to be of intermediate chemosensitivity, less responsive than synovial sarcoma, but more chemosensitive than refractory diseases such as alveolar soft part sarcoma. The partial response rate with the best available chemotherapy is likely to be in the range of 25–30% (24). Controversy surrounds the use of adjuvant chemotherapy. A meta-analysis has shown a significant benefit at 10 years in terms of progression-free survival for both local and distant relapse (25). However, the magnitude of any overall survival benefit is small ($\sim 4\%$ and not statistically significant). Chemotherapy might be used to improve local disease control for marginally resected lesions at sites where an adequate dose of radiotherapy is difficult to deliver.

Recent advances in sarcoma therapy have resulted from an improved understanding of the molecular biology of individual diseases. The discovery of mutations in the *c-kit* gene, resulting in overexpression of a constitutively activated c-kit molecule in gastrointestinal stromal tumors, has been of paramount therapeutic importance. This has not only resulted in CD117 overexpression becoming the hallmark

diagnostic test for this disease but has led to a new form of treatment for a disease that was hitherto untreatable. The receptor tyrosine kinase inhibitor STI571 (Glivec) is a potent inhibitor of KIT and has been reported to result in dramatic tumor regressions in these patients, which thus far appear to be durable (26).

Similarly, it is the hope that new agents, which target the RAS-RAF- mitogen-activated protein/ERK kinase-extracellular signal-regulated kinase pathway, may prove effective against MPNST in NF1. In these tumors, loss of the inhibiting function of neurofibromin results in increased p21-ras signaling. Anti-RAS pathway drugs include farnesyl transferase inhibitors, which block the ability of RAS to reach the membrane where it is activated (27). However, there are now specific inhibitors of targets downstream of RAS, such as mitogen-activated protein/ERK kinase, that are also being developed for clinical study. Given the success of Glivec, it is clear that tyrosine kinase inhibitors can be developed that are both selective and effective, and hopefully one of these agents will prove effective against MPNSTs.

Molecular Biology Consensus Group. Significant progress has been made in recent years in elucidating the molecular genetics and biology of MPNST in NF1. Surgical specimens and cell lines from patients with MPNST and NF1 exhibit loss of *NF1* gene (neurofibromin) expression and high levels of RAS activity (28–30). Studies of benign neurofibromas from NF1 patients have demonstrated that loss of *NF1* gene expression and increased RAS activation alone is not sufficient for MPNST formation, and that additional genetic alterations (p27-Kip1, p53, and p16) are required for malignant transformation (31–35). The generation of mice with targeted mutations in the *NF1* gene has confirmed this notion in that loss of *NF1* expression appears to be sufficient for the formation of tumors with pathological features of plexiform neurofibromas, whereas MPNST development is dependent on functional inactivation of p53 (36, 37).

Our ability to more accurately predict tumor behavior and response to therapy is likely to derive from studies aimed at defining the molecular changes seen in these tumors. A variety of different genetic alterations have been reported in MPNSTs, but it is not clear that any of these are causally related to tumorigenesis or malignant progression. Moreover, it is not known whether a subset of these changes will predict the clinical course or define whether a specific form of therapy is likely to be more efficacious. Additional research is required to define the intracellular signaling pathway abnormalities primarily responsible for plexiform neurofibroma or MPNST growth, and to delineate which specific downstream effectors of RAS mediate RAS mitogenic signaling. Similarly, research efforts to define the genetic changes in addition to *NF1* loss that are required for plexiform neurofibroma malignant transformation also may identify additional therapeutic targets for MPNST drug design. These studies have the potential to identify gene expression profiles that are specifically associated with particular MPNST subtypes or plexiform neurofibromas most likely to undergo malignant change (“molecular fingerprint”).

The importance of an international tissue bank for MPNSTs to facilitate basic science and translational research cannot be overstated. This would involve storing fresh-frozen specimens, corresponding normal nerve specimens when available, and normal tissue or blood, as well as paraffin sections. These specimens need to be well characterized pathologically and to be linked to molecular, pathological, and clinical-epidemiological patient data. Both NF1-associated and sporadic MPNSTs should be stored in this tumor bank to determine whether the noted molecular and clinical-epidemiological characteristics are similar in these two groups.

Conclusions. MPNST is a devastating complication of NF1, which should be managed by multidisciplinary teams of clinicians and

scientists with expertise in the diagnosis and treatment of this disease. Clinical and molecular genetic studies should identify NF1 patients who are at high risk of developing MPNST. The establishment of an international database will permit the standardized recording of clinical, pathological, and treatment data, and outcome measures. The development of imaging methods such as PET scanning will aid in distinguishing MPNST from benign plexiform neurofibromas. Recent advances in molecular genetics have provided exciting opportunities to develop targeted therapies for these tumors, which will be helped by the establishment of an international tissue bank. Our ability to translate these advances into rational clinical trials represents the challenge for the immediate future.

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APPENDIX

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