Multimodal Imaging in Neurofibromatosis Type 1-associated Nerve Sheath Tumors

Multimodale Bildgebung bei Neurofibromatose-Typ-1-assoziierten Nervenscheidentumoren

Key words
- NF1
- neurofibromatosis
- MPNST
- MRI
- PET

Abstract

Neurofibromatosis type 1 (NF1) is a neurogenetic disorder. Individuals with NF1 may develop a variety of benign and malignant tumors of which peripheral nerve sheath tumors represent the most frequent entity. Plexiform neurofibromas may demonstrate a locally destructive growth pattern, may cause severe symptoms and may undergo malignant transformation into malignant peripheral nerve sheath tumors (MPNSTs). Whole-body magnetic resonance imaging (MRI) represents the reference standard for detection of soft tissue tumors in NF1. It allows for identification of individuals with plexiform neurofibromas, for assessment of local tumor extent, and for evaluation of whole-body tumor burden on T2-weighted imaging. Multiparametric MRI may provide a comprehensive characterization of different tissue properties of peripheral nerve sheath tumors, and may identify parameters associated with malignant transformation. Due to the absence of any radiation exposure, whole-body MRI may be used for serial follow-up of individuals with plexiform neurofibromas. 18F-fluorodeoxyglucose positron-emission-tomography (FDG PET/CT) allows a highly sensitive and specific detection of MPNST, and should be used in case of potential malignant transformation of a peripheral nerve sheath tumor. PET/CT provides a sensitive whole-body tumor staging. The use of contrast-enhanced CT for diagnosis of peripheral nerve sheath tumors is limited to special indications. To obtain the most precise readings, optimized examination protocols and dedicated radiologists and nuclear medicine physicians familiar with the complex and variable morphologies of peripheral nerve sheath tumors are required.

Zusammenfassung


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Key points:
- Individuals with NF1 may develop benign and malignant nerve sheath tumors.
- Whole-body MRI is the reference standard to identify nerve sheath tumors in NF1.
- MRI provides a comprehensive characterization of the growth pattern, growth dynamics and extent of nerve sheath tumors.
- 18F-FDG PET/CT provides a sensitivity of 100% and a specificity of 77–95% for detection of malignant transformation.

### Table 1 NIH consensus criteria for diagnosis of neurofibromatosis type 1.

<table>
<thead>
<tr>
<th>criterion</th>
<th>value</th>
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<tbody>
<tr>
<td>≥ 6 café-au-lait spots</td>
<td>–</td>
</tr>
<tr>
<td>&gt; 5 mm for prepubescent children</td>
<td>–</td>
</tr>
<tr>
<td>&gt; 15 mm for postpubertal individuals</td>
<td>–</td>
</tr>
<tr>
<td>axillary or inguinal freckling</td>
<td>–</td>
</tr>
<tr>
<td>≥ 2 neurofibromas or ≥ 1 plexiform neurofibroma</td>
<td>–</td>
</tr>
<tr>
<td>≥ 2 Lisch nodules</td>
<td>–</td>
</tr>
<tr>
<td>defining osseous lesions</td>
<td>–</td>
</tr>
<tr>
<td>sphenoid wing dysplasia</td>
<td>–</td>
</tr>
<tr>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>dysplasia of the long bones</td>
<td>–</td>
</tr>
<tr>
<td>optic nerve glioma</td>
<td>–</td>
</tr>
<tr>
<td>primary relative with NF1 per the criteria specified above</td>
<td>–</td>
</tr>
</tbody>
</table>

NIH – National Institutes of Health.

### Introduction

Neurofibromatosis type 1 (NF1, von Recklinghausen’s disease) is an autosomal-dominant hereditary neurogenic disease with an incidence of 1:2500–1:3000 [1, 2]. However, roughly 50% of affected individuals develop NF1 through a de novo mutation. The first in-depth description of NF1 was published by Friedrich Daniel von Recklinghausen in 1882 [3], and standardized clinical diagnostic criteria have existed since 1987 (Table 1) [4], with genetic analysis – at least for diagnostic purposes – being required only in special cases.

The clinical appearance of NF1 is characterized by wide variability [5, 6]. Cutaneous clinical characteristics of NF1 include café-au-lait spots (light brown hyperpigmentation with smooth borders), axillary as well as inguinal freckling (freckle-like hyperpigmentation in areas usually not exposed to the sun) and Lisch nodules (benign iris hamartoma) [7–10]. Musculoskeletal abnormalities are frequently observed and include scoliosis (in 10–20% of individuals), osteoporosis with significantly elevated risk of fractures, pseudoarthrosis and diagnostically revealing deformations such as congenital sphenoid wing dysplasia and tiabial dysplasia [6, 7, 11, 12]. Common cardiovascular manifestations are a frequent arterial hypertension, hypertrophic cardiomyopathies, pulmonary artery stenosis and other congenital heart defects as well as NF1-associated vasculopathy with stenosis of the renal and cerebral arteries [6, 13, 14]. Central neurocognitive deficits such as visuomotor impairments are a common neurological symptom of NF1. For example, approximately 53% of children with NF have poor handwriting versus only 6% of children in the comparative population. Approximately 39% of children with NF1 have learning disabilities. There are also behavioral disorders and intellectual disabilities. For example, 6–7% of children with NF1 have an IQ below 70 versus 2% of the normal population, and up to 49.5% of children with NF1 develop ADHD [15, 16]. Peripheral sensorimotor deficits are observed particularly in cases of spinal nerve root tumors [7]. While several clinical signs of NF1 are already present at birth, other do not develop until later in the course of the disease. In particular, the number of cutaneous neurofibromas increases with age [9].

NF1 is caused by a germline mutation in the NF1 tumor suppressor gene, which is located on the long arm of chromosome 17 (gene locus q11.2) and codes for the cytoplasmic protein neurofibromin [6, 7]. The protein acts to some extent as a negative regulator of the Ras-proto oncogene, a key molecule for regulating cell growth [17]. Individuals with NF1 have a higher risk of developing a plethora of benign as well as malignant tumors, with peripheral nerve sheath tumors constituting the most common entity [4, 18]. Additional tumors associated with NF1 include, among others, optic nerve gliomas, gastrointestinal stroma tumors (GIST), rhabdomyosarcomas, pheochromocytomas and duodenal carcinoids [7, 19, 20]. Because these tumors in patients with NF1 have the same appearance with medical imaging as non-syndrome-related tumors, it is not necessary to further address such tumors in this survey article.

Neurofibromas constitute the key characteristic of NF1 and are benign schwannomas that develop in the area of the peripheral nerve sheaths and contain, in addition to neoplastic Schwann cells, fibroblasts, macrophages, mast cells and pericytes [18]. These neurofibromas are divided into four subtypes [5, 7]:

- **Cutaneous neurofibroma**: These tumors develop particularly during childhood and early adulthood, numbering several thousand per patient in extreme cases. In addition to the negative cosmetic impact, they can cause local pruritus due to the mast cells they contain [6]. No risk of transformation.

- **Subcutaneous neurofibroma**: Palpable subcutaneous tumors with no risk of transformation [6].

- **Spinal neurofibroma**: These tumors appear in individual or multiple nerve roots and are sometimes associated with sensorimotor deficits (Fig. 1) [21]. No risk of transformation.

- **Diffuse or nodular plexiform neurofibroma**: Plexiform neurofibromas appear in 30–50% of individuals with NF1, are typically present at birth and grow during adolescence [6, 7]. They expand over the length of a nerve, are rich in extracellular matrix and can exhibit infiltrative growth (Fig. 2) [22, 23]. As a result, they can cause pronounced symptoms through compression or destruction of neural structures [6, 23]. A focal malignant transformation into a malignant peripheral nerve sheath tumor can occur within a plexiform neurofibroma.

MPNST are highly malignant, aggressively metastatic tumors with an overall poor prognosis, early oncological reaction being the only curative option [18, 24]. These tu-
**Fig. 1** 20-year-old male patient with multiple spinal neurofibromas. $^{18}$F-FDG PET maximum-intensity-projection a without suspicious metabolism. Elevated glucose consumption of a neurofibroma within the left psoas muscle b, c. Hyperdense neurofibromas on non-enhanced CT d without elevated glucose metabolism e. Multiple spinal neurofibromas, hyperintense on T2w f-j.

**Fig. 2** 31-year-old female patient with multiple subcutaneous and plexiform neurofibromas: coronal T2w a, coronal T1w b, T2w maximum-intensity-projection c-g. Axial T2w h, T1w after contrast i, non-enhanced CT j, PET k and CT after contrast l showing a large plexiform neurofibroma (arrow).
neurofibromas form within preexisting plexiform neurofibromas [18]. Patients with NF1 have a cumulative lifetime risk of approximately 10% for developing an MPNST versus <0.1% for the general population [6, 18, 25]. The poor prognosis also makes early detection of a malignant transformation a must.

Importance of medical imaging for neurofibromatosis type 1-associated tumors

With regard to NF1-associated tumors, the key tasks of medical imaging are:

- Reliable detection of soft tissue tumors for identifying patients with plexiform neurofibromas (risk stratification) and for using as a basis for genotype-phenotype correlation studies (tumor burden), for example.
- Accurate determination of whether a tumor is benign or malignant to facilitate an early diagnosis of a possible malignant transformation. At the same time, however, reliable specific imaging characteristics must be identified to avoid unnecessary diagnostic tumor resections or biopsies with corresponding morbidity and possible mortality.
- Exact determination of the local spread of benign and malignant neurofibromas for visualizing complications, for facilitating ground therapy planning and for therapy monitoring.

Role of various imaging modalities for neurofibromatosis type 1

Magnetic resonance imaging (MRI)

Whole-body MRI allows, with the aid of T2-weighted sequences, automated evaluation of whole-body tumor burden in patients with NF1 [26–28]. At the same time, whole-body MRI allows the possible presence of plexiform neurofibromas to be evaluated (Fig. 2), thereby facilitating stratification of NF1 with identification of groups at risk of developing MPNST [29, 30]. In addition, MRI can contribute to diagnosing the type of peripheral nerve sheath tumors, where a series of image features are associated with MPNST (Tab. 2) [31–33]. However, these characteristics are not present in all MPNST and in some cases clearly overlap with those of benign PNST. Unlike the metabolic activity in 18F-FDG PET (Fig. 3), no singular criterion for reliable differentiation and deciding in favor of or against a performing a biopsy have been found for MRI. Thus the presence of two or more malignancy criteria described as significant is postulated to indicate performing a biopsy.[32]. In addition, criteria described in individual articles as being significantly associated with MPNST have not been reproducible in all studies. In some cases, characteristics ascribed to MPNST such as, for example, an irregular tumor shape were associated more with benign tumors in several studies [31, 35].

A characteristic criterion of peripheral nerve sheath tumors is the presence of what is referred to as target sign (Fig. 3), which is frequently present particularly in the case of subcutaneous neurofibroma. This is characterized by a central hypointense area in an overall homogenous hyperintense spaceoccupying lesion in T2w, and is attributed to a central accumulation of dense collagen-rich stroma [31]. In rare cases, however, this can also be observed with MPNST [33], e.g. when there is a central malignant transformation. A characteristic criterion of MPNST is a significantly larger tumor size compared to benign PNST. Demehri et al. measured a tumor size of 68 ± 18 mm for MPNST and 39 ± 23 for benign PNST. Other research groups yielded similar results, with an a priori threshold value of 5 cm frequently being used (Tab. 2) [31–33, 35]. This is explained by the fact that MPNST form within existing plexiform neurofi-

Tab. 2 Selected publications on diagnostic criteria for determining whether peripheral nerve sheath tumors in NF1 are benign or malignant using MRI [31–33, 35].

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td></td>
<td>MPNST</td>
<td>BPNST</td>
<td>p</td>
<td>MPNST</td>
</tr>
<tr>
<td>tumor size (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>941</td>
<td>691</td>
<td>0.07</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>irregular tumor size</td>
<td>79%</td>
<td>28%</td>
<td>0.02</td>
<td>n/a</td>
</tr>
<tr>
<td>unclear margins</td>
<td>68%</td>
<td>33%</td>
<td>0.03</td>
<td>n/a</td>
</tr>
<tr>
<td>intratumoral lobulation</td>
<td>63%</td>
<td>17%</td>
<td>0.007</td>
<td>n/a</td>
</tr>
<tr>
<td>intratumoral heterogeneity (T1w)</td>
<td>90%</td>
<td>50%</td>
<td>0.01</td>
<td>51%</td>
</tr>
<tr>
<td>irregular or peripheral</td>
<td>74%</td>
<td>33%</td>
<td>0.05</td>
<td>34%</td>
</tr>
<tr>
<td>contrast enhancement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>intratumoral cystic changes</td>
<td>21%</td>
<td>17%</td>
<td>1</td>
<td>39</td>
</tr>
<tr>
<td>peritumoral edema</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>29%</td>
</tr>
<tr>
<td>target sign</td>
<td>0%</td>
<td>67%</td>
<td>&lt;0.0001</td>
<td>n/a</td>
</tr>
</tbody>
</table>

MPNST – malignant peripheral nerve sheath tumors; BPNST – benign peripheral nerve sheath tumor; CE – contrast enhanced;

1 median

Fig. 3 11-year-old female patient with subcutaneous neurofibromas. Target sign: large subcutaneous neurofibroma (arrow) showing central hypodense area on non-enhanced CT a and corresponding hypodense area on T2w b.

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broma, thus resulting in an addition of existing benign tumor mass and malignant tissue portions. Furthermore, this is primarily a result, however, of the often late diagnosis. Poorly defined demarcation with surrounding tissue is another malignancy criterion [31, 33, 35]. However, this is likewise a relatively advanced sign of a malignant transformation, since in this case growth exceeding the capsule must be present, which – given the genesis of MPNST from plexiform neurofibromas – can be expected to appear late. An intratumoral lobulation in T1w can be observed in many MPNST, but also for 12 – 17% of plexiform neurofibromas [31, 33]. The lobulation apparently is rooted in the reticulated growth of the plexiform neurofibromas, which can involve multiple nerve fascicles and lead to a diffuse accumulation of densified nerves [22]. Another characteristic of MPNST is presentation of portions appearing hyperintense in T1w, which lead to an overall inhomogenous appearance of MPNST in T1w [31]. Histologically, this corresponds to intratumoral hemorrhagic areas [31]. An irregular contrast medium enhancement in T1w reflects the presence of various perfused tissue portions within a spaceoccupying lesion, suggests the presence of malignant tumor portions and is significantly associated with MPNST [31]. However, irregular contrast medium enhancement appears also with plexiform neurofibromas [31 – 33], which constitute histologically heterogeneous tumors. Constituting another malignancy criterion, peritumoral edema is present in 29 – 66% of cases of MPNST, yet can also be present with benign nerve sheath tumors [32, 35]. Intratumoral cystic changes in T2w as signs of, e.g., cystically degenerated infarctions with large neurofibromas were likewise associated with MPNST [32]. However, this finding was not reproduced in other studies [31, 33].

In addition to anatomical MRI sequences, quantitative MRI imaging techniques such as diffusion-weighted imaging (DWI) and dynamic contrast-enhanced MRI (DCE-MRI) can be used for characterizing nerve sheath tumors (Fig. 4).

DCE-MRI constitutes a quantitative method for evaluating tumor profusion, for which significantly different imaging patterns have been described particularly when it comes to differentiating benign and malignant soft tissue tumors [34]. In a current article, Demehri et al. observed that when DCE-MRI was used to examine 9 MPNST and 22 nerve sheath tumors, 50% of the MPNST exhibited an early arterial contrast medium enhancement, which, however, was discovered in only 11% of the benign peripheral nerve sheath tumors [35].

Fig. 4 35-year-old female patient with MPNST. Large lobulated head-and-neck tumor on coronal T1w a with restricted diffusion in the ADC map b, inhomogeneous signal on T2w and T1w with fat suppression c, d and signal reduction on DWI (b 100) e compared to the neurofibroma in the left M. erector spinae with target sign (arrow) c and higher ADC-value b.
To put it simply, diffusion-weighted imaging is based on the limited diffusion (random thermal motion of water molecules) owing to the high cell density in tumors [36]. For characterizing soft tissue lesions, the anatomical localization and observation of ADC values – in addition to the signal intensity in DWI – are critical [36]. In a study involving 31 histologically confirmed nerve sheath tumors, the minimal, yet not the median, ADC values were significantly lower in MPNST than in benign nerve sheath tumors. While a sensitivity of 100% and a specificity of 77% MPNST were identified at a minimum ADC value of $< 1.0 \times 10^{-3} \text{mm}^2/\text{s}$, even this limited specificity was observed only in tumors with a diameter of $\geq 4.2 \text{cm}$. An even lower specificity must be assumed for smaller lesions [35]. In another study involving 29 patients, MPNST exhibited in diffusion tensor imaging (DTI) a significantly lower diffusivity than benign tumors (0.900 ± 0.25 versus 1.848 ± 0.40 × $10^{-3} \text{mm}^2/\text{s}$; $p < 0.001$), with this difference not being significant for ADC values from DWI sequences [37]. Even though quantitative MRI parameters may possibly contribute to diagnosing nerve sheath tumors, the existing data is relatively limited, preventing the exact clinical value of these methods with regard to NF1-associated tumors from being definitively evaluated at this time.

Although the diagnostic differentiation of peripheral nerve sheath tumors in MRI can be complex in a single examination, serial MRI facilitates the detection of changes in the appearance of plexiform neurofibromas, which are then highly suggestive of malignant transformation [29]. Owing to its high soft tissue contrast, MRI provides superior detection of the extent of malignant and plexiform nerve sheath tumors as well as evaluation of the neighboring structures (Fig. 5), which is often indispensable for both planning possible surgical therapy and for precise follow-up, in the latter case also because of the absence of radiation exposure among a generally rather young patient population.

Table 3  Recommended SUV$_{\text{max}}$-thresholds for assessing whether peripheral nerve sheath tumors in NF1 are benign or malignant [26, 27].

<table>
<thead>
<tr>
<th>SUV$_{\text{max}}$-threshold</th>
<th>interpretation</th>
<th>consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.5</td>
<td>probably benign</td>
<td>–</td>
</tr>
<tr>
<td>2.5 – 3.5</td>
<td>needs to be tested</td>
<td>follow-up examination</td>
</tr>
<tr>
<td>&gt; 3.5</td>
<td>probably malignant</td>
<td>biopsy</td>
</tr>
</tbody>
</table>

Positron emission tomography / computed tomography (PET/CT)

As a combined metabolic-anatomic method, combined positron emission tomography / computed tomography (PET/CT) using the radiotracer $^{18}$F-Fluorodeoxyglucose (FDG) allows multiple relevant parameters of nerve sheath tumors to be recorded simultaneously. Because of the elevated glucose metabolism, MPNST (Fig. 6) can be detected with both high sensitivity and specificity [38]. At the same time, $^{18}$F-FDG PET/CT permits high-sensitivity whole-body staging in cases of MPNST. Simultaneous CT is highly valuable particularly in cases with typical osseous and pulmonary metastasis locations. For detecting MPNST, threshold values for SUV$_{\text{max}}$ are normally used (Table 3), with each nerve sheath tumor having an SUV$_{\text{max}}$ ≥ 3.5 generally being viewed as potentially malignant [38, 39]. According to the study consulted, the optimal SUV$_{\text{max}}$ varies also depending on the different acquisition protocols between 3.1 and 6.1, with specificities between 77 and 95% being achieved [38–42]. In NF1 patients, an unremarkable PET/CET excludes a malignant transformation with high likelihood, the negative predictive value of $^{18}$F-FDG PET/CT being as high as 100% in newer studies [39]. In addition, the metabolic activity (SUV$_{\text{max}}$) is a better predictor for overall survival than histological grading [43].

The specificity and thus the positive predictive value of $^{18}$F-FDG PET/CT is, however, not completely satisfactory for...
the detection of MPNST. This is due to the fact that in a portion of cases, plexiform neurofibroma can exhibit relevant glucose metabolism [38, 41]. In addition, other tumors associated with NF1—such as phaeochromocytoma or ganglioneuroma—exhibit in some cases pronounced glucose utilization [39, 44] and should thus be taken into consideration during differential diagnosis when they are found at the appropriate location. Cutaneous, subcutaneous and spinal neurofibroma show no relevant uptake of 18F-FDG. To improve the specificity of 18F-FDG PET/CT, modified acquisition protocols with the addition of delayed imaging and normalization of tumor metabolism on a reference tissue are used in addition to standard imaging techniques (Tab. 4) [38, 45–47]. For malignant tumors, it is postulated that tracer uptake increase over time [38]. With regard to the increased specificity resulting from delayed imaging, some studies showed positive results [38], while others showed no significant difference [47]. Normalizing tumor metabolism to a reference tissue should allow the balancing out of interindividual differences in physiological and physical factors which could influence an absolutely comparative SUV quantification, such as difference in blood sugar level or the time of acquisition following tracer injection [46]. According to a current article, it was thus possible to increase specificity from 80% to 90% by using a tumor-to-liver ratio with a threshold value of > 2.6 [45]. In another study by Chirindel et al., normalizing tracer uptake to liver activity allowed the specificity of the early imaging to be increased from 87% to 94% at high sensitivity, while the delayed imaging provided no significant increase in specificity over that of the early imaging [47]. Even if other PET radiopharmaceuticals such as the proliferation marker F-18 fluorothymidine (FLT) are available in principle for in vivo characterization of peripheral nerve sheath tumors and could measure potentially more specific parameters of a malignant transformation, there are currently no larger-scale studies in this regard involving patients with NF1.

Computed tomography (CT)
The role of CT in differentiating peripheral nerve sheath tumors is primarily the subject of older studies involving smaller patient populations [48, 49]. Neurofibromas can exhibit low density on CT. This is due to the presence of lipid-rich Schwann cells, transformed adipocytes, accumulation of interstitial fluid and cystic areas resulting from infarctions and necrosis, particularly in cases of larger and malignant nerve sheath tumors [48]. In addition, perineural fat tissue can be entrapped particularly with the growth of diffuse plexiform neurofibromas, thereby causing lower density values on CT [48]. In our experience, intratumoral density differences in computed tomograms are often already discernable without contrast medium (Fig. 3). After contrast medium is administered, many peripheral nerve

Fig. 6 27-year-old patient with MPNST. Coronal T2w a, coronal T1w b, 18F-FDG PET maximum-intensity-projection c, transversal PET d, transversal non-enhanced CT e and transversal CT after contrast f showing a inhomogeneous tumor with elevated metabolism.
sheath tumors exhibit an inhomogenous contrast enhancement, which is due not only to cystic areas, but also to regions of differing cellularity and collagen density [49]. The contrast enhancement and the inhomogeneous nature thereof do not allow reliable differentiation of benign plexiform and malignant tumors [49, 50]. Contrast-enhanced CT is widely used for NF1 in the process of tumor staging, particularly in conjunction with 18F-FDG PET/CT. Today, other use of contrast-enhanced CT is reserved essentially for special situations such as the further clarification of unclear findings gathered from MRI or PET (e.g., the exact location of the tumor in relation to blood vessels in cases of complex tumor locations) or for the imaging of subcranial tumors.

**Conclusions**

Whole-body MRI is the current reference standard for detecting soft tissue tumors in cases of NF1 and permits not only the reliable identification of individuals with plexiform neurofibromas, but also precise assessment of local tumor extent and evaluation of whole-body tumor burden. Multiparametric MRI can additionally provide a comprehensive characterization of peripheral nerve sheath tumors. It also allows parameters suggestive of MPNST to be detected with sensitivity. Because it involves no radiation exposure, whole-body MRI is suited for serial follow-up in NF1 patients. To optimally diagnose individuals with NF1, specialized examination protocols should be employed, and radiologists and nuclear medicine physicians should be familiar with the complex and variable morphology of peripheral nerve sheath tumors.

**References**


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**Table 4** Selected publications on diagnostic accuracy of 18F-FDG PET and PET/CT for assessing whether peripheral nerve sheath tumors in patients with NF1 are malignant or benign [38 – 41, 45 – 47].

<table>
<thead>
<tr>
<th>authors</th>
<th>number of patients</th>
<th>number of lesions (MPNST)</th>
<th>time of imaging</th>
<th>Quantified parameter</th>
<th>threshold value</th>
<th>median glucose utilization</th>
<th>sensitivity</th>
<th>specificity</th>
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<tr>
<td>Warbey et al. [38]</td>
<td>69</td>
<td>85 (21)</td>
<td>1.5 h.p.i.</td>
<td>SUV&lt;sub&gt;max&lt;/sub&gt;</td>
<td>&gt;2.4</td>
<td>n/a</td>
<td>n/a</td>
<td>100%</td>
</tr>
<tr>
<td>Salamon et al. [39]</td>
<td>50</td>
<td>164 (19)</td>
<td>1 h.p.i.</td>
<td>SUV&lt;sub&gt;max&lt;/sub&gt;</td>
<td>&gt;3.1</td>
<td>n/a</td>
<td>n/a</td>
<td>100%</td>
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<tr>
<td>Fermer et al. [40]</td>
<td>105</td>
<td>116 (29)</td>
<td>1–4 h.p.i.</td>
<td>SUV&lt;sub&gt;max&lt;/sub&gt;</td>
<td>&gt;Liver + no drop after 4 h</td>
<td>5.7±2.6</td>
<td>1.5±1.1</td>
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<tr>
<td>Benz et al. [41]</td>
<td>34</td>
<td>40 (17)</td>
<td>1 h.p.i.</td>
<td>SUV&lt;sub&gt;max&lt;/sub&gt;</td>
<td>≥6.1</td>
<td>12.8±8.6</td>
<td>2.3±0.7</td>
<td>94%</td>
</tr>
<tr>
<td>Salamon et al. [45]</td>
<td>49</td>
<td>152 (18)</td>
<td>1 h.p.i.</td>
<td>Tumor-liver-ratio</td>
<td>&gt;2.6</td>
<td>n/a</td>
<td>n/a</td>
<td>100%</td>
</tr>
<tr>
<td>Combemale et al. [46]</td>
<td>113</td>
<td>145 (40)</td>
<td>1 h.p.i.</td>
<td>Tumor-liver-ratio</td>
<td>&gt;1.5</td>
<td>n/a</td>
<td>n/a</td>
<td>97%</td>
</tr>
<tr>
<td>Chirindel et al. [47]</td>
<td>41</td>
<td>93 (24)</td>
<td>1 h.p.i.</td>
<td>SUV&lt;sub&gt;max&lt;/sub&gt;</td>
<td>≥3.3</td>
<td>5.1±3.4</td>
<td>1.9±0.9</td>
<td>92%</td>
</tr>
<tr>
<td>4 h.p.i.</td>
<td>SUV&lt;sub&gt;max&lt;/sub&gt;</td>
<td>&gt;3.8</td>
<td>2.3±1.2</td>
<td>96%</td>
<td>88%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 h.p.i.</td>
<td>Tumor-liver-ratio</td>
<td>&gt;2.7</td>
<td>n/a</td>
<td>n/a</td>
<td>92%</td>
<td>94%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 h.p.i.</td>
<td>Tumor-liver-ratio</td>
<td>&gt;4.3</td>
<td>n/a</td>
<td>n/a</td>
<td>96%</td>
<td>93%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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