Multimodal Imaging in Neurofibromatosis Type 1-associated Nerve Sheath Tumors
Multimodale Bildgebung bei Neurofibromatose-Typ-1-assoziierten Nervenscheidentumoren

Authors
J. Salamon1, V. F. Mautner2, G. Adam1, T. Derlin3

Affiliations
1 Department of Diagnostic and Interventional Radiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
2 Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
3 Department of Nuclear Medicine, Hannover Medical School, Hannover, Germany

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.

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.

Citation Format:

Zusammenfassung
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 (Tab. 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 tibial 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 resection being the only curative option [18, 24]. These tumors are highly malignant, aggressively metastatic tumors with an overall poor prognosis, early oncological resection being the only curative option [18, 24]. These tumors are highly malignant, aggressively metastatic tumors with an overall poor prognosis, early oncological resection being the only curative option [18, 24].

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

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

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Fig. 1 20-year-old male patient with multiple spinal neurofibromas. 18F-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, 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 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 (Tab. 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 neurofibromas, 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 (Tab. 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].

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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 $< 1.0 \times 10^{-3}$ mm$^2$/s, even this limited specificity was observed only in tumors with a diameter of $\geq 4.2$ 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 ($0.900 \pm 0.25$ versus $1.848 \pm 0.40 \times 10^{-3}$ mm$^2$/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

<table>
<thead>
<tr>
<th>SUV$_{max}$-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>
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### 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$_{max}$ are normally used (Tab. 3), with each nerve sheath tumor having an SUV$_{max} \geq 3.5$ generally being viewed as potentially malignant [38, 39]. According to the study consulted, the optimal SUV$_{max}$ 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 being as high as 100% in newer studies [39]. In addition, the metabolic activity (SUV$_{max}$) is a better predictor for overall survival than pathological grading [43]. The specificity and thus the positive predictive value of $^{18}$F-FDG PET/CT is, however, not completely satisfactory for

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**Fig. 5** 2-year-old female patient with plexiform neurofibroma. Large lobulated head-and-neck tumor on coronal T1w a with inhomogeneous signal on T2w b and intraspinal growth (T1w and T2w, c–e). $^{18}$F-FDG PET maximum-intensity-projection f without suspicious metabolism as seen on transversal PET g; corresponding non-enhanced CT h.
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](image-url) 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 enhance-
ment, 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 plexi-
form 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 re-
served 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 im-
age of subcranial tumors.

Conclusions

Whole-body MRI is the current reference standard for de-
tecting soft tissue tumors in cases of NF1 and permits not
only the reliable identification of individuals with plexi-
form neurofibromas, but also precise assessment of local
tumor extent and evaluation of whole-body tumor burden.
Multiparametric MRI can additionally provide a com-
prehensive 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
detected with sensitivity. Because it involves no radiation
mors. It also allows parameters suggestive of MPNST to be
hensive characterization of peripheral nerve sheath tu-
form neurofibromas, but also precise assessment of local
only the reliable identification of individuals with plexi-
form neurofibromas, with sensitivity.

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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</thead>
<tbody>
<tr>
<td>Warbey et al. [38]</td>
<td>69</td>
<td>85 (21)</td>
<td>1.5 h.p.i.</td>
<td>SUVmax</td>
<td>&gt; 2.4</td>
<td>n/a</td>
<td>n/a</td>
<td>100 %</td>
</tr>
<tr>
<td>Salomon et al. [39]</td>
<td>50</td>
<td>164 (19)</td>
<td>1 h.p.i.</td>
<td>SUVmax</td>
<td>≥ 3.5</td>
<td>8.4 + 3.2</td>
<td>2.6 + 1.2</td>
<td>100 %</td>
</tr>
<tr>
<td>Fer ner et al. [40]</td>
<td>105</td>
<td>116 (29)</td>
<td>1 + 4 h.p.i.</td>
<td>SUVmax</td>
<td>&gt; Liver + no drop after 4 h</td>
<td>5.7 ± 2.6</td>
<td>1.5 ± 1.1</td>
<td>89 %</td>
</tr>
<tr>
<td>Benz et al. [41]</td>
<td>34</td>
<td>40 (17)</td>
<td>1 h.p.i.</td>
<td>SUVmax</td>
<td>≥ 6.1</td>
<td>12.8 ± 8.6</td>
<td>2.3 ± 0.7</td>
<td>94 %</td>
</tr>
<tr>
<td>Salomon 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>Combem ale 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>Chiri ndel et al. [47]</td>
<td>41</td>
<td>93 (24)</td>
<td>1 h.p.i.</td>
<td>SUVmax</td>
<td>&gt; 3.2</td>
<td>6.5 ± 2.9</td>
<td>2.0 ± 0.9</td>
<td>92 %</td>
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<td>4 h.p.i.</td>
<td>SUVmax</td>
<td>&gt; 4.1</td>
<td>8.3 ± 3.8</td>
<td>2.3 ± 1.2</td>
<td>96 %</td>
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<td>92 %</td>
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<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>
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</tbody>
</table>

References
1 Lammert M, Friedman JM, Kluwe L et al. Prevalence of neurofibromato-
sis 1 in German children at elementary school enrollment. Arch Der-
matom 2005; 141: 71 – 74
2 Huson SM, Parber PS, Compston DA. Von Recklinghausen neurofibro-
matosis: a clinical and population study in south-east Wales. Brain
1988; 111: 1355 – 1381
3 Reynolds RM, Brown ning GC, Naw raz I et al. Von Recklinghausen’s neu-
1554
4 National Institutes of Health Consensus Development Conference
5 Fer ner RE, Huson SM, Thomas N et al. Guidelines for the diagnosis and
management of individuals with Neurofibromatosis 1 (NF1). J Med Ge-
et 2007; 44: 81 – 88
6 Williams VC, Lucas J, Babccock MA et al. Neurofibromatosis type 1 revis-
7 Hirbe AC, Catmann DH. Neurofibromatosis type 1: a multidisciplinary
8 De Schepper S, Bouneau J, Vander Haegen Y et al. Café-au-lait spots in
neurofibromatosis type 1 and in healthy control individuals: hyper-
pigmentation of a different kind? Arch Dermatol Res 2006; 297:
449 – 449
9 Duong TA, Bastuji-Garin S, Valeylie-Allanore I et al. Evolving pattern
with age of cutaneous signs in neurofibromatosis type 1: a cross-sectional
study of 728 patients. Dermatology 2011; 222: 269 – 273
10 Bailey S, Sloan JL, Pernov A et al. A quantitative assessment of the burden
and distribution of Lisch nodules in adults with neurofibromatosis
11 Jaremko JL, MacMahon PJ, Torriani M et al. Whole-body MRI in neuro-
rorofibromatosis: incidental findings and prevalence of scoliosis. Skele-
tal Radiol 2012; 41: 917 – 923
12 Elefteriou F, Kolanczky M, Schindeler A et al. Skeletal abnormalities in
neurofibromatosis type 1: approaches to therapeutic options. Am J
Med Genet A 2009; 149A: 2327 – 2338
13 Friedman JM, Arbiser J, Epstein JA et al. Cardiovascular disease in neuro-
rorofibromatosis 1: report of the NF1 Cardiovascular Task Force. Genet
Med 2002; 4: 105 – 111
14 Nguyen R, Mir TS, Kluwe L et al. Cardiac characterization of 16 patients

Salamon J et al. Multimodal Imaging in... Fortschr Röntgenstr 2015; 187: 1084–1092

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Derlin T, Hagel C, Mautner VF. Syndromic abdominal ganglioneuroma: a rare cause of false-positive findings in the F-18 FDG PET / CT in neurofibromatosis type 1. Fortschr Röntgenstr 2014; 186: 706 – 707

Salamon J, Veldhoen S, Apostolova I et al. 18F-FDG PET/CT for detection of malignant peripheral nerve sheath tumours in neurofibromatosis type 1: tumour-to-liver ratio is superior to an SUVmax cut-off. Eur Radiol 2014; 24: 405 – 412


Chirindel A, Chaudhry M, Blakeley J et al. 18F-FDG PET/CT qualitative and quantitative evaluation in NF1 patients for Detection of Malignant Transformation – comparison of early to delayed imaging with and without liver activity normalization. J Nucl Med 2015

