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

Alin Chirindel 1,2, Muhammad Chaudhry 1,3, Jaishri O. Blakeley 4, Richard Wahl 1

1. Russell H. Morgan Department of Radiology and Radiological Science, Division of Nuclear Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
2. Robert Koch Str.3, 79106, Freiburg, Germany, DKFZ- German Cancer Consortium Partner Site Freiburg, Department of Radiation Oncology Freiburg University, Germany
3. Johns Hopkins Aramco Healthcare, Dhahran, KSA
4. Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Corresponding author: Richard L. Wahl, MD
Russell H. Morgan Department of Radiology and Radiological Science, Division of Nuclear Medicine, Johns Hopkins University School of Medicine, Room 3223 JHOC. 601 North Caroline Street, Baltimore, Maryland, USA
e-mail: rwahl@jhmi.edu
Phone: +1-410-614-3764
Fax: +1-443-287-2933

Running title: Dual time-point PET/CT in NF1
Abstract

Objectives: 18F-FDG-PET/CT has shown increased accuracy compared to morphologic imaging in differentiating malignant peripheral nerve sheath tumors (MPNST) from benign neurofibromas (BNF) in patients with neurofibromatosis type-1 (NF1). Delayed 18F-PET imaging typically enhances malignant tumor to background. Our goal was to compare the effectiveness of (1) early (1-hour) and delayed (4-hour) 18F-FDG-PET/CT imaging in differentiating MPNSTs from BNFs in patients with NF1, (2) with and without liver activity normalization.

Methods: NF1 patients presenting new symptoms or enlarging lesions were clinically evaluated with early and delayed 18F-FDG PET/CT imaging. SULmax (maximum standardized uptake value derived for lean body) as well as SULmax/liver (lesion uptake adjusted to mean liver activity) were obtained for all sites identified with abnormal metabolic activity. Qualitative and quantitative evaluations, including ROC comparison of early and delayed imaging sessions, were carried out. Histopathology and clinical follow-up (1-9 years) were considered as gold standard.

Results: 41 NF1 patients with early and delayed 18F-FDG-PET/CT scans were identified and 93 lesions were retrospectively analyzed, representing 24 MPNSTs (all histologically confirmed) and 69 BNFs (26 histologically confirmed). Qualitative evaluation on early imaging showed sensitivity, specificity, PPV and NPV for separating MPNSTs from BNFs of 91%, 84%, 67% and 96% versus 91%, 81%, 63% and 96% on 4-hr delayed imaging. The mean SULmax was significantly higher for MPNSTs compared to BNFs on both early scans (6.5 versus 2.0, p<0.01) and delayed imaging (8.3 versus 2.3, p<0.02). However, SULmax overlap between benign and malignant lesions persisted even after normalization to mean liver activity. ROC-derived best SULmax cut-offs were 3.2 on early (AUC 0.973) and 4.1 on delayed scans (AUC 0.978). ROC analysis for SULmax/liver improved test specificity (94% vs 87%, p<0.05) on early and (93% vs 88%, p<0.05) on delayed imaging.

Conclusion: Qualitative interpretation of 18F-FDG-PET/CT discriminates MPNSTs from BNFs in NF1 patients with similar accuracy on both early and delayed imaging. Quantitative data showed better sensitivity on delayed acquisition and best test specificity with lesion-SULmax normalization to liver activity, more so than with delayed imaging at 4 hours.
Keywords: 18F-FDG-PET/CT; early and delayed; NF1; quantitative and qualitative
Introduction:

Neurofibromatosis type 1 (NF1) is one of the most common autosomal dominant Mendelian diseases with a worldwide estimated prevalence of 1/3000 (1). The NF1 gene (chr17q11.2) codes a protein called neurofibromin, which is part of the p21-ras oncogene family (2). Clinical features in patients with NF1 typically include café-au-lait spots, cutaneous and plexiform neurofibromas (BNF), optic glioma, Lisch nodules and bone dysplasia (3). Individuals with plexiform neurofibromas harbor an increased risk of transformation into malignant peripheral nerve sheath tumors (MPNST), with a relative lifetime risk of 8-13% (4,5).

Although of profound prognostic and therapeutic consequences, distinguishing between benign and malignant lesions proves to be difficult. Both benign and malignant lesions (especially in a synchronous context) have similar clinical manifestations such as changes in consistency or size, unremitting pain, or new neurological findings (6). Morphologic imaging cannot reliably differentiate benign from malignant transformed lesions, especially in tumors with significant heterogeneity (7). Accurate histological evaluation is often challenging due to tumor sampling error, leading to extensive and possibly repeated surgical interventions (8,9).

18F-FDG-PET/CT metabolic imaging has been shown to be able to detect soft tissue sarcomas, with positive correlation between tumor intensity uptake and histologic grade (10). However, when standard qualitative and quantitative 18F-FDG-PET was applied in NF1, mixed success was noticed due to both false negative and false positive identification of MPNST (11-14). Modifications to PET acquisition and post-imaging analysis have been attempted in order to improve test performance (Table 1), particularly by adding delayed PET imaging to the acquisition protocol and by lesion SUV normalization to normal tissue activity (11,14,15). The rationale for dual time PET imaging is that the activity within benign lesions reportedly typically plateaus after 30 minutes while malignant tumors have rising SUVs over approximately 4 h, allowing for a better separation (16). However, this approach has residual false positive and negative rates, it is resource intensive and it exposes the patients to additional radiation from CT.
Qualitative PET evaluation in patients with NF1 has demonstrated overall good sensitivity (89-100%) and specificity (72-95%) in differentiating BNF from MPNSTs (17-19), although an explicit set of criteria for accurate visual interpretation has never been validated. Quantitatively, several SUV cut-offs have been proposed to best detect and separate malignant from benign lesions in NF1 patients (Table 1). The wide range for these quantitative uptake thresholds (1.5-6.1) may be due to differences in acquisition protocols (different imaging time-points, partial volume effects), scanner performance and analysis methods (16,20). Such variability limits the use of 18F-FDG-PET in clinical practice.

At Johns Hopkins University, our practice has been to acquire whole body early (1-hr post injection) and delayed (4-hr from injection) imaging when possible for all NF1 patients. In this study we assess the utility of visual and quantitative criteria derived from early and delayed whole body 18F-PET/CT scans to discriminate BNFs from MPNSTs.

Material and methods

Patient population

This retrospective study of clinically acquired PET scans was approved by the institutional IRB committee. Radiology database was queried with the key words “NF1, neurofibromatosis or neurofibroma” from January 2003 until August 2013. Forty-one NF1 patients were identified with early (1-hour) and delayed (4-hours) PET scans and appropriate clinical data (Figure 1). A total of 74 early and delayed PET-sessions were evaluated, representing 41 baseline and 33 follow-up studies (18 patients with one follow-up, 6 with 2 and one patient with 3) with 93 lesions (24 MPNSTs and 69 BNFs) included (Table 2).

18F-FDG PET/CT acquisition

Following at least a 4-h fast, the patients received an intravenous injection of $[^{18}\text{F}]$ 2-fluoro-2-deoxy-D-glucose (18F-FDG) according to a weight-based formula (for adults 1.3x7.4MBq/Kg and for children 7.4MBq/kg) with mean injected activity of 566.1 MBq±181.3 (range 111-925). All 18F-
PET/CT scans were acquired with a vertex to toes protocol and were performed on a GE Discovery Rx-VCT (General Electric Medical Systems, Waukesha, WI) LSO-crystal, 64-slice scanner in 3D acquisition mode and 4.15 minutes per bed position. Reconstruction was performed using ordered subset expectation maximization algorithm, with 128x128 matrix, 21 subsets, 2 iterations, 3mm post reconstruction Gaussian filter, standard Z filter, 4.7 mm pixel and 3.27 mm slice thickness. PET data were reconstructed with and without CT-based attenuation correction and decay-corrected.

The mean baseline serum glucose was 93.1 mg/dl (±13.1) with mean uptake time of 65.3 min (±10.8) for the early and 248.3 min (±22.3) for the delayed scans.

**Qualitative lesion identification and evaluation**

Early 18F-PET/CT scans were evaluated by one board certified Nuclear Medicine physician with 18 months of additional clinical PET/CT fellowship training. Sites of abnormally increased metabolic activity were qualitatively dichotomized as either “suspected malignant” or “benign”. Interpretation criteria for malignant lesions were as follows:

“Intensity rule” = sites of abnormal metabolic activity associated with morphological lesions and demonstrating significantly more intense 18F-FDG uptake relative to liver activity

“Anatomic rule” = sites of metabolic activity, satisfying the “intensity rule”, without obvious morphological correlation, which were identified at concerning locations (musculature, nerve root/plexus) and/or appeared asymmetric compared to the contralateral side

All other sites of abnormal metabolic activity (with or without morphologic correlation) which did not satisfy the previously explained qualitative rules were read as “benign” lesions.

The qualitative evaluation for the delayed scans was carried out independently from the early qualitative analysis so that all the lesions could again be dichotomized as “benign” or “suspected malignant”.

**Lesion inclusion criteria**
On baseline early and delayed 18F-PET/CT scans lesions accepted for analysis were as follows: (1) all sites fulfilling the qualitative criteria for a “suspected malignant” lesion, (2) all additional sites with clinical or prior imaging suspicion for malignancy and (3) up to 5 lesions per scan which were qualitatively evaluated as “benign” lesions (if more than 5 “benign” lesions were identified, the most 18F-FDG avid or qualitatively concerning lesions were included).

On follow-up (7-29 months) early and delayed PET/CT scans were included (1) new and/or increasingly suspicious lesions on follow-up clinical/morphological examination and (2) new sites of metabolic activity satisfying the qualitative criteria for “suspected malignant” lesions.

The duplicate lesions from the initial scan which were not of clinical/imaging concern and which appeared stable on follow-up PET/CT scans were not included in the analysis.

Quantitative analysis

Standardized uptake value for lean body mass (SULmax) were measured on a GE Advanced Workstation (software 4.6), by placing a volume of interest (VOI) on the axial PET images with CT cross-reference to ensure correct lesion localization. We tried to minimize differences in measuring lesion activity by starting with a predefined VOI. When necessary, manual adjustments were applied to accommodate lesions’ extensions and to avoid potentially “contaminating” intense activity within adjacent normal tissue. The SULmax represented lesion highest SUL and was measured on both the early and delayed scans at the equivalent image level (20).

Mean liver uptake (calculated for each PET session) represented the average activity within a 30mm spherical VOI placed in the right middle lobe of the liver. Normalization of lesion-SULmax was performed to the corresponding PET-session liver activity (lesion SULmax/liver SULmean).

Statistical analysis

Histopathology from biopsy/surgery and clinical follow-up (median of 3 years; range 1-9 years) obtained from pathology department and chart review was regarded as gold standard. Sensitivity,
specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated using standard formulae. Descriptive statistics for lesion SULmax was performed using IBM SPSS software package (version 20.0).

Nonparametric Mann–Whitney–Wilcoxon tests as well as ROC curves were applied for comparative analyses, with a significance level of 0.05.

Results

Early and delayed PET/CT scans

Qualitative analysis:

There were 93 sites identified with abnormal metabolic activity, of which 89 were recorded from the 41 baseline and 4 from follow-up scans (Table 2).

Qualitative evaluation of the early imaging reported 60 sites as “benign” lesions and 33 as “suspected malignant”. Subsequent analysis of delayed 18F-PET/CTs showed 58 “benign” and 35 “suspected malignant”, hence, 2/60 “benign” readings from early evaluation were interpreted as “suspected malignant” on late evaluation. Final histopathology and clinical follow-up revealed 69 BNFs and 24 MPNSTs, with surgical excision/biopsy available for 26 of BNF and 24 MPNST. We acknowledge that histopathology data is not available for all benign lesions as patients are not routinely referred for surgery if indices suggest a benign lesion. However, all patients have been carefully evaluated and none of these lesions showed changes compatible with malignant transformation during clinical or imaging follow-up (median 3 years, range 1-9).

Correlation with pathology and clinical follow-up revealed 11 false positive (FP) and 2 false negative (FN) readings on early 18F-PET/CTs and 13 FP and 2 FN on delayed scans. The 2 discordant sites between early and delayed imaging proved to be FP readings on the delayed evaluation.

The sensitivity, specificity, PPV and NPV for detection of MPNST vs BNF on early images were 91% (95%CI 73-99), 84% (95%CI 73-92), 67% (95%CI 48-82) and 96% (95%CI 88-99),
respectively. On delayed images the sensitivity and NPV were similar with a slightly decreased specificity of 81% (95%CI 70-90) and PPV of 63% (95%CI 45-79).

Quantitative analysis:

The average early SULmax for the lesions identified on histology or follow-up as BNF was 2.0 (±0.9) and for those confirmed as malignant it was 6.5 (±2.9). On the delayed imaging the average BNF SULmax was 2.3 (±1.2) and average MPNST SULmax was 8.3 (±3.8). Nonparametric Mann-Whitney U-tests comparing the distribution and ranking of the SULmax values showed a statistically significant difference between BNF versus MPNST on both early (p<0.01) and delayed (p<0.02) PET scans.

However, no statistical difference was noticed between the early and delayed SULmax for either BNF’s (Z of -1.13, p=0.26) or MPNST’s (Z of -1.8, p=0.07). Whisker plots of SULmax for benign and malignant lesions from both the early to delayed imaging are displayed in Figure 2.

The mean value of BNF-SULmax change (delayed scans “minus” early scans) was 0.3 (±0.7) with a mean increase of 14% (range -41% to +110%). For MPNST lesions the average SULmax change was 1.9 (±1.2) corresponding to a mean 30% increase (range -6% to +70%). There was statistical significance for both absolute and percent change between the SULmax of BNF and MPNST (p<0.05).

When the BNF-SULmax values were adjusted to liver activity (lesion SULmax/liver SULmean), the mean absolute change became 0.7 (±0.7) and the mean percent change was 46% (±38). The mean liver-adjusted MPNST-SULmax absolute change was 3.0 (±1.6) and the mean percent change was 61% (±37). Statistical significance was reached only for absolute change (p<0.05) but not for the percent increase (p>0.09) between the liver-adjusted SULmax for BNF and MPNST.

Histograms of absolute SULmax change in BNF and MPNST lesions between delayed and early images are presented in Figure 3.

ROC analysis of lesion SULmax for the early PET/CT scans revealed AUC of 0.973 (95%CI 0.937-1.00, p<0.05), best SULmax cut-off of 3.2 (for 92% sensitivity and 87% specificity) and maximal sensitivity threshold of 2.5 (77% specificity). For the delayed imaging the AUC was 0.978 (95%CI 0.939-1.00, p<0.001), best SULmax cut-off of 5.0 (for 95% sensitivity and 89% specificity) and maximal sensitivity threshold of 4.0 (78% specificity).
0.947-1.00, p<0.05), with a best cut-off of 4.1 (96% sensitivity and 88% specificity) and a 100%-sensitivity threshold of 3.3 (81% specificity) (Fig. 4).

When lesion SULmax were normalized to liver activity, the AUC for early ROC evaluation was 0.970 with best SULmax of 2.7 (92% sensitivity and 94% specificity) and delayed AUC was 0.983 with a best SULmax cutoff of 4.3 (96% sensitivity and 93% specificity). When lesion/liver uptake was examined for 100% sensitivity, the cut-offs were 1.5 (51% specificity) on early scans and 3.5 (87% specificity) on late scans.

ROC analysis for the absolute and percent change of unadjusted lesion SULmax showed AUC of 0.899 and 0.742, respectively. For liver-normalized absolute and percent change the AUC was 0.921 and 0.638, respectively.

Discussion:

18F-FDG-PET has been reported to be a good, but imperfect, test for distinguishing benign from malignant tumors. Efforts to improve diagnostic performance of the test have included serial acquisitions and quantitative analyses beyond simple qualitative assessments. Our retrospective study evaluated the added benefit of late acquisition protocol as well as qualitative and quantitative interpretation of 18F-PET imaging to differentiate MPNST from BNF in patients with NF1 (14).

Visual evaluation of metabolic activity within lesions was performed in the context of regional background/liver uptake and it was adjusted toward the final radiologic interpretation according to the location and morphologic features from corresponding CT as this is consistent with clinical application of this technique. We achieved reasonable sensitivity and specificity (91% and 84%, respectively) for the early visual assessment (1-hr) with similar sensitivity and slightly decreased specificity (80%) for the delayed visual evaluation (4-hr). These results are consistent with prior reported performance values (11,12,14).

One intrinsic advantage of the qualitative approach is that no specific imaging process or patient information is required before attempting a successful interpretation. This method does not rely on lesion SUV measurement or fixed thresholding, which may vary substantially among scanners, reconstruction
protocols, display/analysis software and radiotracer uptake times (16,20). However, we observed that qualitative evaluation on delayed images did not improve PET diagnostic accuracy vs early images.

In fact, the slight drop in the performance of qualitative assessment on late imaging was driven by two false-positive readings, which were confirmed with histopathology (Fig.5). This highlights a caveat of visual interpretation on delayed images: the increasing contrast between lesion 18F-FDG uptake and decreasing physiologic liver and soft tissue background activity. Therefore, stable BNF metabolic activity can result in a more pronounced subjective interpretation with wrong classification of benign lesions and hence decreased specificity. We acknowledge that a multi-reader qualitative analysis may yield different results from current single-reader evaluation, although strictly predefined “qualitative interpretation criteria” should limit the extent of divergent reading.

In the quantitative evaluation we used the SULmax (derived from lean body mass) and not the more common SUVmax (derived from patient weight) as a more reliable measure of tissue activity to account for variation of individual body habitus (20). There was a significant difference between mean SULmax for benign vs. malignant lesions on both early (p<0.01) and delayed (p<0.02) imaging, which further supports the hypothesis that PET can be used as an imaging discriminator for BNF and MPNST in NF1. The mean SULmax for BNFs and MPNSTs were 2.0 (±1.0) and 6.5 (±2.9) on early PET scans and 2.3 (±1.2) and 8.3 (±3.8) on the delayed, respectively. Further work should evaluate lesion activity in the context of lesions’ size and “deep versus superficial” location.

Time dependent analysis of benign lesion activity showed an unexpected pattern with increasing SULmax from early to delayed imaging for 59% (41/69) of all benign sites. In fact, the absolute measure was more than 1 unit in 8 cases (7 with pathological correlate) and percent ΔSULmax was above 30% in 16 BNF cases (12 with histological proof). After normalization to liver activity even more benign sites had interval increased SULmax on delayed scans: 19 sites with absolute ΔSULmax/liver >1 unit and 44 sites with percent ΔSULmax/liver>30%. This is important to note as prior studies have described a rather universal pattern of decreasing 18F-FDG uptake in benign NF1 lesions (14,21). This observation of increased SULmax on late imaging even in pathologically confirmed benign lesions challenges the
hypothesis that late acquisition successfully overcomes the limitations in specificity of early 18F-FDG-PET.

For the malignant sites, our analysis showed increasing 18F-FDG uptake from early to delayed scans in all but one lesion (percent ΔSULmax of -6%) which was in fact identified on pathology as high grade malignancy. Therefore, universal interpretation of decreasing/stable 18F-FDG uptake as BNF and increasing uptake as malignant could lead to FN and FP in quantitative PET evaluation (Fig.6). Absolute and percent change ROC analysis showed best performance in differentiating malignant vs. benign for the absolute change liver adjusted SULmax (AUC 0.921). However, this was inferior to test performance directly from raw or liver-adjusted BNF and MPNST SULmax (AUCs 0.970-0.983).

Computed “best” joint operating cut-off points were 3.2 and 4.1 for early and delayed ROC curves, respectively. These are slightly higher than previously reported values (3.1 and 3.5, respectively) by Warbey et al.(22) even after accounting for different weight based formulas used to compute SULmax and SUVmax (23). Nevertheless, review of the literature (Table 1) demonstrates wide range of “best” SUVmax cut-points (1.5-6.1), suggesting that an inter-institutional standardization is advisable before any multi-center cooperation.

Two recent studies have proposed that normalization of lesion 18F-FDG uptake to liver activity could improve PET performance in NF1 patients. Salamon et al.(15) reported increased test accuracy (100% sensitivity and 90% specificity) when a threshold of lesion/liver>2.6 was employed, while Combemale et al.(13) reported best results (97% sensitivity and 76% specificity) for a threshold of lesion/liver>1.5.

When applied to our data, neither of these two normalized cut-off values appeared to improve 18F-PET performance in discriminating BNF from malignant lesions: the first suggested threshold missed too many MPNSTs (90% sensitivity) while the second generates unnecessary surgical interventions (51% specificity). In our study, the best liver-normalized cut-off was 2.7 on early imaging (92% sensitivity and 94% specificity) and 4.3 on delayed imaging (96% sensitivity and 93% specificity). Similar to SUVmax cut-points, lesion/liver thresholds will need to be selected and standardized at each institution and for each
trial based on the emphasis desired on sensitivity versus specificity. The liver normalization has considerable potential advantages over the absolute determination of lesion activity, as determining relative values is easier than determining absolute radiotracer uptake.

In summary, we found in 41 NF1 patients with early and delayed acquisition of 18F-FDG-PET and pathologic confirmation of diagnosis that for qualitative evaluation the addition of a delayed acquisition protocol did not substantially improve test accuracy in differentiating BNF versus MPNST. Further, direct comparison of lesion SULmax from early to delayed sessions was not helpful due to unpredictable and confounding increasing activity in >50% of BNF. ROC analysis did improve sensitivity over qualitative assessment and liver normalization had an incremental benefit for test specificity. These effects were similar for both early and delayed acquisitions.

Our data suggests that there is not significant additive information from late acquisition to off-set the patient burden of extended periods of fasting, additional radiation exposure or the institutional resource demands. Based on these results, we would suggest qualitative and quantitative assessment of 18F-FDG-PET at one hour with the understanding that applying this single imaging strategy alone will yield rare FP and FN results and therefore requiring multi-disciplinary collaboration for interpretation of the results in the setting of each clinical scenario. Calibration for liver activity thresholds and SUV max cut-points should be chosen based on center-specific validated data and according to clinical priorities (i.e. sensitivity versus specificity). Similarly, this means that if 18F-FDG-PET is to be applied to multi-center clinical studies, inter-center calibrations and intra-center reliability is required before 18F-FDG-PET could be used as an endpoint across sites and timepoints.

Conclusions

Qualitative interpretation of standard 18F-PET images (at 60 minutes) provides good clinical utility for distinguishing BNF from MPNST (91% sensitivity and 84% specificity) in NF1 patients.

Quantitative data provided better sensitivity on delayed imaging, yet the highest specificity was achieved with lesion-SULmax normalization to liver activity, more so than delayed acquisition.
Quantitation must be interpreted in the context of center-specific ROC analysis. Multi-institutional standardization is advised for setting a meaningful “best” SUV/SUL cut-off for future therapeutic clinical trials where 18F-FDG-PET is used as an endpoint.

Acknowledgment:
We would like to thank Julia Buchanan at Johns Hopkins for her helpful review and advice in preparation of this manuscript.
References:


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Figure 1

Flow-diagram showing the process of patients’ identification.

95 patients
after PET/CT database screening

68 patients
with established diagnosis of NF1

27 patients
excluded from study

41 patients
early and delayed PET/CT imaging

23 patients
other than NF1

2 patients
brain-only

2 patients
corrupted data
Figure 2
Whisker plots (median value with 1st and 3rd quartiles) for BNF and MPNST SULmax on early and delayed PET imaging (A-unadjusted, B-liver activity adjusted SULmax values)
Figure 3
Waterfall plots showing the absolute differences between early and delayed SULmax of BNFs (green bars) and MPNSTs (red bars) representing raw data (A) and liver adjusted data (B). An upward shift in all ΔSUL can be noticed with liver normalization, although a significant overlap between ΔSUL for BNFs and MPNSTs persists.
Figure 4
ROC diagrams for early (blue curves) and delayed (red curve) scans for the unadjusted (top row) and liver activity adjusted (bottom row) lesion SULmax.

AUC = 0.973 (95%CI 0.937-1.00)

AUC = 0.978 (95%CI 0.941-1.00)

AUC = 0.970 (95%CI 0.935-1.00)

AUC = 0.983 (95%CI 0.951-1.00)
Figure 5
Early PET/CT imaging (upper row) shows heterogeneously intense FDG uptake (early SULmax = 3.2) in a brachial plexus lesion (green arrows) which demonstrates increased intensity (delayed SULmax = 5.0) on delayed PET/CT imaging (lower row). Histology from surgical excision revealed a benign plexiform neurofibroma and the patient remained clinically asymptomatic on follow-up (>12 months).
Figure 6:
False negative interpretation with quantitative evaluation.
Early PET/CT imaging shows highly heterogeneous metabolic activity (early SULmax = 4.3) within the pelvis (red arrowhead) which persists albeit with slightly decreased intensity (delayed SULmax = 3.7) on delayed imaging (red arrow). Initial FNA was inconclusive and complete surgical excision showed MPNST. There are extensive bone deformities in this NF1 patient.
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*median; †21 sporadic disease; ‡from ROC; §average 108min; ‖average 252min
TABLE 2

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<td>BNF†</td>
<td>69 (26 on pathology)</td>
</tr>
<tr>
<td>MPNST‡</td>
<td>24 (24 on pathology)</td>
</tr>
</tbody>
</table>

* median; † benign neurofibroma; ‡ malignant peripheral nerve sheath tumor
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

Amin Chirindel, Muhammad Chaudhry, Jaishri Blakeley and Richard L. Wahl

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