

# Dual-time point <sup>18</sup>F<sub>2</sub>FDG-PET/CT imaging may be useful in assessing local recurrent disease in high grade bone and soft tissue sarcoma

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## Abstract

**BACKGROUND:** Sarcomas comprise 1% of malignant tumors in adults but represent a significant diagnostic and therapeutic challenge. Molecular imaging with <sup>18</sup>F<sub>2</sub>FDG PET/CT is a powerful modality in oncology. Its use for initial assessment, evaluation of response to therapy and recurrent disease in most tumors is essential for therapeutic decisions. Its indication in sarcomas is still controversial. One of the indications for PET/CT in sarcomas is detection of recurrences. Nowadays magnetic resonance tomography (MRT) has a crucial role in identification of local recurrences in soft tissue and bone sarcoma. <sup>18</sup>F<sub>2</sub>FDG-PET/CT may serve as a complementary method. Dual time point imaging (DTPI) has been studied for most tumors as a method for differentiating benign from malignant lesions. There is limited data on DTPI in sarcomas. Therefore we studied prospectively patients with suspected local recurrences in the treated area and used DTPI as a method for differentiating benign from malignant tissue. **The aim** of this study was to evaluate the ability of dual-time point PET/CT to enhance sensitivity, specificity, PPV, NPV and accuracy of <sup>18</sup>F<sub>2</sub>FDG PET/CT in high grade and low grade sarcomas.

**MATERIAL AND METHODS:** We conducted a dual-time PET/CT in 15 patients with suspected locally recurrent disease. The delayed scan was conducted on the 120th min in the suspected region. The interpretation of PET/CT was made both upon CT scan and metabolic scans. The percentage change over time per lesion was calculated (%DSUV). The increase in SUVmax with %DSUV > 10% in the late scanning was considered as indicative for malignancy. We assessed the sensitivity, specificity, accuracy, positive and negative predicting value of the interpretation of PET/CT at 60 min and 120 min. All of the patients were followed up for a period of 1–3 years after our examination, either with histologic results, or with an MRT scans.

**RESULTS:** The received sensitivity, specificity and accuracy of <sup>18</sup>F<sub>2</sub>FDG PET/CT interpretation at 120 min in high grade sarcomas were respectively 100%, 80% and 89%. By comparison, in low grade tumors at 120 min scan, these parameters were 50%, 75% and 66%.

**CONCLUSION:** These preliminary data suggests that dual-time imaging in sarcomas improves sensitivity and accuracy in identification of local recurrent disease in high grade sarcomas and have limited role in low grade sarcomas. Further research is necessary to confirm these results.

**KEY words:** soft tissue, bone sarcomas, dual- time-point imaging, <sup>18</sup>F<sub>2</sub>FDG-PET/CT, local recurrence

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## Background

Sarcomas comprise 1% of malignant tumors in adults. They are a large heterogeneous group of entities with different biologi-

cal behavior and the clinical diagnosis of such lesions can be very difficult. Molecular imaging with <sup>18</sup>F<sub>2</sub>FDG PET/CT (fluoro-deoxyglucose-positron emission tomography with computed tomography) is a powerful modality in oncology. Its use for initial assessment, staging, restaging, evaluation of response to therapy and recurrent disease in most tumors is essential for therapeutic decisions. It has been utilized as an alternative pretreatment imaging method for both soft tissue and bone sarcomas [1, 2]. Another use of <sup>18</sup>F<sub>2</sub>FDG-PET/CT is evaluation of response to chemotherapy. Definitive treatment of sarcoma is surgical resection. However, after surgical

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removal, 40% to 60% of the patients will develop local or distant recurrence. Detection of local recurrent disease is still a controversial indication for PET/CT in sarcomas. Nowadays magnetic resonance tomography (MRT) has a crucial role in identification of local recurrences in soft tissue and bone sarcoma. <sup>18</sup>FDG-PET/CT may serve as a complementary method, searching for metabolic activity in treated regions. The accumulation and metabolism of <sup>18</sup>FDG is dependent on many factors. Glucose-6-phosphatase, hexokinase and GLUT transporters appear to be most important. Dual-time-point imaging (DTPI) has been studied for most tumors as a method for differentiating benign from malignant lesions. There is limited data on DTPI in sarcomas. Therefore we studied patients with suspected local recurrences in the treated area prospectively using DTPI as a method for differentiating post treatment inflammation vs. local malignancy.

Our aim was to study the ability of dual-time-point PET/CT to enhance sensitivity, specificity, PPV, NPV and accuracy of <sup>18</sup>FDG PET/CT in high grade and low grade sarcomas.

## Materials and methods

### Patients

For a period of six years (2009–2015), we examined 15 patients with suspected local recurrent disease. The patients were two women and thirteen men, from 27 to 78 years old. The final verification was made by histologic results either with MRT scans and all of them were followed up clinically for a period of 1–6 years after our examination.

### Inclusion parameters

All of the patients had previously locally treated sarcoma and imaging findings suspicious for residual or recurrent disease from other imaging modalities. We performed 120 min scan in those patients who have been treated locally for sarcoma (excision, radiotherapy or alloplastic joint replacement) and had difficult for interpretation PET/CT 60 min scans. We conducted a second scan if the local SUVmax was 2.0 or higher but was not sufficient to be interpreted as a local recurrent disease. We included patients with soft tissue and bone sarcomas of different grades. The number of various histological subtypes of sarcomas according to the AJCC classification and their grading are summarized in Table 1. There were 8 patients with high grade tumors and 6 patients with low grade tumors.

**Table 1.** Type and grade of sarcomas in the examined patients

Type of sarcoma	n	Low grade (n)	High grade (n)
Hondrosarcoma	1		1
Liposarcoma	7	3	4
Ewing sarcoma	1		1
Malignant fibrous histiocyto	1		1
Leiomyosarcoma	2		2
Sinovial sarcoma	1	1	
Fibrosarcoma	1	1	
Osteosarcoma	1	1	

## Methods

The examination was held on Gemini TF PET/CT, Philips, equipped with 16 slice CT. We performed low-dose CT. The PET/CT scan was held at two time points, at 60 min and at 120 min. The early scan was obtained from the skull base to mid-thigh, whereas the second scan was acquired only for the area of interest.

PET/CT imaging was performed in patients three months after radiotherapy and one month after surgery or chemotherapy. All of the patients fasted for at least 6 h before the examination to ensure standardized glucose metabolism. At the time of <sup>18</sup>FDG administration, fasting plasma glucose values were lower than 150 mg/dL in all patients. Depending on the patients' weight, a dose of 185–555 mBq was administrated through a catheter inserted into an antecubital vein.

### Interpretation

The interpretation of PET/CT was made upon CT scan, metabolic scan and fused scans. We used SUVmax-based quantification for differentiation of benign from malignant lesions. Studies have demonstrated significant variability of SUVmax values in test-retest measurements, ranging from 6 to 10 percent [3] with increase in variability with higher SUVmax values. The percentage change over time per lesion was calculated (%DSUV). Zuang et al. published similar results in DTPI with PET/CT in a variety of tumors. The average SUV of the lesions in known cancer patients increased from 3.96 at the first time point to 4.72 at the second time point (+19.2% ± 9.6%; n = 31; P < 0.001) [4]. As reproducibility of SUVmax is subject to significant variation, we accepted as indicative for malignancy the increase in SUVmax with %DSUV > 10% in the late scanning. The sensitivity, specificity, accuracy; PPV and NPV were estimated in all of the patients and in the two groups — with low and with high grade tumors.

## Results

We assessed the sensitivity, specificity, positive (PPV), negative predictive value (NPV) and accuracy in all of the cases at 60 and 120 min and separately in high grade and low grade sarcomas at 120 min. Results are listed in Tables 2 and 3. The evaluation was made for PET/CT interpretations at 60 min and at 120 min.

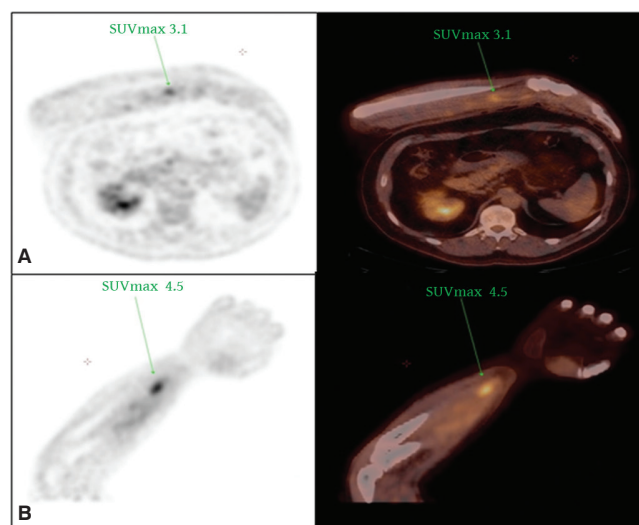
True positive results at 120 min were obtained in 3 patients with high grade tumors and in one patient with low grade tumor (Figure 1). True negative results were obtained in

**Table 2.** True positive, true negative, false positive and false negative results in patients at 60 min and 120 min, and in high and low grade sarcomas at 120 min

	All patients		High grade sarcomas	Low grade sarcomas
	60 min	120 min	120 min	120 min
TP	2	4	3	1
TN	5	8	5	3
FP	5	2	1	1
FN	3	1	0	1

**Table 3.** Results of the sensitivity, specificity, PPV, NPV and accuracy in all of the patients and in two groups of patients: with high grade and with low grade sarcomas

	All patients		High grade sarcomas	Low grade sarcomas
	60 min	120 min	120 min	120 min
Sensitivity	40%	80%	100%	50%
Specificity	50%	80%	83%	75%
PPV	29%	89%	75%	50%
NPV	63%	89%	100%	75%
Accuracy	47%	80%	89%	67%



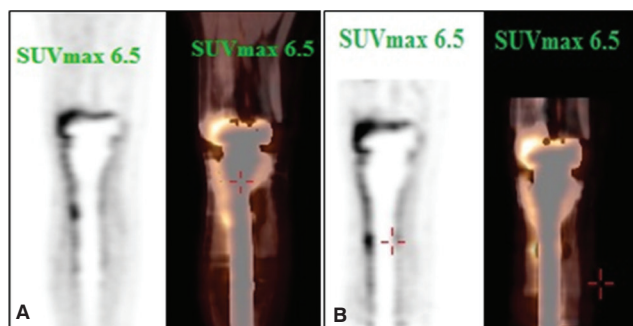
**Figure 1.** A patient with MFH of the right forearm: **A.** Equivocal 60 min scan with SUVmax in the operation area of 3.1; **B.** The 120 min scan was positive with SUVmax 4.5, later confirmed by histology as a recurrent tumor

5 patients with high grade tumors and 3 patients with low grade tumors (Figure 2).

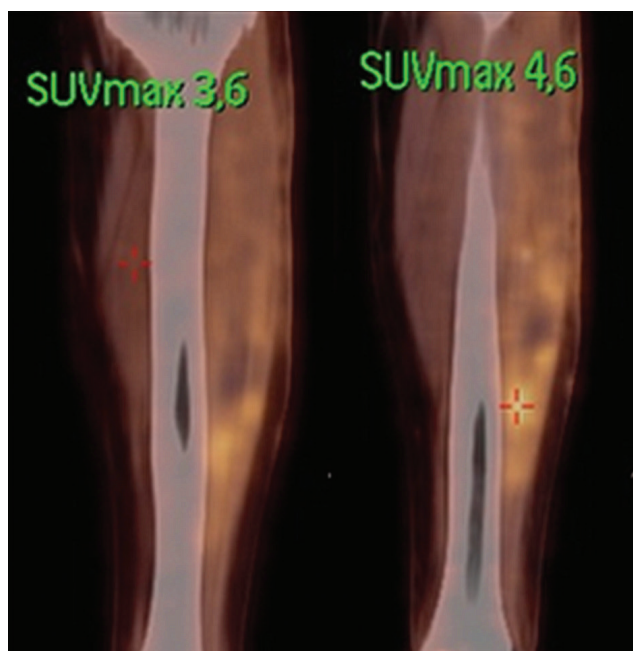
The 120 min scan was not helpful to reveal two of the false positives at 60 min PET/CT scan. (Figure 3 and 4) These two cases, one in high grade and one in low grade group, significantly raised their SUVmax at 120 min. Both of the cases were with chronic osteomyelitis after local treatment — one after the tumor excision and the other after excision and radiotherapy.

There were three cases of **false negative** PET/CT interpretations for recurrent disease at 60 min scan because of low to medium SUVmax 2.8–3.1. The three of them became positive at the 120 min scan with SUVmax increase of 39–42%. All of them were high grade tumors. There was only one case with low grade tumor and false negative result at 120 min. The 60 min scan was correctly interpreted as positive. It was with inhomogeneous uptake in the treated area and SUVmax 3.1 at 60 min scan suspicious for recurrent disease. SUVmax did not increase at 120 min. and was interpreted falsely as negative. That patient had many local recurrences followed by local excisions. After the histology result it was proved to be tumor tissue.

The total sensitivity of the 60 min PET/CT scan for determination of a recurrent disease was only 40%. By the 120 min scan



**Figure 2.** A patient with high grade chondrosarcoma five years after chemotherapy and tumor excision with alloplastic replacement of the right knee joint; **A.** (Early scan) Although the high SUVmax at 60 min scan — 6.5, at the late scan (**B**) this value did not change — true negative result. This person was followed up for 5 years without recurrent disease

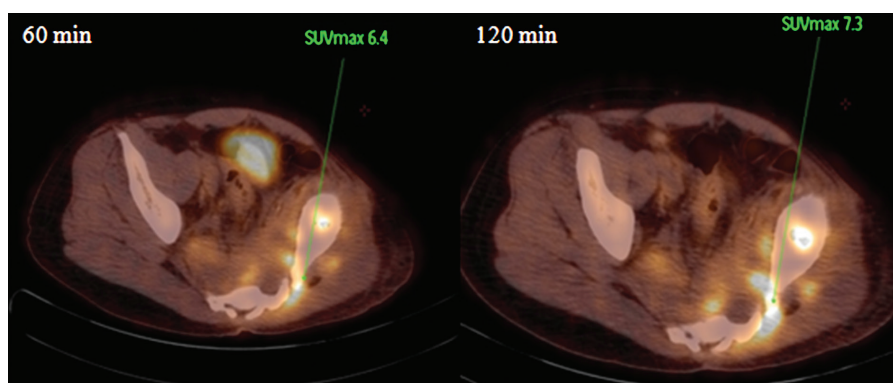


**Figure 3.** A patient with low grade fibrosarcoma three months after tumor excision and fibular resection. The 120 min scan showed 27.8% increase in activity in the primary tumor area. The result was proved false positive, as the patient had no tumor tissue but only inflammatory cells

methodology, we managed to determine the recurrent disease in all of the patients with high grade sarcomas and only in 50% in those with low grade tumors. The specificity of the method was better for high grade sarcomas 83%. The specificity was reduced because of the false positive results in two patients with chronic osteomyelitis.

The PPV was better in patients with high grade sarcomas — 75% vs 50% in low grade sarcomas. The NPV was better in the late study; in high grade sarcomas it was 100%, revealing all of the patients without disease.

Accuracy in identifying recurrent disease in high grade sarcomas, using the dual-time-point PET/CT scan was 89%, vs. 67% in low grade sarcomas.



**Figure 4.** A patient with Ewing sarcoma 18 years after operation and radiotherapy. A fracture of the left iliac bone is seen. The SUVmax at 120 min scan increased by 14.1% — a false positive result, due to chronic osteomyelitis

## Discussion

PET/CT was studied as a helpful instrument for initial assessment in sarcoma, but also for evaluation of response to therapy [5] and detection of recurrences in STS (soft tissue sarcoma) and BS (bone sarcoma). During the initial workup of sarcomas, MRT provides better description and definition of the local extent of the tumor. PET/CT has been found to be useful in prognostication, grading and assessing response to chemotherapy [2, 6, 7]. SUVmax has been shown to correlate with tumor grade and progression [8, 9]. Lodge et al. [10] noted that in high grade sarcomas, the maximal  $^{18}\text{F}$  uptake is reached at 4 h whereas benign lesions achieve such values within 30 min. False negative findings were often found in low grade sarcomas.

We used SUVmax-based quantification for revealing malignant lesions in the treated area of the primary tumor. Studies have demonstrated significant variability of SUVmax values in test-retest measurements, ranging from 6 to 10 percent [3, 4] with increase in variability with higher SUVmax values. Evaluating the DTPI value in lung nodules, Matthies et al concluded that dual-time-point scanning with a threshold value of 10% increase between scan 1 and scan 2 reached a sensitivity of 100% with a specificity of 89% [11]. We also accepted that a change of SUVmax higher or equal to 10% was significant for interpretation of malignancy at the 120 min scan.

The logic behind delayed  $^{18}\text{F}$  PET/CT imaging is based on the known fact that most types of malignant cells have significantly increased ratios of hexokinase to glucose-6-phosphatase activities, which allow  $^{18}\text{F}$ -deoxyglucose-6-phosphate to accumulate to a much higher level over time than in the normal cells. There is insufficient data on the role of PET/CT in patients with suspected recurrent sarcoma after local therapy. In rhabdomyosarcoma PET/CT was found useful for detecting recurrent disease in treated patients. [12] It may be useful for initial staging too because of the possibility of nodal metastases and unknown distant metastases. In these patients management intent may change from curative to palliative, thereby sparing patients the morbidity associated with non-beneficial aggressive treatment. A few articles are focused on the performance of DTPI and delayed time-point imaging in assessing residual/recurrent lesions after therapy in breast cancer and in head and neck cancer [13, 14]. PET/CT should avoid unnecessary biopsy through ruling out residual or recurrent active

disease. Patient outcomes may be improved through reduced treatment morbidity.

The major value of DTPI is the increased **sensitivity** due to continued clearance of background activity and continued  $^{18}\text{F}$  accumulation in malignant lesions. In order to homogenize the groups of patients, we divided them into two groups — with low and high grade sarcomas. In our investigation, we had only one false negative result at 120 min in low grade sarcoma, and no false negatives in high grade sarcomas. All of the **false negative** high grade sarcomas at 60 min turned to **true positives** at 120 min scan, which was the most important achievement in our investigation. The yielded sensitivity at 120 min increased from 40% to 80% for all cases. In high grade sarcomas group we managed to reach 100% sensitivity at 120 min, which was significantly better result than in the low grade sarcomas group only 50% ( $p = 0.034$ ). Tumor heterogeneity, the small size of the recurrent tumor and low grade tumor (low metabolic activity) may contribute to variable performance of DTPI  $^{18}\text{F}$  PET/CT imaging [15, 16]. Tumor heterogeneity is based on variations in tumor cells (tumor genotype, differentiation) or in the environment (stromal matrix and tumor location, tissue vascularity and tumor size, and immune status, etc.). Tumor heterogeneity in sarcomas is very often. In our cases the only false negative result at 120 min was a patient with many recurrent episodes and treatments. He had a low grade tumor. This suggested the limited value of DTPI for the characterization of non- $^{18}\text{F}$  avid tumors which was reported also in pancreatic cancer with low SUVmax [17].

Dual-time-point imaging has been used to increase **specificity** of  $^{18}\text{F}$  PET for discriminating benign from malignant lesions. That is exceptionally important in the treated area, where operations and local radiotherapy may cause inflammatory comp-point  $^{18}\text{F}$  PET imaging in this regard, and the technique has been studied in a wide variety of malignancies, including those of head and neck [18], lung [11], breast [19–21], gallbladder [22], cervix [23] and glioma [24]. In all of them authors concluded that delayed  $^{18}\text{F}$  PET imaging is more helpful than early scans for evaluating malignant lesions. However, exceptions exist, and some studies have demonstrated significant overlap of  $^{18}\text{F}$  uptake patterns between benign and malignant lesions on delayed time-point images. In many of these studies, dual time point PET improved both the sensitivity and the specificity of PET/CT. This can be explained by two factors: while continuing increased uptake in the malignant lesions allows differentiation from benign lesions with higher specificity, increased

lesion-to-background leads to higher sensitivity with this method. In the majority of normal tissues (the blood pool, liver, spleen, lungs, pancreas, inguinal nodes, and skeletal muscles),  $^{18}\text{F}$ FDG uptake decreases significantly from 1 to 3 h after radiotracer injection, although SUV remains stable in some tissues (parotid gland, thyroid gland, and prostate gland) and increases in other tissues (myocardium and bone marrow) [25].

The specificity of this method in our study was increase from 50% in all cases to 80% at 120 min imaging. In high grade tumors group our study reached specificity 83% at 120 min scan (60 min scan specificity in this group was 67%). The specificity in low grade tumors group also was better at 120 min scan (75% vs 25% in early scan). We could not reduce two of the false positive results with chronic post treatment inflammation. All of the **true negatives** in both groups at 60 min scan remained TN at 120 min scan. Our method was useful to reveal three of the true negatives: two cases after tumor excision and one with alloplastic joint and high SUVmax at 60 min scan. At the late scan the SUVmax did not change or lowered, with 19% in a low grade liposarcoma.

There are numerous reports in the literature of **false-positive** findings on  $^{18}\text{F}$ FDG PET imaging due to granulomas or active inflammation. The granulomas may arise many years after the initial trauma or procedure in the form of tumor-like soft-tissue masses [26–28]. Multiple studies have indicated that lesions of active inflammation and infection may have higher  $^{18}\text{F}$ FDG activity on DTPI, similar to that in malignant lesions, thus resulting in sub-optimal diagnostic performance of DTPI [29–31]. There were two false positive cases among our patients, both with osteomyelitis, which remained false positive at late scans. Respectively, their SUVmax values were: SUVmax (60 min) 3,6/SUVmax (120) 4.6 and SUVmax (60 min) 6,4/SUVmax (120) 7.3. This was a change in the SUVmax with respectively 27.8% and 14.1%. This results in future indicates the need for more careful selection of the patients for PET/CT scan and necessity of histologic confirmation after PET/CT positive findings. On the other hand, our methodology was able to resolve the problem with the metabolic active lesions at 60 min scan in three cases with active inflammation. One of the cases was a patient after alloplastic joint replacement with SUVmax (60 min) 6.5. This value stayed the same at 120 min scan and was interpreted as a negative for recurrent disease, lately confirmed by 3-year follow up. Another case was a patient with low grade tumor excision in whom SUVmax (60 min) was 4.2. After the late scan it decreased by 19% — SUVmax (120 min) 3.4. The third case also had a stable SUVmax value at the early and delayed scan (SUVmax 2.9) and was interpreted as negative after the 120 min scan. It was a patient with a high grade tumor. All of these data showed that increased  $^{18}\text{F}$ FDG uptake on delayed time-point images should not be used as the sole criterion in interpreting  $^{18}\text{F}$ FDG PET studies. Correlation with other imaging findings, as well as the patient's history, should also be taken into consideration. And the late scans could improve the specificity both in high grade and low grade sarcomas.

The **PPV** was very low at 60 min scan for all patients — 29%, which was because of too many complicated cases with false positive scans at that time point. Our methodology managed to increase the PPV — from 29% to 67% at 120 min scan, resolving 3 of 5 cases with false positive and all three false negative 60 min scans (changing the classification into true positives). In high grade sarcomas group the gained PPV was 75% vs. 50% in low grade tumors group.

In different studies the NPV of  $^{18}\text{F}$ FDG-PET/CT in revealing recurrent disease varies from 75 to 100%. Other studies did not separate the subjects into groups according to their tumor differentiation. In our investigation NPV was 100% in high grade sarcomas at 120 min scan compared with 63% at 60 min scan and 89% at 120 min scan in all patients. In low grade tumors the NPV was 75%. At 120 min scan three of the false positive subjects turned into true negatives, because the SUVmax value did not change or got lower. Other false positives at 60 min were two cases with inflammatory complications. Excluding those two subjects, our methodology was useful for revealing all of the patients without recurrent disease.

Accuracy of the method also improved the values in the whole group — 47% at 60 min scans and 80% at 120 min scans. It was again better, although not significantly, in high grade tumors group 89% vs. 67% in low grade tumors.

## Conclusion

Most malignant (and some inflammatory) lesions have increased  $^{18}\text{F}$ FDG uptake on delayed time-point images. Our study suggests that dual- time  $^{18}\text{F}$ FDG-PET/CT in sarcomas might have a valuable role in detecting local recurrent disease in high grade sarcomas, as the sensitivity of the method gained significantly better results than in low grade sarcomas group at the same time point. The specificity, PPV and NPV are better in patients without late radiation and surgery complications. Accuracy was also better in high grade sarcomas. These results suggest that we must carefully select the patients for late PET/CT scan and have thorough information about current inflammations in the treated area.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

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