Comparison of ^{11}C-Choline and ^{11}C-Methionine PET/CT in Multiple Myeloma

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Purpose: PET/CT with both ^{11}C-choline and ^{11}C-methionine has recently been reported to offer advantages over ^{18}F-FDG for imaging in multiple myeloma (MM). The aim of this study was to directly compare the diagnostic performance of both non-FDG radiotracers in MM patients.

Methods: Nineteen patients with a history of MM (n = 18) or solitary bone plasmacytoma (n = 1) underwent both ^{11}C-choline and ^{11}C-methionine PET/CT for diagnostic imaging. In this retrospective analysis, scans were compared on a patient and on a lesion basis. In 12 patients, respective tracer uptake in the iliac crest was correlated with the extent of malignant bone marrow plasma cell infiltration.

Results: ^{11}C-methionine detected more intramedullary MM lesions in 8 (42.1%) of 19 patients. In the remainder (11/19 [57.9%]), both ^{11}C-choline and ^{11}C-methionine provided equal results. ^{11}C-methionine demonstrated higher lesion-to-muscle ratios ($P = 0.0001$). In the 12 patients in whom a recent bone marrow biopsy was available, SUVmean as well as SUVmax correlated significantly with the degree of malignant plasma cell infiltration for both ^{11}C-methionine (SUVmean: $r = 0.85$, $P < 0.001$; SUVmax: $r = 0.82$, $P = 0.001$) and ^{11}C-choline (SUVmean: $r = 0.72$, $P < 0.008$; SUVmax: $r = 0.73$; $P = 0.006$).

Conclusions: Our data suggest that ^{11}C-methionine PET/CT might be more sensitive than ^{11}C-choline PET/CT for the detection of active MM lesions.

^{18}F-FDG PET/CT is the standard nuclear medicine technique in multiple myeloma (MM) and has been increasingly used in the management of MM patients, particularly in prognostication and response assessment.[1–9] However, limitations of FDG PET/CT include lack of sensitivity and specificity, for example, in cases with diffuse bone marrow (BM) infiltration, low hexokinase-2 expression (false-negative), or with inflammatory lesions (false-positive).[10–12] To overcome some of the limitations of FDG, pilot studies have investigated the suitability of newer non-FDG PET tracers targeting different metabolic pathways or receptors on the myeloma cell surface. We and others have reported on the superiority of the radiolabeled amino acid L-methyl-^{11}C-methionine for both disease detection and very early response assessment in MM.[13–19] Other alternatives include ^{68}Ga-pentixafor for imaging *C-X-C* motif chemokine receptor CXCR4 expression on the myeloma cell[20–22] as well as ^{11}C-acetate[23,24] and ^{11}C- or ^{18}F-labeled choline[25,26] as markers of cell membrane proliferation/turnover. However, a direct comparison of these non-FDG tracers has yet to be performed. This study aimed to compare ^{11}C-methionine and ^{11}C-choline PET/CT in patients with advanced MM.

MATERIALS AND METHODS

^{11}C-choline and ^{11}C-methionine were administered under the conditions of the pharmaceutical law (German Medicinal Products Act, AMG §13 2b) and in accordance with the responsible regulator bodies (Regierung von Oberfranken). All patients gave written informed consent to ^{11}C-choline and ^{11}C-methionine PET/CT imaging.

Patients

Nineteen patients (12 males, 7 females; aged 42–82 years; mean age, 60 ± 11 years) with pretreated MM (n = 18) or solitary bone plasmacytoma (n = 1) were enrolled. All MM patients had been pretreated with various (chemo)therapeutic regimens including proteasome inhibitors and immunomodulatory drugs (median, 2 lines of previous treatment; range, 1–4). Fourteen of 19 subjects had undergone tandem autologous stem cell transplantation. The patient with solitary bone plasmacytoma had received external beam radiation for the solitary lesion.

At the time point of PET/CT scanning, information on degree of myeloma BM infiltration based on iliac crest biopsy was available in 12 of 19 patients. The median interval between BM biopsy and first PET imaging was 10 days (range, 0–31 days), with no therapy administered in between. No extramedullary disease was known in any of the patients. Patients' characteristics are given in Table 1.

PET/CT

^{11}C-choline and ^{11}C-methionine were synthesized in-house with a 16-MeV Cyclotron (GE PETtrace 6; GE Healthcare, Milwaukee, Wis). Imaging was performed on an integrated PET/CT scanner (Siemens Biograph mCT 64; Siemens, Knoxville, Tenn) with a time interval between the scans of 1 day in 14 of the 19 patients and 2, 3, 7, 9, and 10 days in the other 5 patients.

^{11}C-choline (719 ± 86 MBq) and ^{11}C-methionine (656 ± 121 MBq) were injected intravenously. CT scans were acquired after 5 minutes (^{11}C-choline) or 20 minutes (^{11}C-methionine),

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All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.
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TABLE 1. Patient Characteristics

Patient	Sex	Age, y	Myeloma Type	Cytogenetic Risk	Previous Lines of Therapy	Autologous SCT	Reason for Imaging	^{11}C-Methionine Positive	^{11}C-Choline Positive	More Lesions
1	F	51	Asecretory	N/A	2	None	Disease progression	Yes	Yes	equal
2	M	76	IgGκ	Standard	1	None	Disease progression	Yes	Yes	^{11}C-MET
3	M	48	LCλ	Standard	1	2	Disease progression	Yes	Yes	^{11}C-MET
4	F	82	IgGκ	N/A	3	None	Disease progression	Yes	Yes	equal
5	F	71	IgGκ	High	4	None	Follow-up	Yes	Yes	^{11}C-MET
6	F	60	Asecretory	N/A	3	2	Disease progression	Yes	Yes	equal
7	M	72	IgGκ	Standard	2	2	Disease progression	Yes	Yes	^{11}C-MET
8	M	73	IgGκ	Standard	4	2	Disease monitoring	Yes	Yes	equal
9	M	53	IgGλ	Standard	2	2	Disease progression	Yes	Yes	^{11}C-MET
10	F	65	IgGκ	Standard	2	2	Follow-up	No	No	equal
11	M	50	IgGκ	Standard	2	2	Disease progression	Yes	No	^{11}C-MET
12	M	57	IgGκ	Standard	4	2	Disease progression	Yes	Yes	equal
13	M	61	IgGλ	Standard	3	3	Disease progression	Yes	Yes	equal
14	M	45	SBP	Standard	1	None	Follow-up	No	No	equal
15	M	50	IgGλ	Standard	2	2	Disease progression	Yes	Yes	^{11}C-MET
16	F	67	IgGλ	Standard	1	2	Follow-up	No	No	equal
17	M	42	Asecretory	Standard	3	2	Follow-up	No	No	equal
18	M	64	LCλ	Standard	3	2	Disease progression	Yes	Yes	equal
19	F	61	IgGλ	Standard	2	2	Disease progression	Yes	Yes	^{11}C-MET

Presence of del(17p), t(4;14), t(14;16), t(14;20) and chromosome 1 abnormalities were considered as high risk, whereas all other karyotypes were classified as standard risk. Suspicion of disease progression was established both clinically, serologically (M gradient, involved free light-chain levels, β_2-microglobulin), or by BM biopsy.

F indicates female; LC, light chain; M, male; N/A, not available; SCT, stem cell transplantation.

respectively, using contrast-enhanced (depending on kidney function; dose modulation with a quality reference of 210 mAs) or low-dose spiral CT (80 mAs, 120 kV, a 512 × 512 matrix, 5-mm slice thickness, increment of 30 mm/s, rotation time of 0.5 second, and pitch index of 0.8) including the skull to the proximal thighs. Consecutively, PET emission data were acquired in 3-dimensional mode with 2-minute emission time per bed position. After decay and scatter correction, PET data were reconstructed iteratively (TrueX HD PET, 3 iterations, 24 subsets, Gaussian filtering: 2 mm; 200 × 200 matrix) with attenuation correction using a dedicated software (HD PET; Siemens Esoft, Erlangen, Germany).

Image Analysis

In this retrospective analysis, lesions were visually determined for both ^{11}C-choline and ^{11}C-methionine as disseminated intense or focally increased tracer retention as compared with surrounding normal tissue or contralateral structures as previously described.[18] Presence and number of intramedullary and extramedullary disease as well as location of focal lesions (FLs) were recorded. In the presence of lesions too numerous to count (>100), the category "disseminated" was introduced. Analysis both on a patient and a lesion basis was performed.

For calculation of lesion-to-blood and lesion-to-muscle ratios, circular background regions of interest with a diameter of 15 mm (right ventricle) and 30 mm (musculus gluteus maximus) were defined for every patient. SUVmax of the individual hottest myeloma lesion was divided by the mean of the respective region of interest (blood pool and muscle) for derivation of ratios.

In order to correlate tracer uptake with BM involvement, a circular region of interest with a diameter of 15 mm was placed over the respective posterior superior iliac spine, and SUVmax and SUVmean were derived. Both SUVs were compared with infiltration of malignant myeloma cells, as determined by BM biopsy.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics 25 (SPSS, Inc, Chicago, Ill). Quantitative values were tested for normal distribution by the Kolmogorov-Smirnov test. The tests used for data analysis are named together with the results. All statistical tests were performed 2-sided, and $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Eighteen (94.7%) of 19 patients presented with previously established MM; the remaining patient (patient 14) had been diagnosed with solitary bone plasmacytoma. At time of imaging, 13 (68.4%) of 19 subjects were referred for further workup of serologically progressive disease; the remainder (6/19 [31.6%]) underwent imaging as part of routine follow-up examinations.

In the 12 (63.2%) of 19 patients in whom information on the degree of iliac BM infiltration with MM plasma cells was available, the degree of infiltration ranged from 0% to 50% (median, 20%). Patients' characteristics are summarized in Table 1. A flowchart of patient selection, imaging results, and outcome is given in Supplementary Figure 1 (Supplemental Digital Content 1, http://links.lww.com/CNM/A197).

Patient-Based Analysis

^{11}C-methionine PET/CT detected active MM in 15 (78.9%) of 19 patients, ^{11}C-choline PET/CT in 14 (73.7%) of 19 patients, respectively (patient 11 being exclusively positive in ^{11}C-methionine PET/CT; Fig. 1). In the remaining 4 (21.1%) of 19 subjects, no metabolically active myeloma could be revealed. During a median follow-up of 20 months (range, 18–21 months), these 4 patients showed no sign of disease progression. Because of radiologically active disease and serological MM progression, the exclusively

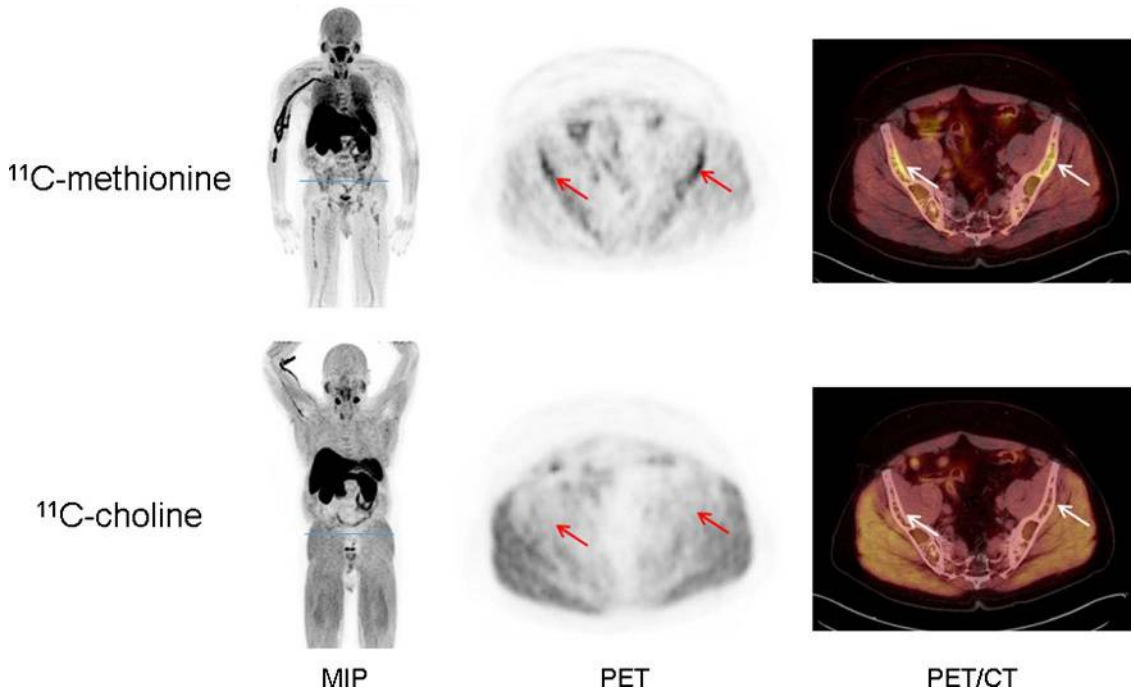

FIGURE 1. Viable MM exclusively detected by ^{11}C-methionine PET/CT. Display of maximum intensity projections and transaxial PET/(CT) slices of a 50-year-old man with a history of IgGκ MM who was referred due to serological disease progression. Viable ntramedullary myeloma was exclusively detected by ^{11}C-methionine PET/CT.

^{1}C-methionine PET-positive patient was treated with a combination herapy of lenalidomide and dexamethasone that achieved a very good partial response.

No extramedullary disease was recorded. Regarding intramedullary MM lesions, ^{11}C-methionine PET/CT revealed involvement of the appendicular skeleton in 12 (63.2%) of 19 patients, with 1 case being missed with ^{11}C-choline (^{11}C-choline–positive lesions in 11/19 patients [57.9%]).

Lesion-Based Analysis

Imaging with ^{11}C-methionine demonstrated more FLs than ^{11}C-choline PET/CT in 8 (42.1%) of 19 patients ($P < 0.01$; Fig. 2).

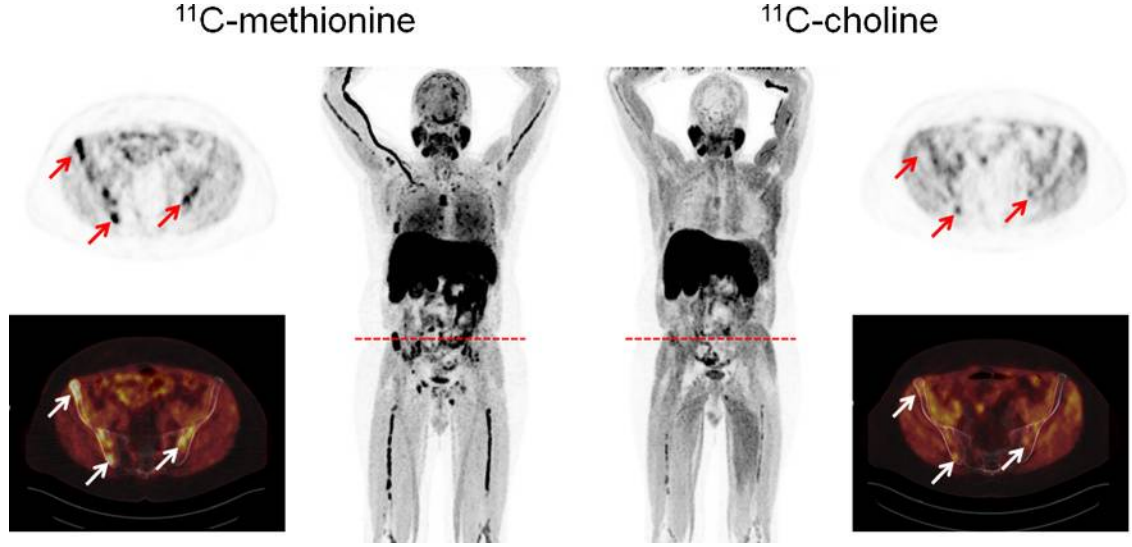

FIGURE 2. Example of higher sensitivity of ^{11}C-methionine in comparison to ^{11}C-choline. Display of transaxial PET and fused PET/CT images (outer columns) and maximum intensity projections (inner columns) of a patient (patient 9) with a history of IgGλ myeloma who was referred due to suspicion of disease progression. In this patient, ^{11}C-methionine PET/CT detected more intramedullary FLs with a higher lesion-to-background contrast as compared with ^{11}C-choline PET/CT. Of note, involvement of the extremities is markedly more pronounced in ^{11}C-methionine PET/CT.

In the remaining patients (11/19 [57.9%]), an equal number of MM manifestations was detected with both tracers.

^{11}C-methionine PET/CT detected more than 20 FLs in 2 (10.5%) of 19 patients; in 7 (36.8%) of 19 subjects, a disseminated pattern of disease was identified. Six (31.6%) of 19 subjects had fewer than 20 FLs; the remaining 4 (21.1%) of 19 individuals presented without any ^{11}C-methionine-avid lesions. With ^{11}C-choline, 5 (26.3%) of 19 patients were negative, 8 (42.1%) of 19 subjects had fewer than 20 FLs, 2 (10.5%) of 19 had more than 20 FLs, and 4 (21.1%) of 19 had a disseminated pattern (Fig. 3).

Lesion-to-Blood and Lesion-to-Muscle Ratios

Of the 15 patients with positive PET, 10 had a higher lesion-to-blood ratio in ^{11}C-methionine PET/CT (P = 0.30; binomial probability). The mean lesion-to-blood ratios were 11.1 ± 6.4 for ^{11}C-methionine and 9.6 ± 3.4 for ^{11}C-choline (P = 0.11; paired t test). In all 15 patients (P < 0.0001; binomial probability), lesion-to-muscle ratios were higher after ^{11}C-methionine, which showed significantly higher ratios as compared with ^{11}C-choline, 18.7 ± 11.6 versus 8.8 ± 5.7, respectively (P = 0.0001; paired t test).

Correlation of Tracer Uptake With Malignant Plasma Cell BM Infiltration

In the 12 patients in whom BM infiltration was assessed by immunohistochemistry, ^{11}C-choline and ^{11}C-methionine uptake values were strongly correlated with each other (SUVmean: R^2 = 0.54, P < 0.01, Pearson; SUVmax: R^2 = 0.34, P < 0.05, Pearson). For both tracers, SUVmean as well as SUVmax correlated significantly with the degree of malignant plasma cell infiltration. Correlation was higher for ^{11}C-methionine (SUVmean: R^2 = 0.72, P < 0.001, Pearson; SUVmax: R^2 = 0.67, P = 0.001, Pearson) as compared with ^{11}C-choline (SUVmean: R^2 = 0.52, P < 0.008, Pearson; SUVmax: R^2 = 0.54, P = 0.006, Pearson), but did not reach statistical significance (SUVmean: P = 0.17, SUVmax: P = 0.30, Steiger).[27] The individual numbers for all biopsies available are given in Supplementary Table 1 (Supplemental Digital Content 2, http://links.lww.com/CNM/A198).

DISCUSSION

To the best of our knowledge, this pilot study is the first head-to-head comparison of ^{11}C-methionine and ^{11}C-labeled choline for metabolic imaging of MM. Previous reports have demonstrated both tracers to be more sensitive than ^{18}F-FDG for detecting MM lesions.[14,17,18,25,28]

Choline as a small precursor of phospholipids is involved in membrane synthesis and metabolism as well as cell growth and therefore utilized to an increasing degree by malignant tumor cells including MM plasma cells. A pilot study by Nanni and colleagues[25] was the first to compare ^{11}C-choline PET/CT and ^{18}F-FDG PET/CT in MM with more lesions depicted by ^{11}C-choline PET/CT in 3 of 10 patients. Because ^{11}C-choline has been approved by the US Food and Drug Administration for PET imaging (in recurrent prostate cancer),[29] this tracer holds promise also to be manufactured and used by various myeloma centers in the United States.

In our cohort, ^{11}C-methionine provided advantages over ^{11}C-choline in terms of higher sensitivity in detecting a higher number of intramedullary lesions in approximately 40% of patients. Additionally, ^{11}C-methionine provided higher lesion-to-background contrast than ^{11}C-choline. Its uptake in the iliac crest correlated to a higher degree with the extent of malignant plasma cell infiltration (as obtained from iliac crest biopsy), thereby supporting our previous results.[17] However, it has still to be demonstrated in how far superior sensitivity of ^{11}C-methionine PET/CT translates into improved patient prognostication and management. A potential suitable clinical scenario for ^{11}C-methionine is the assessment of minimal residual disease (MRD). In a recent study enrolling newly diagnosed MM patients undergoing upfront chemotherapy with subsequent autologous stem cell transplantation and maintenance therapy, ^{18}F-FDG PET/CT and MRD assessment by flow cytometry showed both techniques to be complementary to each other, with subjects with both ^{18}F PET/CT–negative and MRD-negative results experiencing longer progression-free survival than those with a positive result in either method.[8] Because MRD assessment relies on (random) BM biopsy, whole-body imaging with PET/CT might help to account for the heterogeneous and patchy disease distribution inside and outside the BM cavity. In this setting, ^{11}C-methionine as the most sensitive PET tracer could have a major impact on treatment strategies. Noteworthy, the 4 patients included in this cohort with serological and imaging complete remission did not experience disease relapse during the follow-up period. Achievement of both BM-based MRD and ^{11}C-methionine PET/CT negativity might be a valid end point for future prospective trials.

It has to be mentioned that some of the drawbacks of ^{18}F-FDG PET/CT also apply to amino acid imaging, with lack of standardization being one of the most prominent issues. Recently,

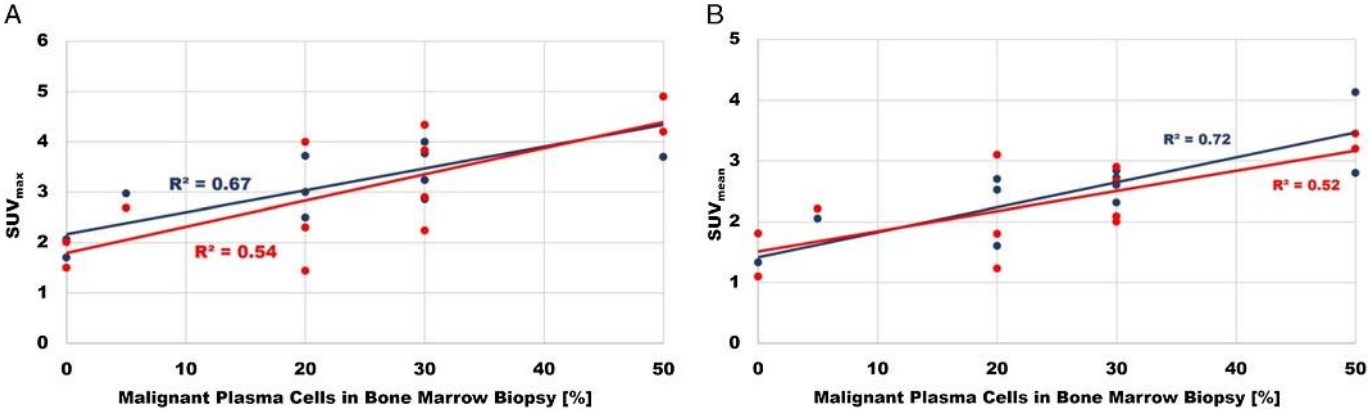

FIGURE 3. Correlation of histological malignant plasma cell BM infiltration (sample from iliac crest) and PET-derived ^{11}C-methionine (blue) and ^{11}C-choline (red) uptake (SUVmean and SUVmax). Whereas iliac crest uptake (SUVmean and SUVmax) of both ^{11}C-choline and ^{11}C-methionine is significantly correlated with the degree of malignant plasma cell infiltration, correlation was higher for ^{11}C-methionine (SUVmean: r = 0.85, P < 0.001, Pearson; SUVmax: r = 0.82, P = 0.001, Pearson) as compared with ^{11}C-choline (SUVmean: r = 0.72, P < 0.008, Pearson; SUVmax: r = 0.73, P = 0.006, Pearson).

novel criteria for reporting of ^{18}F-FDG PET/CT were proposed by an Italian expert panel,[30] in principle using a 5-point scale (Deauville criteria) as established for malignant lymphoma.[31] However, this approach is not fully transferrable to non–^{18}F-FDG tracers as high physiologic liver uptake excludes its use as reference. In the present study, mainly mediastinal blood pool and/or surrounding normal tissue were used to define PET negativity. Appropriate thresholds for ^{11}C-methionine PET/CT positivity/negativity should be further assessed in prospective trials.

This study has several limitations. It comprised only a small number of patients and is retrospective in nature. Although uptake of exclusively ^{11}C-methionine–avid (^{11}C-choline–negative) lesions was typical for MM, histopathologic confirmation of these lesions was not available.

CONCLUSIONS

According to these data, 11C-methionine PET/CT appears to be more sensitive than 11C-choline PET/CT for the detection of active MM lesions.

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