

# The value of $^{18}\text{F}$ -FDG PET/CT in the prediction of clinical outcomes of patients with acute leukemia treated with allogeneic hematopoietic stem cell transplantation

ZIXUAN ZHAO<sup>1\*</sup>, YEYE ZHOU<sup>1\*</sup>, JING WANG<sup>2</sup>, TONGTONG ZHANG<sup>2</sup>,  
JIHUI LI<sup>1</sup>, BIN ZHANG<sup>1</sup>, QINGRU LI<sup>1</sup> and SHENGMING DENG<sup>1</sup>

Departments of <sup>1</sup>Nuclear Medicine and <sup>2</sup>Hematology, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215006, P.R. China

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**Abstract.** The present study aimed to determine whether  $^{18}\text{F}$ -FDG PET/CT performed before and/or after allogeneic hematopoietic stem cell transplantation (allo-HSCT) can predict clinical outcomes in acute leukemia (AL). A total of 79 examinations comprising 72 patients with AL who underwent  $^{18}\text{F}$ -FDG PET/CT before and/or after allo-HSCT were retrospectively enrolled between January 2011 and January 2019. Outcomes were assessed using overall survival (OS) and disease-free survival (DFS). A total of 63 examinations were PET-positive, while 16 examinations were PET-negative. Increased BM and splenic  $^{18}\text{F}$ -FDG uptake were observed in 24 (19/79) and 14% (11/79) of examinations, respectively.  $^{18}\text{F}$ -FDG-avid lymph nodes were observed in 38% (30/79) of examinations.  $\text{E}_\text{N}\text{E}_\text{M}\text{E}_\text{S}$  involvement was detected in 44% (35/79) of examinations. The presence of  $\text{E}_\text{N}\text{E}_\text{M}\text{E}_\text{S}$  involvement [OS hazard ratio (HR), 6.399; 95% confidence interval (CI), 1.843-22.224;  $P=0.003$ ; post-HSCT OS: HR, 7.203; 95% CI, 1.510-34.369;  $P=0.013$ ; DFS HR, 3.671; 95% CI, 1.145-11.768;  $P=0.029$ ], post-transplantation minimal residual disease (DFS HR, 4.381; 95% CI, 1.594-12.040;  $P=0.004$ ; pre-HSCT OS HR, 11.455; 95% CI, 1.336-98.179;  $P=0.026$ ) and disease status (OS HR, 0.330; 95% CI, 0.128-0.848;  $P=0.021$ ; post-HSCT OS HR, 0.195; 95% CI, 0.050-0.762;  $P=0.019$ ; DFS: HR, 0.278; 95% CI, 0.091-0.851;  $P=0.025$ ) could serve as an adverse prognostic factor in patients with AL treated with allo-HSCT.  $^{18}\text{F}$ -FDG PET/CT before and/or after allo-HSCT was a predictor for OS and DFS in patients

with AL.  $\text{E}_\text{N}\text{E}_\text{M}\text{E}_\text{S}$  involvement detected using  $^{18}\text{F}$ -FDG PET/CT may help identify patients with AL who are likely to have unfavorable clinical outcomes.

## Introduction

As a type of hematopoietic system disease, acute leukemia (AL) is characterized by the malignant transformation of hematopoietic stem and precursor cells within the bone marrow (BM) or thymus (1). AL primarily comprises of acute lymphoblastic (ALL), myeloblastic (AML), undifferentiated (AUL) and mixed-lineage leukemia (AMLL) (2). AL has become a global health concern due to its increasing incidence over the past decade (3). The worldwide incidence of AML has gradually increased from  $63.84 \times 10^3$  cases in 1990 to  $119.57 \times 10^3$  cases in 2017, showing an increase of 87.3% (4). The USA has diagnosed approximately 5,960 new cases of ALL and reported 1,470 ALL-associated mortalities in 2018 (5). To date, allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only potentially curative treatment for AL (6). However, allo-HSCT is associated with high-risk of non-relapse-associated mortality and disease relapse, which are causes of mortality of patients with AL who receive allo-HSCT treatment (7). It has been reported that the incidence of relapse and risk of non-relapse mortality of core binding factor AML are 19.8 and 22.5% for relapse and 20.9 and 23.3% for non-relapse mortality, respectively (8). Therefore, reliable prognostic factors are necessary to predict patient outcomes at the time of transplantation.

Positron emission tomography (PET)/CT using the radio-labeled glucose analog  $^{18}\text{F}$ -2'-deoxy-2'-fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) has been widely used for diagnosis, staging and prognosis prediction of malignant disease, including hematological malignancy (9,10). Although a number of studies concerning the prognostic value of  $^{18}\text{F}$ -FDG PET/CT in patients with multiple myeloma or lymphoma undergoing HSCT have been published (11-13), the prognostic value of  $^{18}\text{F}$ -FDG PET/CT imaging in patients with AL has yet to be established. The present study aimed to determine whether  $^{18}\text{F}$ -FDG PET/CT performed before and/or after allo-HSCT could be used to predict clinical outcomes in AL.

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*Correspondence to:* Dr Shengming Deng, Department of Nuclear Medicine, The First Affiliated Hospital of Soochow University, 188 Shizi Street, Suzhou, Jiangsu 215006, P.R. China  
E-mail: dshming@163.com

\*Contributed equally

**Key words:** fluorodeoxy glucose F18, positron emission tomography/CT, acute leukemia, hematopoietic stem cell transplantation

## Materials and methods

**Ethical approval.** The present retrospective study (trial registration no. ChiCTR1900024823) was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (Suzhou, China; approval no. 2019055), with a waiver of informed consent.

**Patients.** From January 2011 to January 2019, patients with AL who underwent <sup>18</sup>F-FDG PET/CT before or after allo-HSCT were retrospectively enrolled in the present study. The following inclusion criteria were used: Histologically confirmed as AL and patients who underwent <sup>18</sup>F-FDG PET/CT before or after allo-HSCT. The following exclusion criteria were used: i) Patients with lymphoma cell leukemia, ii) digital image data unavailable for retrospective analysis, iii) patients who received granulocyte colony-stimulating factor (G-CSF) therapy <1 month before PET/CT scan and iv) time interval between day 0 of allo-HSCT and PET/CT scan >12 months. Patients were followed-up for ≥4 months after allo-HSCT. Follow-up data were collected through clinic or over the phone, with an average follow-up of 25.2 months.

A total of 96 patients with AL were retrospectively reviewed in the present study. A total of 24 patients were excluded from the final analysis. Among these, 15 patients had lymphoma cell leukemia, three received G-CSF therapy <1 month before PET/CT scan and six underwent PET/CT scan >12 months before or after allo-HSCT. A total of 72 patients [21 female, 51 male; mean age ± standard deviation (SD), 31±13 years; range, 7-60 years] were retrospectively enrolled in the final analysis.

Risk stratification of patients with AML was primarily assessed according to European Leukemia Net (ELN) 2017 (14) and risk stratification of patients with ALL was primarily assessed according to the NCCN Guidelines (15). For patients with insufficient information for NCCN 2019 and ELN 2017, risk stratification was independently evaluated by two experienced hematologists, and results were recorded by consensus. According to NCCN 2019 Guidelines, ALL was divided into high-risk and low-risk, while AML was divided into high-risk, intermediate-risk and low-risk according to ELN 2017. Therefore, in order to better analyze risk stratification, low-risk and intermediate-risk patients with AML were combined as low-risk ones.

**Image acquisition.** <sup>18</sup>F-FDG PET/CT imaging was performed using a standard whole-body protocol as previously described (15). All patients were fasted for ≥6 h before <sup>18</sup>F-FDG PET/CT examination. The baseline blood glucose level was <11 mmol/l. At 60 min after administration of <sup>18</sup>F-FDG (dose, 0.12 mCi/kg), <sup>18</sup>F-FDG PET/CT was performed using a Discovery STE PET/CT scanner (General Electric Medical Systems, Milwaukee, WI, USA). Transmission data were acquired via whole-body CT (140 kV; 120 mA; pitch, 1.75; transaxial FOV, 700 mm; slice thickness, 3.75 mm; rotation time, 0.8 sec). PET emission data in 3D-mode were analyzed from the vertex of the skull to the proximal thigh, with 2-3 min per bed position. Transverse PET slices were reconstructed using a standard iterative algorithm (ordered-subset expectation maximization), with low-dose CT data utilized for image

Table I. Patient characteristics.

Characteristics	N
Age, years	
≤20	20
>20	52
Mean ± standard deviation (range) <sup>a</sup>	31±13 (7-60)
Sex	
Female	21
Male	51
Acute leukemia type	
Lymphoblastic	33
Myeloblastic	36
Mixed-lineage	3
<i>De novo</i> or secondary	
<i>De novo</i>	69
Secondary	3
Before or after allogeneic hematopoietic stem cell transplantation	
Before	19
After	46
Before and after	7
Median follow-up	21 months
Lactate dehydrogenase	
High	42
Normal	30
White blood cell count at diagnosis, x10 <sup>9</sup> /l	
≤20	45
>20	27
Risk stratification	
Good	20
Poor	49
Unknown	3
Disease status	
Complete remission	54
Non-remission	18
Pre-transplantation MRD	
Positive	43
Negative	18
Post-transplantation MRD	
Positive	22
Negative	20

<sup>a</sup>Presented as mean ± standard deviation (range). MRD, minimal residual disease.

fusion and attenuation correction, using the Xeleris workstation software (GE Healthcare; ADW4.1).

**Image analysis.** <sup>18</sup>F-FDG PET/CT images were independently evaluated by two experienced nuclear medicine physicians who were blinded to the clinical information of all subjects, and the results were recorded by consensus. Increased <sup>18</sup>F-FDG uptake in the BM and spleen was defined as diffuse

Table II. Univariate and multivariate analysis of OS of all PET/CT examinations.

A, Univariate analysis		
Parameters	P-value	Hazard ratio (95% CI)
Sex, Male vs. Female	0.8524	0.9200 (0.3840-2.2070)
Age, >21 years	0.5771	1.3620 (0.4600-4.0390)
Risk stratification	0.1642	1.8720 (0.7740-4.5270)
White blood cell count, >20x10 <sup>9</sup> /l	0.0772	2.1740 (0.9190-5.1420)
Elevated lactate dehydrogenase, >245 U/l	0.5077	0.7590 (0.3350-1.7170)
Acute leukemia type	0.1690	1.8250 (0.7740-4.3000)
PET-positive	0.1234	2.0900 (0.8182-5.3370)
Increased BM <sup>18</sup> F-FDG uptake	0.4406	0.6850 (0.2620-1.7910)
Focal BM <sup>18</sup> F-FDG uptake	0.3840	1.2950 (0.0360-4.3590)
Increased splenic <sup>18</sup> F-FDG uptake	0.6955	0.8480 (0.3720-1.9340)
<sup>18</sup> F-FDG-avid lymph nodes >1.5 cm	0.0140	2.8710 (1.0950-7.5290)
E <sub>N</sub> E <sub>M</sub> E <sub>S</sub> involvement	0.0003	4.5450 (2.0080-10.2900)
Disease status	0.0009	0.1930 (0.0726-0.5100)
Pre-transplantation MRD	0.1737	2.1150 (0.7188-6.2240)
Post-transplantation MRD	0.0017 <sup>a</sup>	4.5940 (1.7740-11.9000)
B, Multivariate analysis		
Parameters	P-value	Hazard ratio (95% CI)
E <sub>N</sub> E <sub>M</sub> E <sub>S</sub> involvement	0.0030	6.3990 (1.8430-22.2240)
<sup>18</sup> F-FDG-avid lymph nodes >1.5 cm	0.6620	-
Disease status	0.0210	0.3300 (0.1280-0.8480)
Post-transplantation MRD	0.1180	-

PET, positron emission tomography; BM: Bone marrow; <sup>18</sup>F-FDG, <sup>18</sup>F-2'-deoxy-2'-fluorodeoxyglucose; E<sub>N</sub>E<sub>M</sub>E<sub>S</sub>, extranodal, extramedullary and extrasplenic; MRD, minimal residual disease.

and/or focal <sup>18</sup>F-FDG uptake  $\geq$  normal liver (16,17). The region of interest located in the right lobe of the liver served as the reference. Diffuse or focal <sup>18</sup>F-FDG uptake above the mediastinal blood pool or background uptake excluding infectious, inflammatory or other neoplastic diseases was considered as other PET-positive (18).

**Statistical analysis.** GraphPad Prism (version 5.0; GraphPad Software, Inc.) and SPSS software (version 19.0; IBM, Corp.) were used for statistical analysis. In order to assess the prognostic value of <sup>18</sup>F-FDG PET/CT imaging, overall survival (OS) and disease-free survival (DFS) were selected as the endpoints. OS was defined as the period from the date of allo-HSCT to the date of death. DFS was defined as the period from the date of allo-HSCT to the date of relapse or death. OS and DFS were estimated via the Kaplan-Meier method, and differences among groups were evaluated by a log-rank test. The relation between factors associated with OS and DFS was estimated using the Kaplan-Meier method, and the log-rank test was used for univariate analysis. For multivariate analysis, risk factors with statistical significance upon univariate analysis were introduced into a Cox proportional hazards model. P<0.05 was considered to indicate a statistically significant difference.

## Results

**Characteristics of patients.** A total of 72 patients (21 females, 51 males; mean age  $\pm$  SD, 31 $\pm$ 13 years; range, 7-60 years) were enrolled between January 2011 and January 2019. Of these 72 patients, 33 had ALL, 36 had AML and three had AMLL. In addition, 19 patients underwent <sup>18</sup>F-FDG PET/CT before allo-HSCT, 46 underwent <sup>18</sup>F-FDG PET/CT after allo-HSCT and seven underwent <sup>18</sup>F-FDG PET/CT both before and after allo-HSCT. Therefore, 79 examinations of 72 patients were enrolled in the study. The median follow-up was 21 months. The white blood cell count at diagnosis was >20x10<sup>9</sup>/l in 27 patients. The lactate dehydrogenase levels (>245 U/L) were high in 42 patients (19). Detailed characteristics of patients are presented in Table I.

**PET/CT results.** A total of 63 examinations were <sup>18</sup>F-FDG PET positive, whereas 16 examinations were <sup>18</sup>F-FDG PET negative. Increased BM <sup>18</sup>F-FDG uptake was observed in 24% (19/79) of examinations, including a homogeneous/diffuse pattern throughout the body in 13 examinations and an inhomogeneous/focal pattern or co-existing inhomogeneous/focal and homogeneous/diffuse patterns in six examinations.

Table III. Univariate and multivariate analysis of disease-free survival of all PET/CT examinations.

A, Univariate analysis		
Parameters	P-value	Hazard ratio (95% CI)
Sex, Male vs. Female	0.8031	0.900 (0.398-2.038)
Age, >21 years	0.5537	1.339 (0.510-3.520)
Risk stratification	0.9173	0.958 (0.423-2.166)
White blood cell count, >20x10 <sup>9</sup> /l	0.4990	1.307 (0.602-2.840)
Elevated lactate dehydrogenase, >245 U/l	0.2326	0.632 (0.297-1.343)
Acute leukemia type	0.3659	1.426 (0.661-3.078)
PET-positive	0.2950	1.621 (0.656-4.004)
Increased BM <sup>18</sup> F-FDG uptake	0.8546	0.920 (0.376-2.249)
Focal BM <sup>18</sup> F-FDG uptake	0.5620	1.567 (0.470-5.226)
Increased splenic <sup>18</sup> F-FDG uptake	0.2911	0.661 (0.306-1.426)
<sup>18</sup> F-FDG-avid lymph nodes >1.5 cm	0.0080	3.743 (1.515-9.245)
E <sub>N</sub> E <sub>M</sub> E <sub>S</sub> involvement	0.0005	3.793 (1.782-8.071)
Disease status	0.0091	0.285 (0.111-0.732)
Pre-transplantation MRD	0.3819	1.489 (0.610-3.634)
Post-transplantation MRD	0.0016	4.171 (1.722-10.100)
B, Multivariate analysis		
Parameters	P-value	Hazard ratio (95% CI)
E <sub>N</sub> E <sub>M</sub> E <sub>S</sub> involvement	0.0950	-
<sup>18</sup> F-FDG-avid lymph nodes >1.5 cm	0.2190	-
Disease status	0.2340	-
Post-transplantation MRD	0.0040 <sup>a</sup>	4.381 (1.594-12.040)

<sup>a</sup>P<0.05. PET, positron emission tomography; BM, bone marrow; <sup>18</sup>F-FDG, 18F-2'-deoxy-2'-fluorodeoxyglucose; ENEMES: Extranodal, extramedullary and extrasplenic; MRD, minimal residual disease.

Increased splenic <sup>18</sup>F-FDG uptake was detected in 14% (11/79) of examinations, including a homogeneous/diffuse pattern in 10 examinations and an inhomogeneous/focal pattern in one examination. <sup>18</sup>F-FDG-avid lymph nodes were observed in 38% (30/79) of examinations, including lymph nodes >1.5 cm in eight examinations and lymph nodes ≤1.5 cm in 22 examinations. One patient with lymph nodes <1.5 cm in short axis demonstrated inflammation.

E<sub>N</sub>E<sub>M</sub>E<sub>S</sub> involvement was detected by PET/CT in 44% (35/79) of examinations. The most common <sup>18</sup>F-FDG-avid site was bone [16% (13/79) of examinations]. Other <sup>18</sup>F-FDG-avid sites included nasopharynx (eight, including two inflammations), soft tissue (seven), lung (five, including three inflammations), breast (four), testes (three), brain (three, including one abscess), kidney, heart, skin, pleura, parotid gland, liver (two each), adrenal, uterus, eyelid and submandibular gland (one examination each).

*Prognosis prediction of all PET/CT examinations.* Univariate and multivariate Cox regression analysis of all 79 examinations was used to assess the effect of <sup>18</sup>F-FDG PET/CT variables and clinical parameters on OS and DFS (Tables II and III). In univariate analysis, <sup>18</sup>F-FDG-avid lymph nodes >1.5 cm, E<sub>N</sub>E<sub>M</sub>E<sub>S</sub> involvement, disease status and post-transplantation

minimal residual disease (MRD) were significantly associated with OS and DFS. However, only E<sub>N</sub>E<sub>M</sub>E<sub>S</sub> involvement [hazard ratio (HR), 6.399; 95% CI, 1.843-22.224; P=0.003] and disease status (HR, 0.330; 95% CI, 0.128-0.848; P=0.021) were significantly associated with OS in multivariate analysis and only post-transplantation MRD was significantly associated with DFS (HR, 4.381; 95% CI, 1.594-12.040; P=0.004).

Kaplan-Meier analysis for OS of all 79 examinations showed that patients with negative E<sub>N</sub>E<sub>M</sub>E<sub>S</sub> involvement and complete remission (CR) had a better OS compared with patients with non-remission (NR) and positive E<sub>N</sub>E<sub>M</sub>E<sub>S</sub> involvement (Fig. 1A and C, respectively). The median OS was 28 months in patients with E<sub>N</sub>E<sub>M</sub>E<sub>S</sub> involvement; patients without E<sub>N</sub>E<sub>M</sub>E<sub>S</sub> involvement did not reach the median OS (P<0.001). The median OS was 24 months in patients with CR; patients with NR did not reach the median OS (P<0.001). Kaplan-Meier analysis demonstrated that patients with positive E<sub>N</sub>E<sub>M</sub>E<sub>S</sub> involvement and NR exhibited a shorter DFS compared with patients with negative E<sub>N</sub>E<sub>M</sub>E<sub>S</sub> involvement and CR (Fig. 1B and D, respectively). Kaplan-Meier analysis for OS showed that the patients with positive post-transplantation MRD had a shorter OS (median OS, 24 months) compared with patients in the negative post-transplantation MRD group (median OS, not reached; P<0.01; Fig. 1E). Kaplan-Meier

Table IV. Univariate and multivariate analysis of OS after allo-HSCT.

A, Univariate analysis.

Parameters	P-value	Hazard ratio (95% CI)
Sex, Male vs. Female	0.4427	1.48400 (0.54190-4.06200)
Age, >21 years	0.9861	1.013000 (0.22840-4.49700)
Risk stratification	0.1832	1.95600 (0.72830-5.25600)
White blood cell count, >20x10 <sup>9</sup> /l	0.1070	3.33000 (1.24000-8.94500)
Elevated lactate dehydrogenase, >245 U/l	0.6205	0.79020 (0.31100-2.00700)
Acute leukemia type	0.3711	0.65000 (0.25300-1.67100)
Increased bone marrow <sup>18</sup> F-FDG uptake	0.8303	0.81620 (0.12750-5.22700)
Increased splenic <sup>18</sup> F-FDG uptake	0.7893	0.87170 (0.31830-2.38700)
<sup>18</sup> F-FDG-avid lymph nodes >1.5 cm	0.0100 <sup>a</sup>	0.11100 (0.02100-0.57500)
E <sub>N</sub> E <sub>M</sub> E <sub>S</sub> involvement	0.0044	3.87800 (1.52600-9.85400)
Disease status	0.0080 <sup>a</sup>	0.20440 (0.06316-0.66130)
Pre-transplantation MRD	0.0743	2.83200 (0.90290-8.88200)
Post-transplantation MRD	0.0463	3.24300 (1.01900-10.32000)

B, Multivariate analysis

Parameters	P-value	Hazard ratio (95% CI)
E <sub>N</sub> E <sub>M</sub> E <sub>S</sub> involvement	0.0130	7.20300 (1.51000-34.36900)
<sup>18</sup> F-FDG-avid lymph nodes >1.5 cm	0.8920	-
Disease status	0.0190	0.19500 (0.05000-0.76200)

<sup>a</sup>P<0.05. MRD, minimal residual disease; PET: Positron emission tomography; <sup>18</sup>F-FDG: <sup>18</sup>F-2'-deoxy-2'-fluorodeoxyglucose; E<sub>N</sub>E<sub>M</sub>E<sub>S</sub>: Extranodal, extramedullary and extrasplenic.

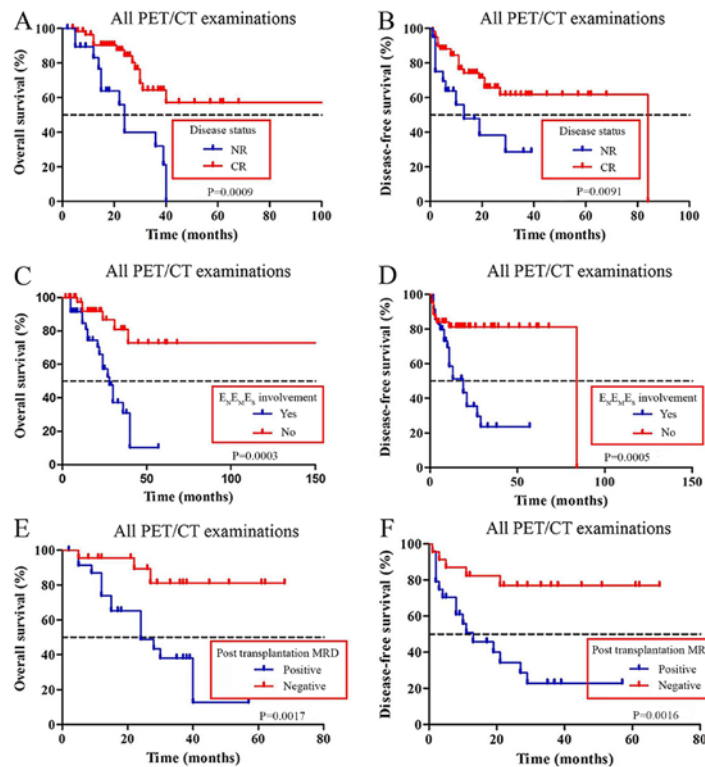


Figure 1. Kaplan-Meier analysis for overall survival and disease-free survival according to (A and B) disease status, (C and D) presence of E<sub>N</sub>E<sub>M</sub>E<sub>S</sub> involvement and (E and F) post-transplant MRD in patients with AL. The dotted line represents 50% survival rate. E<sub>N</sub>E<sub>M</sub>E<sub>S</sub>, extranodal, extramedullary and extrasplenic; MRD, minimal residual disease; PET, positron emission tomography; NR, non-remission; CR, complete remission.

Table V. Univariate and multivariate analysis of disease-free survival after allo-HSCT.

A, Univariate analysis		
Parameters	P-value	Hazard ratio (95% CI)
Sex, Male vs. Female	0.2981	1.6600 (0.6391-4.3110)
Age, >21 years	0.9243	0.9405 (0.2654-3.3320)
Risk stratification	0.8912	1.0650 (0.4308-2.6340)
White blood cell count, >20x10 <sup>9</sup> /l	0.3043	1.5590 (0.6680-3.6400)
Elevated lactate dehydrogenase, >245 U/l	0.1586	0.5393 (0.2286-1.2720)
Acute leukemia type	0.4395	0.7129 (0.3023-1.6810)
Increased bone marrow <sup>18</sup> F-FDG uptake	0.2394	3.6020 (0.4259-30.4600)
Increased splenic <sup>18</sup> F-FDG uptake	0.4104	0.6315 (0.2114-1.8870)
<sup>18</sup> F-FDG-avid lymph nodes >1.5 cm	0.0143	0.1980 (0.0560-0.7060)
E <sub>N</sub> E <sub>M</sub> E <sub>S</sub> involvement	0.0002	5.03700 (2.1550-11.7700)
Disease status	0.0467	0.3375 (0.1157-0.9842)
Pre-transplantation MRD	0.5118	1.4060 (0.5081-3.8890)
Post-transplantation MRD	0.0335	3.0720 (1.0920-8.6460)
B, Multivariate analysis		
Parameters	P-value	Hazard ratio (95% CI)
E <sub>N</sub> E <sub>M</sub> E <sub>S</sub> involvement	0.0290	3.6710 (1.1450-11.7680)
<sup>18</sup> F-FDG-avid lymph nodes >1.5 cm	0.0630	-
Disease status	0.0250	0.2780 (0.0910-0.8510)

MRD, minimal residual disease; PET, positron emission tomography; <sup>18</sup>F-FDG, <sup>18</sup>F-2'-deoxy-2'-fluorodeoxyglucose; E<sub>N</sub>E<sub>M</sub>E<sub>S</sub>, extranodal, extramedullary and extrasplenic.

Table VI. Univariate and multivariate analysis of OS before allo-HSCT.

A, Univariate analysis		
Parameters	P-value	Hazard ratio (95% CI)
Sex, Male vs. Female	0.08140	0.21240 (0.037180-1.21300)
Age, >21 years	0.54090	1.77200 (0.28310-11.10000)
Risk stratification	0.62150	1.71400 (0.25320-11.61000)
White blood cell count, >20x10 <sup>9</sup> /l	0.72150	0.69950 (0.09806-4.99100)
Elevated lactate dehydrogenase, >245 U/l	0.86300	0.86450 (0.16540-4.51900)
Acute leukemia type	0.33770	3.16700 (0.29990-33.45000)
Increased bone marrow <sup>18</sup> F-FDG uptake	0.45810	0.52100 (0.09307-2.91600)
Increased splenic <sup>18</sup> F-FDG uptake	0.90260	1.12300 (0.17450-7.23000)
<sup>18</sup> F-FDG-avid lymph nodes >1.5 cm	0.77450	0.31300 (0.01500-6.40900)
E <sub>N</sub> E <sub>M</sub> E <sub>S</sub> involvement	0.03320 <sup>a</sup>	6.16500 (1.15600-32.88000)
Disease status	0.02170 <sup>a</sup>	0.11280 (0.01750-0.72740)
Pre-transplantation MRD	0.62630	0.50040 (0.03083-8.12000)
Post-transplantation MRD	0.00360 <sup>a</sup>	14.58000 (2.40600-88.37000)
B, Multivariate analysis		
Parameters	P-value	Hazard ratio (95% CI)
E <sub>N</sub> E <sub>M</sub> E <sub>S</sub> involvement	0.32900	-
Disease status	0.69100	-
Post-transplantation MRD	0.02600 <sup>a</sup>	11.45500 (1.33600-98.17900)

<sup>a</sup>Statistically significant. MRD, minimal residual disease; PET, positron emission tomography; <sup>18</sup>F-FDG: <sup>18</sup>F-2'-deoxy-2'-fluorodeoxyglucose; E<sub>N</sub>E<sub>M</sub>E<sub>S</sub>: Extranodal, extramedullary and extrasplenic.

Table VII. Univariate analysis of disease-free survival before allo-HSCT.

Parameters	P-value	Hazard ratio (95% CI)
Sex, Male vs. Female	0.3185	0.42490 (0.07905-2.28400)
Age, >21 years	0.4728	1.90700 (0.32730-11.11000)
Risk stratification	0.7556	0.75070 (0.12340-4.56700)
White blood cell count, >20x10 <sup>9</sup> /l	0.1786	0.26510 (0.03831-1.83500)
Elevated lactate dehydrogenase, >245 U/l	0.8126	0.82120 (0.16100-4.18700)
Acute leukemia type	0.9503	1.06000 (0.17150-6.54600)
Increased BM <sup>18</sup> F-FDG uptake	0.8113	1.22500 (0.23190-6.46900)
Increased splenic <sup>18</sup> F-FDG uptake	0.8397	0.84530 (0.16590-4.30600)
<sup>18</sup> F-FDG-avid lymph nodes >1.5 cm	0.1130	0.17000 (0.01400-2.09100)
E <sub>N</sub> E <sub>M</sub> E <sub>S</sub> involvement	0.6853	1.40400 (0.27180-7.25700)
Disease status	0.0633	0.14470 (0.01882-1.11300)
Pre-transplantation MRD	0.6146	1.63900 (0.23960-11.21000)
Post-transplantation MRD	0.0065	15.91000 (2.17100-116.60000)

MRD, minimal residual disease; BM, bone marrow; <sup>18</sup>F-FDG, <sup>18</sup>F-2'-deoxy-2'-fluorodeoxyglucose; E<sub>N</sub>E<sub>M</sub>E<sub>S</sub>, extranodal, extramedullary and extrasplenic.

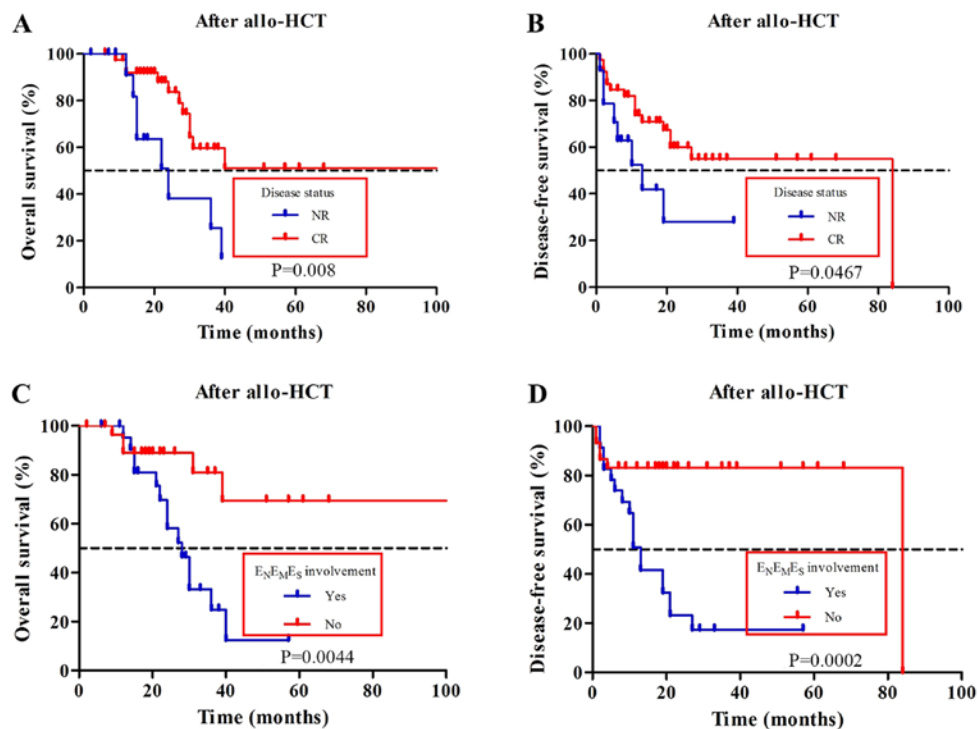


Figure 2. Kaplan-Meier analysis for overall survival and disease-free survival of patients with acute leukemia according to (A and B) disease status and (C and D) presence of E<sub>N</sub>E<sub>M</sub>E<sub>S</sub> involvement detected via <sup>18</sup>F-2'-deoxy-2'-fluorodeoxyglucose positron emission tomography/CT scan after allo-HSCT. The dotted line represents 50% survival rate. E<sub>N</sub>E<sub>M</sub>E<sub>S</sub>, extranodal, extramedullary and extrasplenic; allo-HSCT, allogeneic hematopoietic stem cell transplantation; NR, non-remission; CR, complete remission.

analysis for DFS showed that patients with positive post-transplantation MRD had a shorter DFS (median DFS, 29 months) compared with the patients in the negative post-transplantation MRD group (median DFS, not reached; P<0.01; Fig. 1F).

*Prognosis prediction of examinations after or before allo-HSCT.* For 53 examinations after allo-HSCT, <sup>18</sup>F-FDG-avid lymph nodes >1.5 cm (OS, P=0.010; DFS, P=0.014), E<sub>N</sub>E<sub>M</sub>E<sub>S</sub>

involvement (OS, P=0.0044; DFS, P=0.0002) (Fig. 2C and D, respectively), disease status (OS, P=0.008; DFS, P=0.467) (Fig. 2A and B respectively) and post-transplantation MRD (OS, P=0.046; DFS, P=0.034) were all univariately associated with OS and DFS (Tables IV and V). In multivariate analysis, E<sub>N</sub>E<sub>M</sub>E<sub>S</sub> involvement (OS: HR, 7.203; 95% CI, 1.510-34.369; P=0.013; DFS: HR, 3.671; 95% CI, 1.145-11.768; P=0.029) and disease status (OS: HR, 0.195; 95% CI, 0.050-0.762; P=0.019;

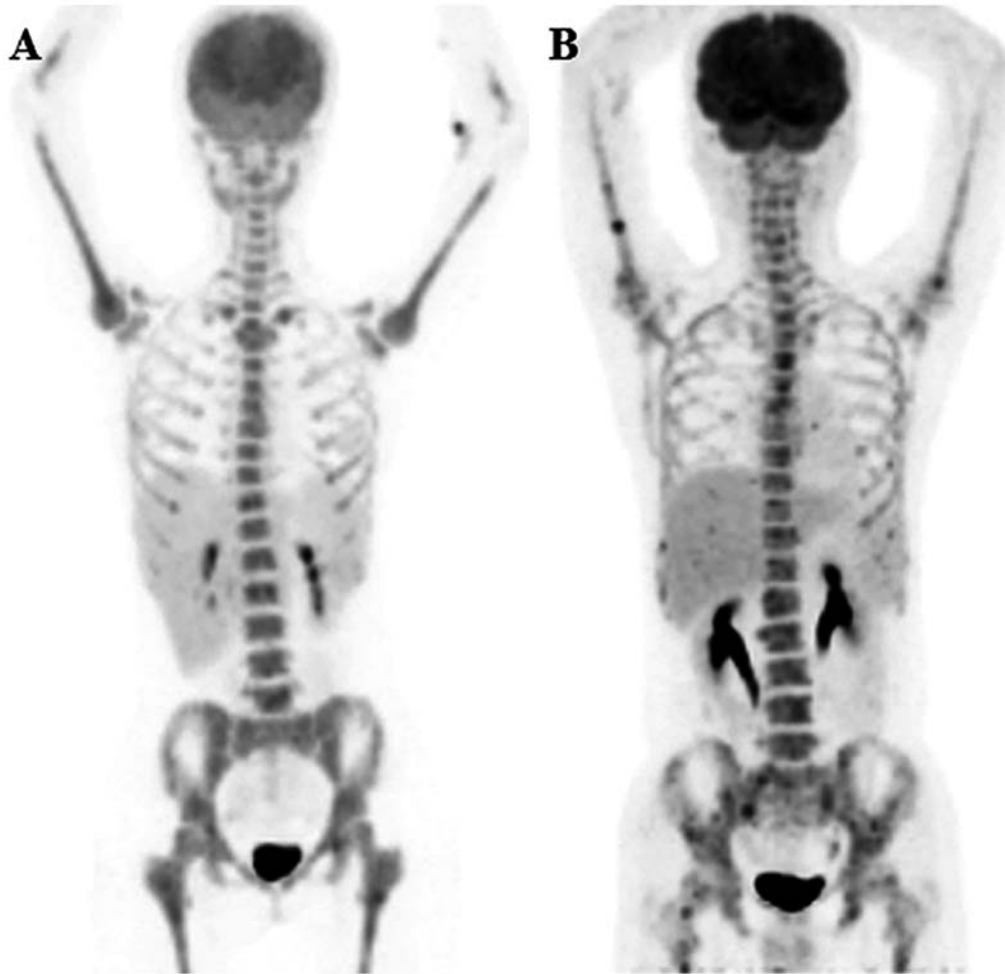


Figure 3.  $^{18}\text{F}$ -2'-deoxy-2'-fluorodeoxyglucose PET/CT images of a (A) 15-year-old girl and (B) 20-year-old man with acute leukemia prior to allogeneic hematopoietic stem cell transplantation. Maximum-intensity projection PET images show diffuse homogeneous BM uptake and co-existence of focal and diffuse BM uptake, respectively. Both patients were alive at the time of the present study with a follow-up time of 11 and 62 months, respectively. PET, positron emission tomography; BM, bone marrow.

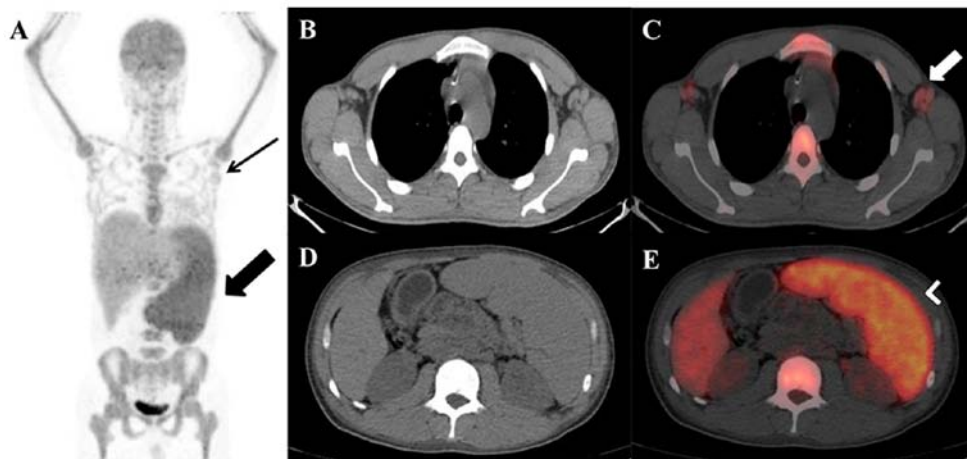


Figure 4.  $^{18}\text{F}$ -FDG PET/CT imaging in a 29-year-old man with ALL prior to allo-HSCT. (A) Maximum intensity projection PET image showed increased  $^{18}\text{F}$ -FDG uptake in splenic parenchyma (thick black arrow), lymph nodes (thin black arrow) and BM in a 29-year-old man with acute lymphoblastic leukemia prior to allo-HSCT. (B-E) Axial PET/CT image revealed splenomegaly (arrowhead) and enlarged axillary lymph nodes (small bold white arrow) of increased  $^{18}\text{F}$ -FDG uptake. The patient was alive at the time of the present study, with a follow-up time of 9 months. PET, positron emission tomography;  $^{18}\text{F}$ -FDG,  $^{18}\text{F}$ -2'-deoxy-2'-fluorodeoxyglucose.

DFS: HR, 0.278; 95% CI, 0.091-0.851;  $P=0.025$ ) were significantly associated with OS and DFS (Tables IV and V). For 26

examinations before allo-HSCT, univariate analysis showed that  $E_N E_M E_S$  involvement ( $P=0.0332$ ), post-transplantation



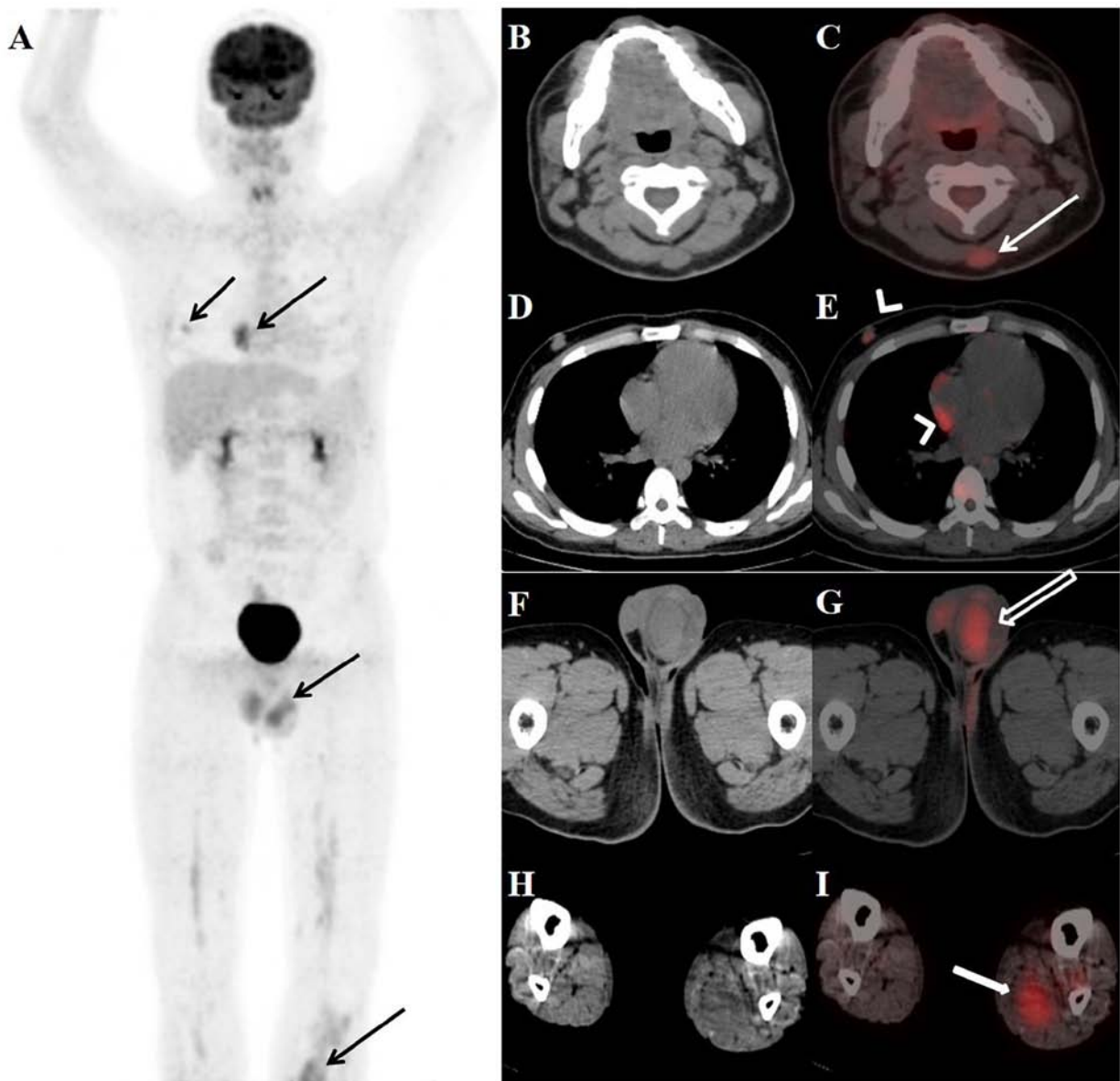


Figure 5.  $^{18}\text{F}$ -FDG PET/CT imaging in a 22-year-old man with AML after allo-HSCT. (A) Maximum intensity projection PET image showed increased  $^{18}\text{F}$ -2'-deoxy-2'-fluorodeoxyglucose uptake in  $E_N E_M E_S$  sites (black arrow) in a 22-year-old man with acute myeloblastic leukemia after allogeneic human stem cell transplantation. Transverse CT and fusion images showed increased metabolic activity in (B and C) subcutaneous nodules (thin white arrow), (D and E) cardiac region (arrow heads), (F and G) testes (hollow bold white arrow) and (H and I) muscles (long bold white arrow). The patient died at 15 months after PET/CT scan. PET, positron emission tomography;  $E_N E_M E_S$ , extranodal, extramedullary and extrasplenic.

MRD ( $P=0.0036$ ) and disease status ( $P=0.0217$ ) were significantly associated with OS (Table VI). Multivariate Cox regression analysis showed that only post-transplantation MRD was significantly associated with OS (HR, 11.455; 95% CI, 1.336-98.179;  $P=0.026$ ) (Table VI). Post-transplantation MRD was significantly associated with DFS ( $P=0.0065$ ) (Table VII).

An example of diffuse homogeneous BM uptake and co-existence of focal and diffuse BM uptake is shown in Fig. 3. Fig. 4 presents an example of  $^{18}\text{F}$ -FDG PET/CT examinations with splenic and lymph node uptake. Figs. 5 and 6 present examples of  $^{18}\text{F}$ -FDG PET/CT examinations with  $E_N E_M E_S$  site uptake.

## Discussion

$^{18}\text{F}$ -FDG PET/CT is not regularly used in the assessment of leukemia (20). However, a number of clinical studies and case

reports have demonstrated the potential of  $^{18}\text{F}$ -FDG PET/CT in the diagnosis of leukemic bone marrow infiltration and extramedullary disease (EMD), evaluation of granulocytic sarcoma, detection of Richter's syndrome and assessment of graft vs. host disease (21-23). The present study aimed to investigate the prognostic value of  $^{18}\text{F}$ -FDG PET/CT in patients with AL treated with allo-HSCT. Although increased  $^{18}\text{F}$ -FDG uptake by BM, spleen and lymph nodes was observed in patients with AL, none of these factors were independent predictors of OS. Only  $E_N E_M E_S$  involvement was significantly associated with OS.

Since AL is a hematological malignancy that originates from BM, increased BM uptake of  $^{18}\text{F}$ -FDG can be observed in patients with AL (24). However, increased BM  $^{18}\text{F}$ -FDG uptake can also be observed in benign etiologies and other types of malignant infiltration (25,26). Jeong *et al* (27), performed a meta-analysis to evaluate the prognostic value

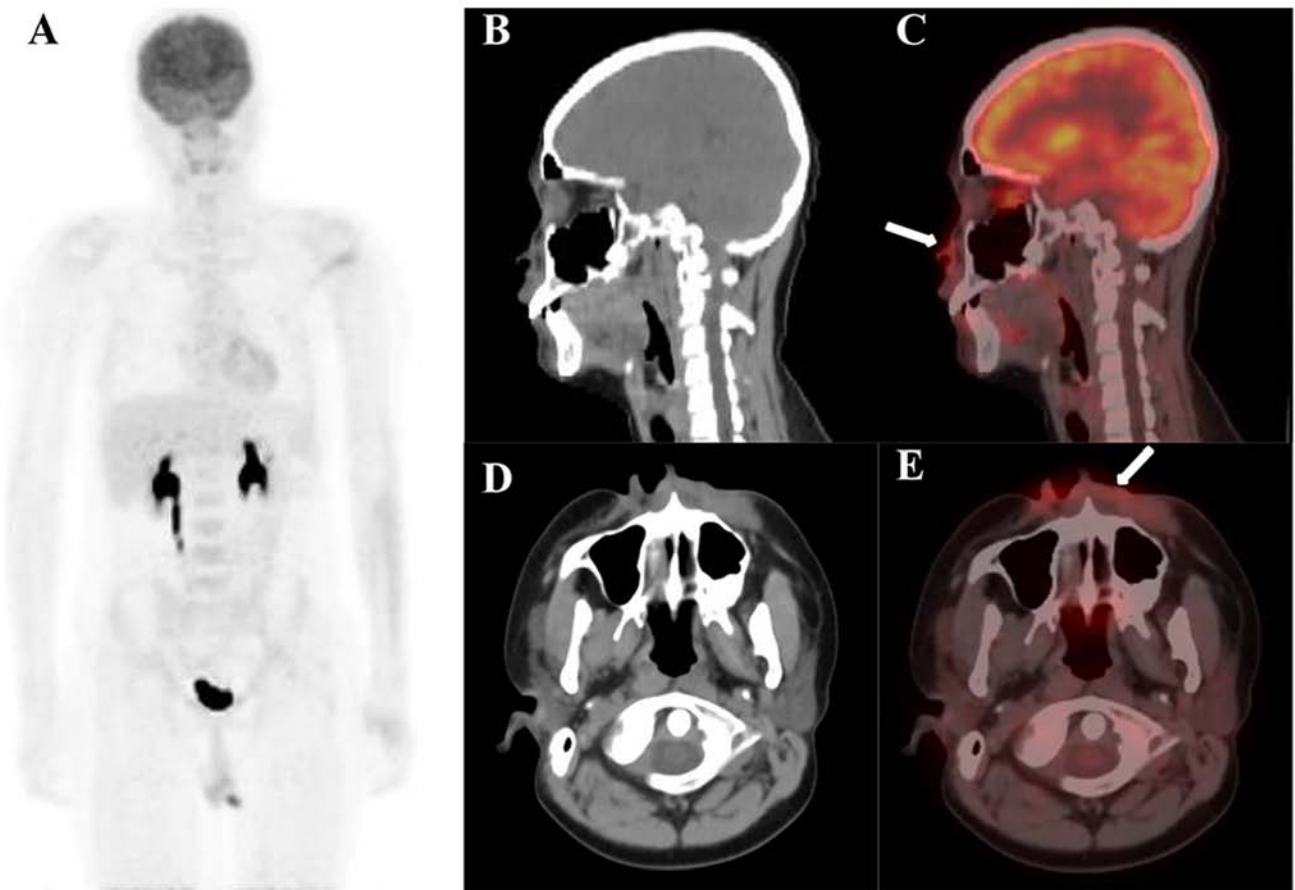


Figure 6.  $^{18}\text{F}$ -FDG PET/CT imaging in a 15-year-old boy with AML after allo-HSCT. (A) Maximum intensity projection PET image showed no notable abnormal  $^{18}\text{F}$ -FDG uptake in the whole body of a 15-year-old boy with acute myeloblastic leukemia following allogeneic hematopoietic stem cell transplantation. (B and C) Sagittal and (D and E) axial images revealed increased  $^{18}\text{F}$ -FDG uptake in the soft tissue of left cheek (white arrow). The patient died at 36 months after PET/CT scan. PET, positron emission tomography;  $^{18}\text{F}$ -FDG,  $^{18}\text{F}$ -2'-deoxy-2'-fluorodeoxyglucose.

of  $^{18}\text{F}$ -FDG BM uptake in patients with a number of types of solid tumor and found that patients with a low level of  $^{18}\text{F}$ -FDG BM uptake have a longer OS compared with those with high levels of  $^{18}\text{F}$ -FDG BM uptake. Abe *et al* (28) demonstrated that patients with peripheral T cell lymphoma with BM involvement detected by PET/CT exhibited a significantly shorter OS compared with those without BM involvement, even among patients with negative BM histology. However, certain studies have drawn the opposite conclusion that high levels of  $^{18}\text{F}$ -FDG BM uptake have no impact on survival, which is consistent with the results of the present study (29,30). However, none of the aforementioned studies investigated patients with AL. Elevated  $^{18}\text{F}$ -FDG BM uptake in patients with AL may be different from that in other patients, because BM is the source of leukemic cells and the primary site of leukemia. Moreover, elevated  $^{18}\text{F}$ -FDG BM uptake may be associated with reactive myelopoiesis and inflammation, which occurs more frequently in patients with AL (31).

The spleen is a primary location of extramedullary AL (10). In numerous studies involving patients with a different types of cancer, splenic  $^{18}\text{F}$ -FDG uptake has been demonstrated to be an independent prognostic factor for predicting recurrence of cancer or OS (32,33). However, the present study demonstrated that elevated splenic  $^{18}\text{F}$ -FDG uptake had no impact on prognosis of patients with AL. It is well known that the spleen functions as a coordinator of immune response, a filter of the

circulating blood, and a reservoir for circulating cells and platelets (34). Additionally, the spleen has several responsibilities, including hemoglobin degradation, hematopoiesis and iron recovery and plasma volume regulation (35). For patients with solid tumors, splenic metabolism primarily reflects the systemic inflammatory response to cancer (36). However, splenic metabolism on  $^{18}\text{F}$ -FDG PET/CT may represent the complex processes of hematopoiesis, which reflects both systemic inflammation and hematological imbalance (32).

There is debate concerning the prognostic significance of EMD in AL. A number of studies involving patients with AL have reported that EMD is an independent prognostic factor for OS (37,38), whereas other studies have demonstrated that EMD has no impact on prognosis (39,40). EMD in these studies was diagnosed by clinical examination. Since not all extramedullary sites are easily detectable, EMD may have been under-diagnosed.  $^{18}\text{F}$ -FDG PET/CT is a sensitive imaging modality for diagnosing EMD in AL (7,19). Kumar *et al* (41) compared  $^{18}\text{F}$ -FDG PET/CT and CT in terms of response and prognosis of patients with AML with EMD and found that PET/CT can identify more lesions and cases of metabolically progressive disease compared with CT alone, thus affecting management. In accordance with these results, the present study demonstrated that  $\text{E}_\text{N}\text{E}_\text{M}\text{E}_\text{S}$  involvement detected by  $^{18}\text{F}$ -FDG PET/CT could serve as an adverse prognostic factor of patients with AL before and/or after allo-HSCT.

There are a number of limitations in the present study. First, it was a retrospective study with a relatively small number of patients. Further prospective studies with larger sample size are necessary to confirm the findings of the present study. Second, the time interval between allo-HSCT and PET/CT scans was heterogeneous, ranging from 0-12 months. PET/CT scans before and after allo-HSCT were only performed in seven patients. Since  $^{18}\text{F}$ -FDG PET/CT is not regularly used in the assessment of leukemia, there are no conclusive data on the optimum interval between allo-HSCT and PET/CT scans. Moreover, the retrospective nature of the present study did not permit regulation of the time interval between allo-HSCT and PET/CT evaluation. Further multiple time point studies are required to identify the optimum time point for PET/CT scans. Finally, not all positive  $\text{E}_\text{N}\text{E}_\text{M}\text{E}_\text{S}$  lesions, particularly EMD in lymph nodes, were confirmed by histopathology.

The present data indicated that  $^{18}\text{F}$ -FDG PET/CT imaging serves a key prognostic role in the evaluation of patients with AL before and/or after allo-HSCT.  $\text{E}_\text{N}\text{E}_\text{M}\text{E}_\text{S}$  involvement detected by  $^{18}\text{F}$ -FDG PET/CT may identify patients with AL with an unfavorable outcome. Prospective clinical studies with larger cohorts are required to conclusively define the prognostic role of  $^{18}\text{F}$ -FDG PET/CT in patients with AL treated with allo-HSCT.

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#### Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

#### Authors' contributions

ZXZ, YYZ and SMD conceived the study and wrote and revised the manuscript. JW, TTZ and JHL reviewed, collected and analyzed the data. BZ, QRL and SMD designed the study and acquired the data. All authors contributed to the drafting of the manuscript. All authors read and approved the final manuscript.

#### Ethics approval and consent to participate

The present retrospective study (trial registration no. ChiCTR1900024823) was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (Suzhou, China; approval no. 2019055), with a waiver of informed consent.

#### Patient consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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