Medicine®

OPEN

Prognostic value of ^{18}F-fluorodeoxyglucose bone marrow uptake in patients with solid tumors
A meta-analysis

Shin Young Jeong, MD PhD[a,b], Seong-Jang Kim, MD PhD[c,d,e,*], Kyoungjune Pak, MD PhD[c], Sang-Woo Lee, MD PhD[a,b], Byeong-Cheol Ahn, MD PhD[a,b], Jaetae Lee, MD PhD[a,b]

Abstract

Background: Several studies have reported the prognostic value of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) bone marrow uptake (BMU) measured by ^{18}F-FDG positron emission tomography (^{18}F-FDG PET) in various cancers. We performed a meta-analysis to evaluate the prognostic value of ^{18}F-FDG BMU in patients with solid tumors.

Methods: Systematic searches of MEDLINE and Embase databases were performed using the keywords "^{18}F-FDG," "bone marrow," and "prognosis." All published human studies of the prognostic value of ^{18}F-FDG BMU in patients with solid tumors were searched. The primary outcome was event-free survival (EFS), and the secondary endpoint was overall survival (OS); both of these were extracted directly from each study. The effects of ^{18}F-FDG BMU on survival were assessed by using hazard ratios (HRs).

Results: Ten studies with 1197 patients (8 studies reporting EFS in 1096 patients and 7 studies reporting OS in 836 patients) were included. In the EFS analysis, the combined HR was 1.75 (95% confidence interval [CI]: 1.45–2.11, $P < .00001$) in the random effects model ($I^2 = 51\%$, $P = .05$). The combined HR of OS was 1.40 (95% CI: 1.13–1.73, $P = .002$) in the random effects model ($I^2 = 52\%$, $P = .05$).

Conclusion: This meta-analysis has demonstrated that patients with a low level of ^{18}F-FDG BMU have better EFS and OS than those with a high level of ^{18}F-FDG BMU. Based on our results, we suggest that ^{18}F-FDG BMU could be used as a biomarker for stratifying the risk of tumor progression in patients with solid tumors.

Abbreviations: BLR = bone marrow to liver uptake ratio, BMU = bone marrow uptake, CI = confidence interval, EFS = event-free survival, ^{18}F-FDG = ^{18}F-fluorodeoxyglucose, HR = hazard ratio, OS = overall survival, PET = positron emission tomography, SUV = standardized uptake value.

Keywords: ^{18}F-fluorodeoxyglucose positron emission tomography, bone marrow, meta-analysis, survival

1. Introduction

Cancer progression is dependent on the tumor microenvironment as well as on the characteristics of the tumor cells, and inflammation in the tumor microenvironment can contribute to tumor cell proliferation, survival, invasion, and metastasis.[1,2] Recently, several studies have shown that systemic inflammation is significantly associated with the prognosis of various types of cancers.[3–5] Systemic inflammatory markers, such as neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, albumin, and C-reactive protein have been shown to be significant prognostic factors for clinical outcomes in patients with solid tumors.[3–5]

Mild bone marrow uptake (BMU) of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) in healthy subjects is well-known; however, some patients with different diseases show relatively high ^{18}F-FDG BMU on positron emission tomography (PET) imaging.[6,7] Previous studies have demonstrated that in patients with malignancy, ^{18}F-FDG BMU can reflect BM activation in response to an inflammatory condition.[6,7] Therefore, ^{18}F-FDG BMU can reflect the systemic inflammatory response.[6,7] Several studies have reported the prognostic value of ^{18}F-FDG BMU measured on PET imaging in various cancers.[8–17] Therefore, we performed a meta-analysis to evaluate the prognostic value of ^{18}F-FDG BMU in patients with solid tumors.

2. Materials and methods

2.1. Literature search and study selection

We performed systematic searches of MEDLINE (from inception to September 2014) and Embase (from inception to September 2014) databases for English-language publications using the following keywords: "positron emission tomography" OR "FDG" or "positron emission tomography-computed tomography" OR

"positron emission tomography computed tomography" OR "PET" OR "PET-CT" OR "PET CT" OR "PET/CT" OR "fluorodeoxyglucose"; "bone marrow" OR "BM"; and "prognostic" OR "prognosis" OR "predictive" OR "survival" OR "outcome." All searches were limited to human studies.

The inclusion criteria included the following: the study included patients with pathologically confirmed malignancies; the study was a case control or cohort study; at least 1 ^{18}F-FDG-PET/CT scan had been performed before at least 1 relevant prognostic factor was assessed, such as overall survival (OS), disease-free survival, event-free survival (EFS), progression-free survival or disease metastasis-free survival; hazard ratios (HRs) and 95% confidence intervals (CIs) were available or could be calculated based on data from the original articles; and the publication was in English. All published studies of the prognostic value of ^{18}F-FDG BMU in patients with solid tumors were searched. Review articles, comments, letters, case reports, conference abstracts, and editorials were excluded. Studies with insufficient data available to calculate the HRs and 95% CIs, without prognostic parameters data, or with less than 10 patients were excluded. If more than 1 published study of the same target group were found in the same institution, only 1 report with the information most relevant to this study was included. Discrepancies were resolved by consensus.[18]

2.2. Data extraction and quality assessment

Data were independently extracted from each article by 2 reviewers and recorded on a standardized form. Univariate HRs and their 95% CIs, P-values for the log-rank test, and the necessary statistics, such as 95% CIs, the number of events, and the number included in each group assessed by using the Kaplan–Meier curves, were recorded. Then, we used the methods suggested by Parmar et al and Williamson et al to convert these data into logHRs and standard errors.[19,20] HR values were calculated by applying a spreadsheet and using the methods suggested by Tierney et al.[21]

Data were extracted from the publications independently by 2 reviewers, and the following information was recorded: first author, year of publication, country, type of solid tumor, parameter of ^{18}F-FDG BMU, number of patients, and clinical endpoints.

We assessed the quality of each included article using the Newcastle–Ottawa scale (www.ohri.ca/programs/clinical_epidemiology/oxford.asp), a comprehensive and systematic reviewing tool that was designed for retrospective and prospective studies. Studies with scores of ≥6 points on the Newcastle-Ottawa scale were considered high-quality studies and included

in this meta-analysis. Discrepancies were resolved by consensus (Table 1). We performed all the analyses based on previously published studies; thus, no ethical approval was required.

2.3. Statistical analysis

The primary outcome was EFS. Data regarding disease-free survival, recurrence-free survival, and distant recurrence-free survival were obtained from the included studies, and they were redefined as EFS, which was measured from the date of initiation of therapy to the date of recurrence or the last day of follow-up.[22] The secondary endpoint was OS, which was defined as the time from the initiation of therapy until death from any cause.

The effects of ^{18}F-FDG BMU on survival were assessed using HRs. Survival data were extracted following a methodology suggested previously.[19] A univariate HR estimate and the 95% CIs were extracted directly from each study if they were provided by the authors. Otherwise, P-values of the log-rank tests, 95% CIs, numbers of events, and numbers of patients at risk were extracted to estimate the HR indirectly. Survival rates calculated from Kaplan–Meier curves were read using Engauge Digitizer version 3.0 (http://digitizer.sourceforge.net) to reconstruct the HR estimate and its variance, assuming that patients were censored at a constant rate during follow-up. An HR > 1 implied worse survival for patients with ^{18}F-FDG BMU, whereas an HR < 1 implied a survival benefit for patients with ^{18}F-FDG BMU.

Heterogeneity among studies was assessed through unadjusted analysis and random-effects models. The following measures were calculated as described previously[23]: I^2 (total heterogeneity/total variability) and v2. Because of the small number of the studies, the Cochran Q test was not used.[23] Meta-regression analysis was performed to search for population characteristics that were unevenly distributed among the studies. Funnel plots were used to assess for publication bias.[24] P-values <.05 were considered to be statistically significant. The data from each study were analyzed using Review Manager (RevMan, Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) and STATA version 15.1 (STATA Corp, College Station, TX).

3. Results

3.1. Study characteristics

After the comprehensive computerized search was performed and the references lists were extensively cross-checked, our

Table 1

Methodological quality of the potentially included studies according to Newcastle–Ottawa scale in this meta-analysis.

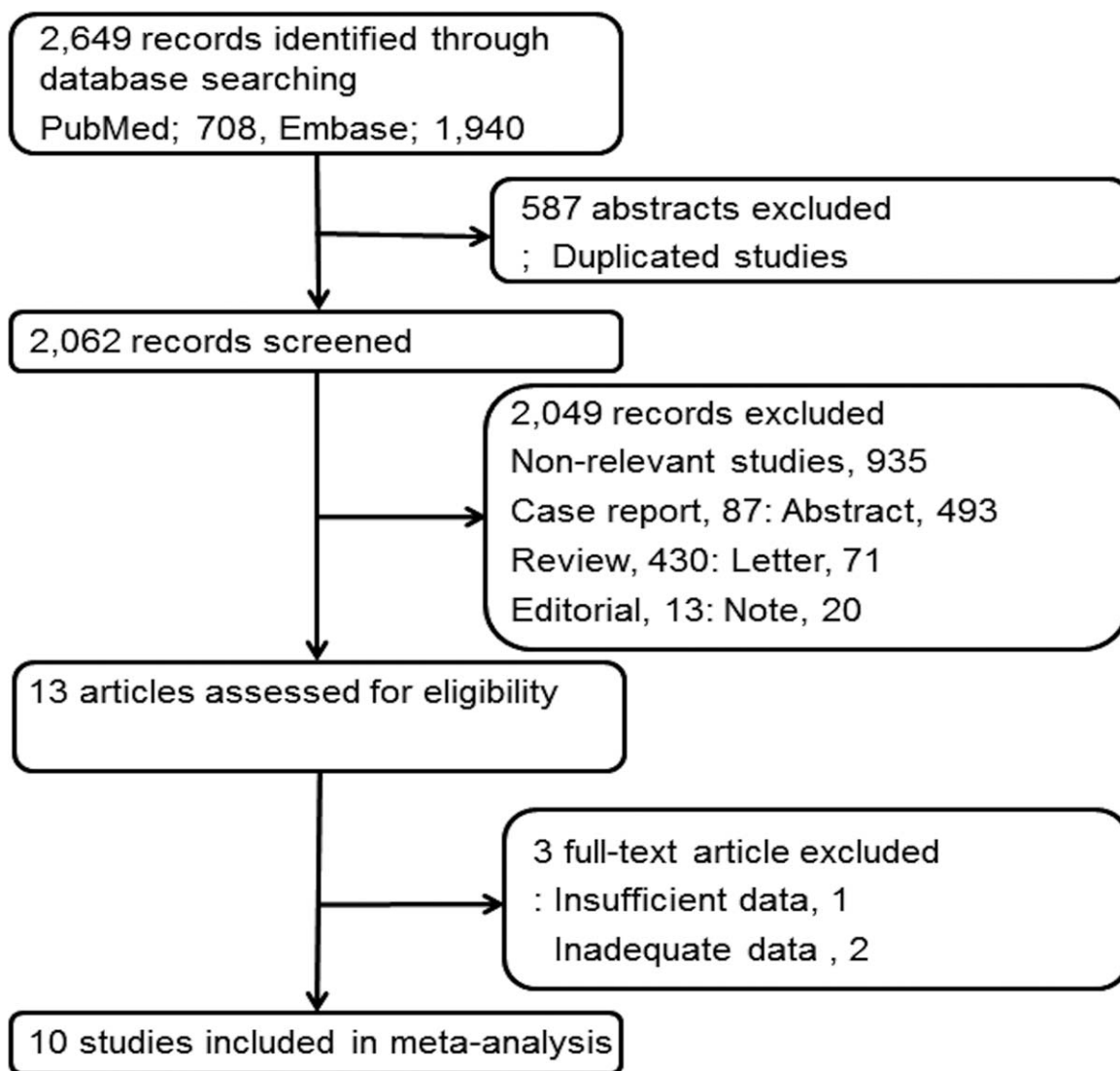| First author	Year	Selection (score)	Comparability (score)	Outcome (score)	Total (score)
Lee J	2107	2	2	3	7
Chang C	2017	2	2	3	7
Lee J	2017	2	2	3	7
Lee J	2017	2	2	3	7
Lee J	2017	2	2	3	7
Lee J	2016	3	2	3	8
Lee J	2016	2	2	3	7
Prevost S	2006	3	2	3	8
Ozmen O	2016	2	2	2	6
Lee J	2018	2	2	3	7

Figure 1. Flow chart of the study selection process.

research yielded 2648 records; 587 of these records were duplicated abstracts and were excluded after reviewing the title and abstract. In addition, 935 nonrelevant studies, 87 case reports, 493 conference abstracts, 71 letters, 13 editorials, 20 notes, and 430 review articles were excluded. The remaining 13 full-text articles were assessed for eligibility, and 3 articles were excluded due to inadequate data for the calculation of survival. Finally, 10 studies, involving 1267 patients, were eligible for inclusion in the meta-analysis.[8–17] The detailed procedure is shown in Figure 1. Quality assessment of all the 10 studies was conducted (Table 1).

The prognostic value of ^{18}F-FDG BMU was assessed by analyzing EFS in 1096 patients and OS in 836. There were 6 types of tumors in this study: lung cancer in four studies; lymphoma in 2 studies; and cervical cancer, colorectal cancer, malignant mesothelioma, and gastric cancer each in 1 study. The parameters of ^{18}F-FDG BMU used were BM to liver uptake ratio (BLR) in 5 studies and mean standardized uptake value (SUV$_{mean}$) in four studies.

3.2. Heterogeneity analysis

I^2 values were 51 ($P = .05$) for event and 52 ($P = .05$) for all-cause death. The meta-regression analysis showed that all population characteristics listed in Table 2 were not significant sources of heterogeneity among the studies. Visual inspection of the funnel plot suggested no evidence of publication bias (Supplemental Fig. 1 and Supplemental Fig 2, http://links.lww.com/MD/C574). The study characteristics are summarized in Table 2.

3.3. Survival analysis

Eight studies[8–13,17] analyzed EFS in 1096 patients, and 7 studies[9,12–17] that reported OS in 836 patients were included to calculate the combined HRs. The HR of EFS ranged between 2.07 and 26.51, and the HR of OS ranged between 0.745 and 20.69. In the EFS analysis, the combined HR was 1.75 (95% CI: 1.45–2.11, $P < .00001$) in the random effects model ($I^2 = 51\%$, $P = .05$). The combined HR of death in the OS analysis was 1.40 (95% CI: 1.13–1.73, $P = .002$) in the random effects model ($I^2 =$

Table 2

Studies included in the current meta-analysis.

First author	Year	Country	No. of patients	Type of tumor	Parameter of 18F-FDG BM uptake	Site of 18F-FDG BM uptake measurement	Follow-up, mo	Endpoints
Lee J	2107	Korea	60	Lymphoma[*]	BLR	T&L spines	22.5	PFS
Chang C	2017	Taiwan	70	Lymphoma[†]	Mean SUV	Sternum	36	PFS, OS
Lee J	2017	Korea	226	Colorectal cancer	Mean SUV	T&L spines	32.3	RFS
Lee J	2017	Korea	145	Cervical cancer	BLR	T&L spines	26.2	PFS, DRFS
Lee J	2017	Korea	309	Gastric cancer	BLR	T&L spines	33.8	RFS, OS
Lee J	2016	Korea	110	Lung cancer[‡]	BLR	T&L spines	22.3	RFS, OS
Lee J	2016	Korea	106	Lung cancer[§]	BLR	T&L spines	18.9	PFS, OS
Prevost S	2006	Canada	120	Lung cancer	Mean SUV	Lumbar spines	18.5	OS
Ozmen O	2016	Turkey	51	Malignant mesothelioma	BLR	Lumbar spine	2.3–4.7 y	OS
Lee J	2018	Korea	70	SCLC	Mean SUV	T&L spines	10.8	RFS, OS

BLR = bone marrow-to-liver mean SUV ratio; BM = bone marrow; DRFS = distant recurrence-free survival; OS = overall survival; PFS = progression-free survival; RFS = recurrence-free survival; SCLC = small cell lung cancer; SUV = standardized uptake value; T&L = thoracic and lumbar.

[*] Lymphoma without clinical evidence of bone marrow involvement.

[†] Diffuse large B-cell lymphoma.

[‡] Nonsmall cell lung cancer treated with curative surgical resection.

[§] Inoperable nonsmall cell lung cancer treated with chemoradiotherapy.

52%, $P = .05$). The forest plots for EFS and OS are represented in Figures 2 and 3, respectively.

4. Discussion

This is the first meta-analysis, to our knowledge, to demonstrate the value of 18F-FDG BMU in mortality prediction in patients with solid tumors. Patients with high 18F-FDG BMU had significantly shorter EFS and OS compared with those with low 18F-FDG BMU.

The BM produces blood cells, which includes leukocytes, erythrocytes, and platelets. Most of the hematopoietic cells produced in the BM are of the neutrophil cell series.[6] The BM can show a mildly increased FDG uptake in a healthy person. Furthermore, some patients with different diseases can show relatively high BMU on 18F-FDG PET imaging.[6,7] Previous
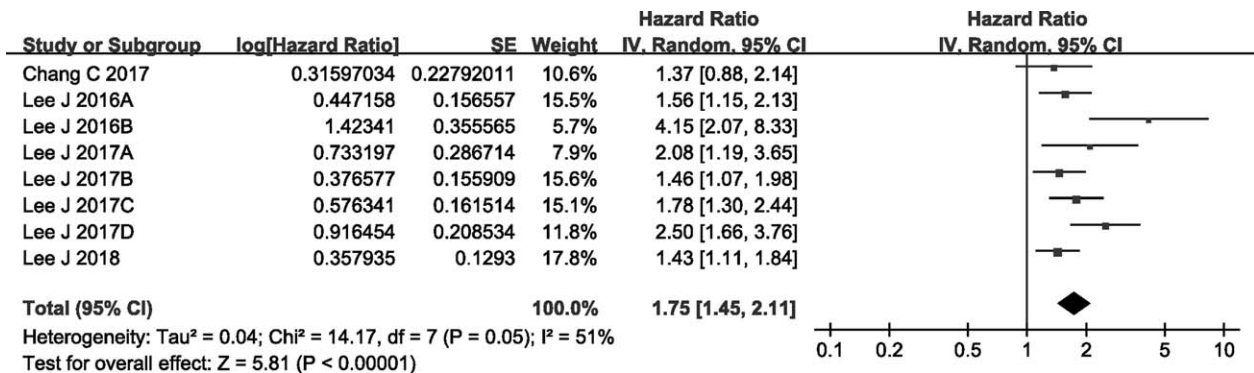

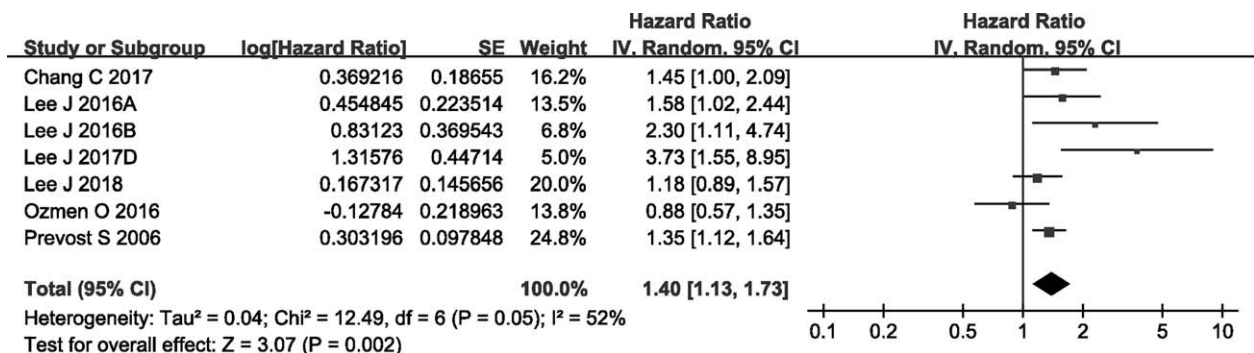Figure 2. Forest plots of the hazard ratios for events in patients.

Figure 3. Forest plots of the hazard ratios for deaths in patients.

studies have demonstrated that in patients with benign or malignant diseases, increased BMU on ^{18}F-FDG PET imaging can reflect activation of the BM in response to an inflammatory condition.[6,7,25] The BM can show increased ^{18}F-FDG uptake because of the systemic inflammatory response to a malignancy.[26] Several studies have reported that inflammation in the tumor microenvironment can contribute to tumor cell proliferation, survival, invasion, and metastasis.[1,2] Several parameters that reflect the systemic inflammatory response to a malignancy have recently been assessed as prognostic factors in the prediction of survival in patients with solid tumors.[27–29] Several studies have explored the relationship between FDG BMU and serum inflammatory markers, and some studies have reported a significant correlation between FDG BMU and serum inflammatory markers.[8,11–13,16]

Owing to the significant correlation between FDG BMU and serum inflammatory markers, some researchers have suggested that increased BMU on ^{18}F-FDG PET imaging might be useful for predicting survival in patients with solid tumors.[8–17] This study has demonstrated that increased BMU on ^{18}F-FDG PET imaging is a prognostic factor in the prediction of EFS and OS. In previous studies, the multivariate analysis also showed that increased BMU on ^{18}F-F DG PET imaging is an independent prognostic factor in the prediction of EFS and OS.

In current study, SUV$_{mean}$ of the BM and BLR were used as parameters for assessing BMU on ^{18}F-FDG PET imaging. A few studies reported both parameters, SUV$_{mean}$ of the BM and BLR, were significant prognostic factors for survival in univariate analysis; however, only BLR has been found to be a significant independent prognostic factor for EFS in multivariate analysis. The present study did not calculate the combined HRs of each parameter. In the present study, we selected the parameter with the better parameter for calculation HR. With the addition of further studies, it is expected that a meta-analysis could be conducted to determine the prognostic values for each parameter.

We acknowledge the limitations of our meta-analysis that are inherent in the data availability. First, all the studies were not prospectively conducted; therefore, selection bias may have affected study quality. Furthermore, the Berkson bias may have affected the outcome. However, although the original registries were retrospective in nature, they were conducted without any interference with the routine clinical practice. Second, many studies were conducted by the same researcher; however, the tumor types in the patients enrolled were different in different studies. Most of the target groups are Asian, and there may be bias. Finally, there is possibly a publication bias against smaller and studies with nonpositive result as suggested by the visual inspection of the funnel plot. For generation of these meta-analysis results, a larger number of prospective consecutive studies might be warranted.

5. Conclusion

In conclusion, although the parameters of ^{18}F-FDG BMU are not standardized and the types of the tumors were different in the published studies, patients with a low level of the parameter of ^{18}F-FDG BMU had better EFS and OS than those with a high level of ^{18}F-FDG BMU. ^{18}F-FDG BMU can be used as a biomarker for stratifying the risk of tumor progression in patients with solid tumors based on the results of this meta-analysis of the published data. However, further large scale cohort studies should be performed to overcome limitations of this study.

Author contributions

Conceptualization: Seong-Jang Kim.
Data curation: Shin Young Jeong, Kyoungjune Pak.
Formal analysis: Shin Young Jeong.
Funding acquisition: Sang-Woo Lee, Byeong-Cheol Ahn, Jaetae Lee.
Investigation: Seong-Jang Kim, Kyoungjune Pak.
Methodology: Shin Young Jeong, Seong-Jang Kim, Kyoungjune Pak, Sang-Woo Lee.
Project administration: Jaetae Lee.
Software: Seong-Jang Kim, Kyoungjune Pak.
Supervision: Seong-Jang Kim, Sang-Woo Lee, Byeong-Cheol Ahn, Jaetae Lee.
Validation: Kyoungjune Pak, Sang-Woo Lee, Jaetae Lee.
Writing – original draft: Shin Young Jeong, Seong-Jang Kim.
Writing – review & editing: Seong-Jang Kim, Kyoungjune Pak, Sang-Woo Lee, Byeong-Cheol Ahn, Jaetae Lee.

References

[1] Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. Nature 2008;454:436–44.
[2] Kundu JK, Surh YJ. Inflammation: gearing the journey to cancer. Mutat Res 2008;659:15–30.
[3] Sun H, Hu P, Shen H, et al. Albumin and neutrophil combined prognostic grade as a new prognostic factor in non-small cell lung cancer: results from a large consecutive cohort. PLoS One 2015;10:e0144663.
[4] Pistelli M, De Lisa M, Ballatore Z, et al. Pre-treatment neutrophil to lymphocyte ratio may be a useful tool in predicting survival in early triple negative breast cancer patients. BMC Cancer 2015; 15:195.
[5] Hsu JT, Liao CK, Le PH, et al. Prognostic value of the preoperative neutrophil to lymphocyte ratio in resectable gastric cancer. Medicine (Baltimore) 2015;94:e1589.
[6] Murata Y, Kubota K, Yukihiro M, et al. Correlations between 18F-FDG uptake by bone marrow and hematological parameters: measurements by PET/CT. Nucl Med Biol 2006;33:999–1004.
[7] Inoue K, Goto R, Okada K, et al. A bone marrow F-18 FDG uptake exceeding the liver uptake may indicate bone marrow hyperactivity. Ann Nucl Med 2009;23:643–9.
[8] Lee JW, Lee SC, Kim HJ, et al. Prognostic value of bone marrow 18F-FDG uptake on PET/CT in lymphoma patients with negative bone marrow involvement. Hell J Nucl Med 2017;20:17–25.
[9] Chang CC, Cho SF, Tu HP, et al. Tumor and bone marrow uptakes on [18F] fluorodeoxyglucose positron emission tomography/computed tomography predict prognosis in patients with diffuse large B-cell lymphoma receiving rituximab-containing chemotherapy. Medicine (Baltimore) 2017;96:e8655.
[10] Lee JW, Baek MJ, Ahn TS, et al. Fluorine-18-fluorodeoxyglucose uptake of bone marrow on PET/CT can predict prognosis in patients with colorectal cancer after curative surgical resection. Eur J Gastroenterol Hepatol 2018;30:187–94.
[11] Lee JW, Jeon S, Mun ST, et al. Prognostic value of fluorine-18 fluorodeoxyglucose uptake of bone marrow on positron emission tomography/computed tomography for prediction of disease progression in cervical cancer. Int J Gynecol Cancer 2017;27:776–83.

[12] Lee JW, Lee MS, Chung IK, et al. Clinical implication of FDG uptake of bone marrow on PET/CT in gastric cancer patients with surgical resection. World J Gastroenterol 2017;23:2385–95.

[13] Lee JW, Na JO, Kang DY, et al. Prognostic significance of FDG uptake of bone marrow on PET/CT in patients with non-small-cell lung cancer after curative surgical resection. Clin Lung Cancer 2017;18:198–206.

[14] Lee JW, Seo KH, Kim ES, et al. The role of 18F-fluorodeoxyglucose uptake of bone marrow on PET/CT in predicting clinical outcomes in non-small cell lung cancer patients treated with chemoradiotherapy. Eur Radiol 2017;27:1912–21.

[15] Prévost S, Boucher L, Larivée P, et al. Bone marrow hypermetabolism on 18F-FDG PET as a survival prognostic factor in non-small cell lung cancer. J Nucl Med 2006;47:559–65.

[16] Ozmen O, Koyuncu A, Koksal D, et al. The potential value of volume-based quantitative PET parameters and increased bone marrow uptake for the prediction of survival in patients with malignant pleural mesothelioma. Nucl Med Commun 2016;37:43–9.

[17] Lee JW, Choi JS, Lyu J, et al. Prognostic significance of 18F-fluorodeoxyglucose uptake of bone marrow measured on positron emission tomography in patients with small cell lung cancer. Lung Cancer 2018;118:41–7.

[18] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.

[19] Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Statist Med 1998;17:2815–34.

[20] Williamson PR, Smith CT, Hutton JL, et al. Aggregate data meta-analysis with time-to-event outcomes. Statist Med 2002;21:3337–51.

[21] Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.

[22] Zhao Q, Feng Y, Mao X, et al. Prognostic value of fluorine-18-fluorodeoxyglucose positron emission tomography or PET-computed tomography in cervical cancer: a meta-analysis. Int J Gynecol Cancer 2013;23:1184–90.

[23] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

[24] Egger M, Davey Smith G, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.

[25] Nunez R, Rini JN, Tronco GG, et al. Correlation of hematologic parameters with bone marrow and spleen uptake in FDG PET. Rev Esp Med Nucl 2005;24:107–12.

[26] Bural GG, Torigian DA, Chen W, et al. Increased 18F-FDG uptake within the reticuloendothelial system in patients with active lung cancer on PET imaging may indicate activation of the systemic immune response. Hell J Nucl Med 2010;13:23–5.

[27] Keam B, Ha H, Kim TM, et al. Neutrophil to lymphocyte ratio improves prognostic prediction of International Prognostic Index for patients with diffuse large B-cell lymphoma treated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone. Leuk Lymphoma 2015;56:2032–8.

[28] Wang KF, Chang BY, Chen XQ, et al. A prognostic model based on pretreatment platelet lymphocyte ratio for stage IE/IIE upper aerodigestive tract extranodal NK/T cell lymphoma, nasal type. Med Oncol 2014;31:318.

[29] Melchardt T, Troppan K, Weiss L, et al. Independent prognostic value of serum markers in diffuse large B-cell lymphoma in the era of the NCCN-IPI. J Natl Compr Canc Netw 2015;13:1501–8.