ORIGINAL ARTICLE
Journal of Digestive Cancer Reports 5(2):91-96, 2017
ISSN 2288-1581
http://www.gicancer.or.kr

The Maximum Standardized Uptake Value of ^{18}F-FDG PET/CT in Diabetic Patients with Metastatic Pancreatic Ductal Adenocarcinoma

Kyu-hyun Paik[1], Hyoung Woo Kim[2], Jong-chan Lee[3], Jingu Kang[4], Yoon Suk Lee[5], Jaihwan Kim[3], Jin-Hyeok Hwang[3]

[1]Department of Internal Medicine, Eulji University College of Medicine, Daejeon; [2]Departments of Internal Medicine, College of Medicine and Medical Research Institute, Chungbuk National University, Cheongju; [3]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam; [4]Department of Internal Medicine, Hallym University Medical School, Seoul; [5]Department of Internal Medicine, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Korea

Background: To evaluate whether DM affects the SUVmax of metastatic lesions on ^{18}F-FDG PET/CT and whether the SUVmax can influence the prognosis of metastatic PDAC patients.
Methods: We conducted a retrospective study of 86 patients with metastatic PDAC who underwent PET/CT before treatment. The SUVmax of primary and metastatic lesions and the ratios of the SUVmax were measured. Long-term survival was evaluated using clinical parameters.
Results: The mean SUVmax of primary lesion was lower in the DM group than in the non-DM group (4.74 vs. 5.96, p=0.009). The SUVmax for all metastatic lesions, except those in the lung, were lower in the DM group than in the non-DM group, and these differences were statistically significant in the lymph nodes and peritoneum. In the 35 patients with hepatic metastasis, higher ratios of the liver SUVmax significantly correlated with shorter OS (HR, 2.625; p=0.013).
Conclusion: DM can influence the lower SUVmax of metastatic lesions as well as primary lesions. The SUVmax ratio of hepatic metastasis could influence on prognosis in metastatic PDAC patients.

Key Words: Pancreatic ductal adenocarcinoma, Metastasis, PET-CT, Diabetes mellitus

INTRODUCTION

It is well known that complete resection is the only way to cure pancreatic ductal adenocarcinoma (PDAC). However less than 20% of patients can undergo surgery due to either a locally advanced tumor or metastasis present at the time of diagnosis.[1] Furthermore, the majority of patients who undergo pancreatectomy inevitably experience recurrence, because occult metastasis is already present at the time of surgery.[2] Thus, many efforts focus on how to avoid unnecessary surgery by using preoperative work-ups.

Recently, there has been considerable interest in identifying metastasis by fluorine-18-fluorodeoxyglucose positron emission tomography coupled with computed tomography (^{18}F-FDG PET/CT). FDG is trapped in cells and competes with glucose for active transport, so elevated blood glucose can affect FDG-uptake in the tissue, influencing diagnostic yield on cancer evaluation. This is especially true for PDAC because PDAC frequently accompanies DM. A recent report showed a decrease in the maximum standardized uptake value (SUVmax) of the primary tumors in PDAC patients with DM, independent of glucose levels.[3] Although several studies have shown that ^{18}F-FDG PET/CT can advantageously detect distant metastasis not detected by CT or magnetic resonance imaging (MRI) in patients with PDAC,[4-7] little is known about whether DM can influence the SUVmax of PET/CT in metastatic lesions in patients with PDAC. Therefore, the current study evaluates whether the DM or elevated serum glucose levels may affect

Received: Nov. 3, 2017, Accepted: Dec. 14, 2017
Corresponding author: **Jin-Hyeok Hwang**, MD, PhD
Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, 82, Gumi-ro 173 Beon-gil, Bundang-gu, Seongnam 13620, Korea
Tel: +82-31-787-7017, Fax: +82-31-787-4051
E-mail: woltoong@snu.ac.kr
*Conflicts of interest: The authors declare no potential conflicts of interest or external source of funding with respect to this manuscript.

the SUVmax of metastatic lesions and whether SUVmax can influence the prognosis of metastatic PDAC patients.

SUBJECTS AND METHODS

1. Subjects

From January 2009 to December 2013, PDAC patients who underwent ^{18}F-FDG PET/CT as an initial diagnostic work-up were reviewed retrospectively. Among them, 96 patients with pathologically verified PDAC who had metastasis on PET/CT were included. Metastasis were pathologically identified, or clinically confirmed during follow-up with sequential radiologic images. Ten patients were excluded due to prior history of surgical resection, systemic chemotherapy, or radiotherapy. Finally, 86 patients were enrolled in this study. DM was diagnosed from patient clinical histories and laboratory test results (hemoglobin A1c [HbA1c] ≥6.5%; fasting plasma glucose ≥126 mg/day; or 2-hour plasma glucose ≥200 mg/dL in repeated testing), following the Standards of Medical Care in Diabetes of the American Diabetes Association.[8] The study was approved by the Institutional Review Board of Seoul National University Bundang Hospital and conformed to the ethical guidelines of the Declaration of Helsinki, 1964, as revised in 2004.

2. Methods

Patients were required to fast for at least 6 h prior to the scan. Plasma glucose levels were measured in all patients before injecting ^{18}F-FDG. ^{18}F-FDG was given intravenously, and a whole-body PET/CT scan was performed 1 h after injection. Regional lymph nodes, bones, liver, lungs, and peritoneum were evaluated to determine the maximum standardized uptake value (SUVmax) in each lesion as well as the primary tumor. The SUV, which was defined as the ratio of the radioactivity concentration to the injected activity divided by body weight, was additionally determined as a parameter of regional radioactivity distribution. The highest SUV in each primary and metastatic lesion was defined as the SUVmax. When multiple metastatic lesions were present, the highest SUV among them was regarded as the SUVmax in each organ.

3. Statistical Analysis

We statistically compared the SUVmax of each metastatic site according to DM status. The primary lesion was used as an internal standard for grading FDG uptake, so the metastatic lesion-to-primary SUVmax ratio was also calculated. Baseline characteristics of the two groups were compared with unpaired t-tests. Spearman's rank correlation coefficients were used to reflect relationships between the SUVmax of primary and metastatic lesions. Additionally, overall survival rates were analyzed by the Kaplan-Meier method. For survival analysis, cutoff values for low and high SUVmax of the primary tumor and distant metastatic sites were used. Each cutoff value was set up with respect to the median value. Patient survival times in different groups were compared using the log-rank test. Parameters predictive for overall survival were assessed using the Cox regression model.

All statistical analyses were performed using SPSS statistics 21.0 software for Windows (IBM Corporation, Armonk, NY, USA). A p-value less than 0.05 was considered statistically significant.

RESULTS

1. Baseline Characteristics

A total of 86 consecutive metastatic PDAC were enrolled in this study. Patient characteristics are listed in Table 1. Forty-eight patients had DM (58.5%, DM group). Among them, 45 patients had already taken DM medication. The mean plasma glucose levels were 128.69±34.34 mg/dL in the DM group and 108.23±20.10 mg/dL in 34 non-DM patients (non-DM group). Tumor location did not differ between the two groups. Lymph nodes (n=54) were the most

Table 1. Baseline patient characteristics

Variables	DM patients (n=48)	Non-DM patients (n=38)	p-value
Sex, male (%)	23 (47.9)	23 (60.5)	0.247
Age (years)	67.7±10.01	66.5±11.27	0.599
BMI (kg/m^2)	22.66±3.50	21.13±3.29	0.041
Location of primary tumor			
Head	18	13	
Body	11	8	
Tail	16	21	
Location of metastasis			
Bone	8 (16.7%)	6 (15.8%)	0.913
Liver	18 (37.5%)	17 (44.7%)	0.500
Lung	5 (10.4%)	7 (18.4%)	0.290
Lymph node	31 (64.6%)	23 (60.5%)	0.701
Peritoneum	11 (22.9%)	14 (36.8%)	0.160

common metastatic site in both groups, followed by the liver (n=35), peritoneum (n=25), bone (n=14) and lung (n=12).

2. SUVmax in Primary and Metastatic Lesions according to DM Status

Table 2 shows that the SUVmax in the primary lesion was lower in the DM group than in the non-DM group (4.74 vs. 5.96, respectively, p=0.009). The SUVmax for all metastatic lesions except those in the lungs were lower in the DM group than in the non-DM group, with statistical significance observed in the lymph nodes (3.44 vs. 4.49, p=0.040) and peritoneum (3.56 vs. 4.85, p=0.023). Although the SUVmax were higher in bone and liver metastasis than in the primary lesion (SUVmax ratio >1) in the DM group, there were no statistically significant differences in SUVmax ratios in metastatic sites between the DM group and non-DM group.

There was a positive correlation between SUVmax of a primary and each metastatic site, with statistical significance shown in lymph nodes (rho=0.390, p=0.003) and liver (rho =0.373, p=0.027, Fig. 1).

3. The Impact of SUVmax or SUVmax Ratio on Overall Survival

The data was further evaluated to examine overall survival (OS). The median follow-up period for all patients was 22 weeks (range, 1-187 weeks). When patients were subdivided using the median SUVmax of the primary lesion (high, ≥ 5.5; low, <5.5), the OS did not differ significantly between the two groups (median, 21 vs. 22 weeks, respectively, p =0.770; Fig. 2A). However, when patients were subdivided using the median SUVmax of 5.5 in hepatic lesions (high, ≥5.5; low, <5.5), the high group had a poorer prognosis

Table 2. SUVmax for primary and metastatic lesions according to diabetes mellitus status

	DM patients (n=48)	Non-DM patients (n=38)	p-value
Primary SUVmax	4.74±1.67	5.96±2.39	0.009
SUVmax of metastatic lesions			
Bone	5.15±1.12	5.87±2.74	0.567
Liver	5.55±1.91	6.05±2.46	0.511
Lung	3.84±1.95	3.56±2.41	0.827
Lymph node	3.44±1.35	4.49±2.05	0.040
Peritoneum	3.56±1.34	4.85±1.27	0.023
SUVmax ratio (metastatic/ primary lesion)			
Bone	1.20±0.51	0.90±0.32	0.207
Liver	1.13±0.40	1.04±0.40	0.534
Lung	0.84±0.42	0.69±0.35	0.536
Lymph node	0.79±0.33	0.78±0.33	0.874
Peritoneum	0.81±0.33	0.87±0.33	0.673

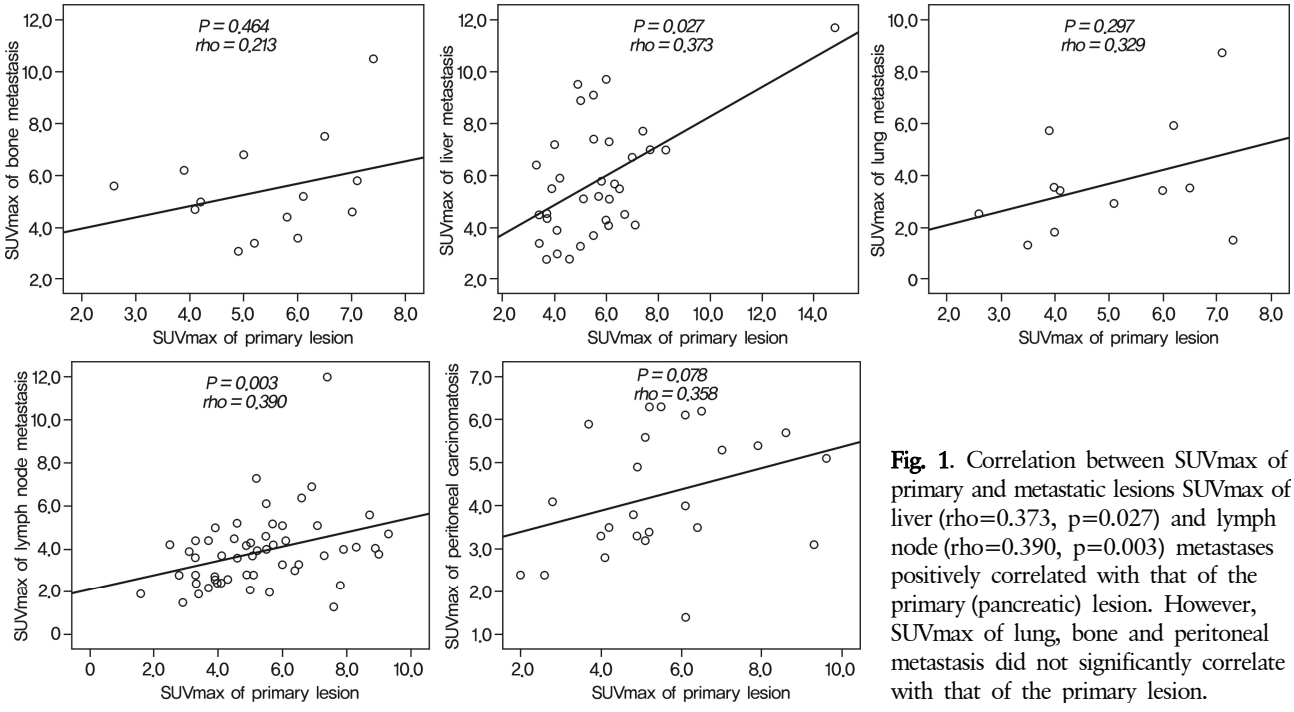

Fig. 1. Correlation between SUVmax of primary and metastatic lesions SUVmax of liver (rho=0.373, p=0.027) and lymph node (rho=0.390, p=0.003) metastases positively correlated with that of the primary (pancreatic) lesion. However, SUVmax of lung, bone and peritoneal metastasis did not significantly correlate with that of the primary lesion.

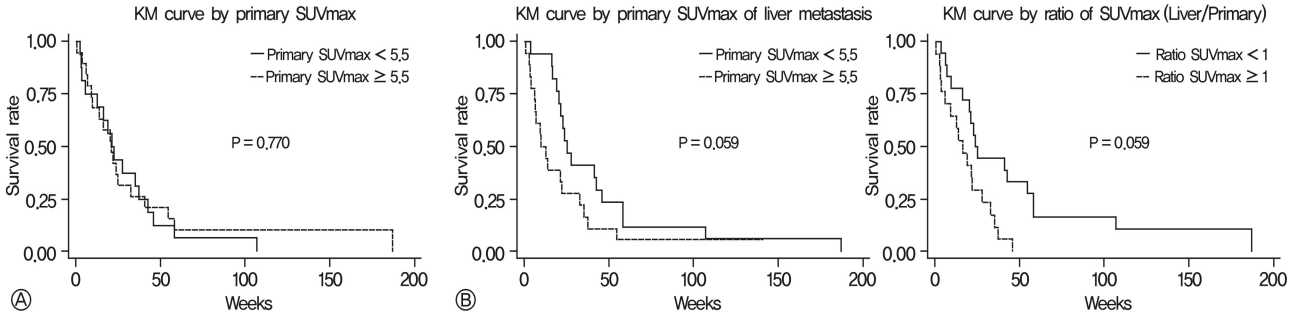

Fig. 2. Kaplan-Meier survival analysis in a subgroup of 35 PDAC patients with hepatic metastasis according to the [18]F-FDG PET/CT SUVmax or SUVmax ratio (**A**) Overall survival of the low (<5.5) primary SUVmax group and the high (≥5.5) primary SUVmax group. No significant differences are observed between the two groups (median, 21 vs. 22 weeks, respectively, p=0.770). (**B**) Kaplan-Meier estimates for OS in patients who had hepatic metastases. Higher SUV max in hepatic metastasis (≥5.5) tend to be associated with poor prognosis, although statistical significance was not achieved (median, 10 vs. 25 weeks, respectively, p=0.059). The patients with high (≥1.0) SUVmax ratios (liver/primary) had shorter OS times than those with low (<1.0) SUVmax ratios (p=0.010).

Table 3. Cox regression analysis for overall survival in PDAC patients with liver metastasis (n=35)

Variables	Univariate		Multivariate	p-value
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	
Gender, female	1.227 (0.601-2.505)	0.574		
Old age (≥64 years)	2.808 (1.329-5.936)	0.007	2.808 (1.329-5.936)	0.007
Diabetes mellitus	0.853 (0.426-1.710)	0.654		
Body mass index (kg/m^2)	1.007 (0.909-1.115)	0.895		
Chemotherapy	0.791 (0.355-1.763)	0.567		
Primary SUVmax				
<5.5	1	Ref		
≥5.5	0.896 (0.451-1.778)	0.753		
SUVmax of liver lesion				
<5.5	1	Ref		
≥5.5	1.913 (0.956-3.831)	0.067		
SUVmax ratio (liver/primary lesion)				
<1.0	1	Ref.	1	Ref.
≥1.0	2.615 (1.218-5.614)	0.014	2.255 (1.056-4.819)	0.036

compared with the low group (median, 10 vs. 25 weeks, respectively, p=0.067). Furthermore, an SUVmax ratio of ≥1.0 for hepatic metastasis was associated with shorter OS (median 17 vs. 24 weeks, p=0.010; Fig. 2B). Using multivariate Cox regression analysis, age ≥64 years old (hazard ratio [HR], 2.808; p=0.007) and liver SUVmax ratio of liver (hazard ratio [HR], 2.615; p=0.014) were independent prognostic predictors for OS (Table 3).

DISCUSSION

[18]F-FDG PET/CT is a relatively recent, noninvasive imaging technique that utilizes specific tissue metabolism, resulting in selective FDG uptake and retention by malignant cells.[9,10] FDG uptake can be affected by blood glucose level, so it is important to know if hyperglycemia or DM can influence malignancy detection, especially in pancreatic cancer, because most PDAC patients have DM or impaired glucose tolerance. Although several reports showed that DM contributes to lower primary SUVmax in PDAC patients,[3,6,11,12] it is not well known if SUVmax for metastatic lesions can be influenced in metastatic PDAC patients. Our study showed that DM tends to lower SUVmax for metastatic lesions in PDAC patients, similarly to primary lesions. The SUVmax ratios for hepatic metastasis could influence prognosis in metastatic

PDAC patients.

In this study, DM was associated with a lower mean SUVmax for metastatic lesions as well as the primary tumor, indicating no difference in SUVmax ratios for each metastatic site according to DM status. Because SUVmax of metastatic sites correlate with primary tumor's metabolic activity, hypermetabolic lesions detected on ^{18}F-FDG PET/CT should be cautiously interpreted in diabetic patients.

Although several studies[13-15] showed that tumor metabolic activity correlates with survival in malignancies, use of the SUVmax of a primary tumor regards as a prognostic factor has thus far been controversial.[16-18] In fact, raw SUVmax were commonly used as sensitivity cutoff values in many studies.[16,18] However, that cannot be generally applicable in clinical situations because the SUVmax was arbitrary for the study. Moreover, DM can decrease FDG uptake of tumor cells, which indicates that SUVmax ratio would be a better indicator than raw SUVmax for metabolic activity evaluations. Therefore, we evaluated SUVmax ratios for metastatic sites, which are the SUV of metastatic lesion normalized to the SUV for the primary tumor, as well as SUVmax as potential prognostic indicators. Our data indicated that the hepatic SUVmax, but not SUVmax for the primary lesion, was a prognostic indicator.

Furthermore, SUVmax ratio (liver/primary) $\geq$1.0 was associated with shorter overall survival (median, 17 vs. 24 weeks). These results suggest that the tumor metabolic activity of hepatic metastasis may be more prognostic than that of the primary lesion or other metastatic lesions. This is supported by recent data that hepatic metastasis are a poor prognostic indicator compared to other metastasis in metastatic PDAC patients.[19-21]

These results were comparable to those of a previous study[22] that evaluated the prognostic value of SUVmax in patients with metastatic gastric cancer. In contrast to our results, this study[22] concluded that gastric SUVmax was an independent predictor of OS, regardless of the SUVmax of metastatic lesions. This distinction could be explained by several factors, including blood glucose levels, GLUT 1 expression, glucose-6-phophatase expression, and tumor heterogeneity according to tumor types.[23]

To the best of our knowledge, this study is the first to suggest that SUVmax ratio (liver/primary) is a prognostic indicator in metastatic PDAC patients although there are some limitations in the study such as the retrospective evaluation of the data, the relatively small sample size, and the lack of pathologic confirmation for all metastatic sites.

CONCLUSIONS

In conclusion, DM can contribute to lower SUVmax for metastatic lesions as well as primary lesions. The survival of PDAC patients with hepatic metastasis can be predicted by evaluating the liver to pancreas SUVmax ratio using ^{18}F-FDG PET/CT. Additionally, further larger prospective studies will be needed to establish the diagnostic and prognostic role of ^{18}F-FDG PET/CT in metastatic PDAC.

Acknowledgements

The authors thank the Medical Research Collaborating Center at Seoul National University Bundang Hospital for statistical analyses.

The authors are indebted to J. Patrick Barron, Professor Emeritus, Tokyo Medical University and Adjunct Professor, Seoul National University Bundang Hospital for his pro bono editing of this manuscript.

REFERENCES

1. Brennan MF, Moccia RD, Klimstra D. Management of adenocarcinoma of the body and tail of the pancreas. Ann Surg 1996;223:506-511; discussion 11-12.
2. Amikura K, Kobari M, Matsuno S. The time of occurrence of liver metastasis in carcinoma of the pancreas. Int J Pancreatol 1995;17:139-146.
3. Chung KH, Park JK, Lee SH, et al. Lower maximum standardized uptake value of fluorine-18 fluorodeoxyglucose positron emission tomography coupled with computed tomography imaging in pancreatic ductal adenocarcinoma patients with diabetes. Am J Surg 2015;209:709-716.
4. Kato T, Fukatsu H, Ito K, et al. Fluorodeoxyglucose positron emission tomography in pancreatic cancer: an unsolved problem. Eur J Nucl Med 1995;22:32-39.
5. Stollfuss JC, Glatting G, Friess H, Kocher F, Berger HG, Reske SN. 2-(fluorine-18)-fluoro-2-deoxy-D-glucose PET in detection of pancreatic cancer: value of quantitative image interpretation. Radiology 1995;195:339-344.
6. Bares R, Klever P, Hauptmann S, et al. F-18 fluorodeoxyglucose PET in vivo evaluation of pancreatic glucose metabolism for detection of pancreatic cancer. Radiology 1994;192:79-86.
7. Roy FN, Beaulieu S, Boucher L, Bourdeau I, Cohade C. Impact of intravenous insulin on ^{18}F-FDG PET in diabetic cancer patients. J Nucl Med 2009;50:178-183.
8. American Diabetes A. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33 Suppl 1:S62-69.
9. Tann M, Sandrasegaran K, Jennings SG, Skandarajah A,

McHenry L, Schmidt CM. Positron-emission tomography and computed tomography of cystic pancreatic masses. Clin Radiol 2007;62:745-751.
10. Sperti C, Pasquali C, Chierichetti F, Liessi G, Ferlin G, Pedrazzoli S. Value of 18-fluorodeoxyglucose positron emission tomography in the management of patients with cystic tumors of the pancreas. Ann Surg 2001;234:675-680.
11. Zimny M, Fass J, Bares R, et al. Fluorodeoxyglucose positron emission tomography and the prognosis of pancreatic carcinoma. Scand J Gastroenterol 2000;35:883-888.
12. Diederichs CG, Staib L, Vogel J, et al. Values and limitations of ^{18}F-fluorodeoxyglucose-positron-emission tomography with preoperative evaluation of patients with pancreatic masses. Pancreas 2000;20:109-116.
13. Delbeke D, Martin WH. Positron emission tomography imaging in oncology. Radiol Clin North Am 2001;39:883-917.
14. Hustinx R, Benard F, Alavi A. Whole-body FDG-PET imaging in the management of patients with cancer. Semin Nucl Med 2002;32:35-46.
15. Patronas NJ, Di Chiro G, Kufta C, et al. Prediction of survival in glioma patients by means of positron emission tomography. J Neurosurg 1985;62:816-822.
16. Sperti C, Pasquali C, Chierichetti F, Ferronato A, Decet G, Pedrazzoli S. 18-Fluorodeoxyglucose positron emission tomography in predicting survival of patients with pancreatic carcinoma. J Gastrointest Surg 2003;7:953-9; discussion 9-60.
17. Nakata B, Nishimura S, Ishikawa T, et al. Prognostic predictive value of ^{18}F-fluorodeoxyglucose positron emission tomography for patients with pancreatic cancer. Int J Oncol 2001;19:53-58.
18. Nakata B, Chung YS, Nishimura S, et al. ^{18}F-fluorodeoxyglucose positron emission tomography and the prognosis of patients with pancreatic adenocarcinoma. Cancer 1997;79:695-699.
19. Kim HW, Lee JC, Paik KH, Lee YS, Hwang JH, Kim J. Initial Metastatic Site as a Prognostic Factor in Patients With Stage IV Pancreatic Ductal Adenocarcinoma. Medicine (Baltimore) 2015;94:e1012.
20. Forssell H, Wester M, Akesson K, Johansson S. A proposed model for prediction of survival based on a follow-up study in unresectable pancreatic cancer. BMJ Open 2013;3:e004064.
21. Morizane C, Okusaka T, Morita S, et al. Construction and validation of a prognostic index for patients with metastatic pancreatic adenocarcinoma. Pancreas 2011;40:415-421.
22. Park JC, Lee JH, Cheoi K, et al. Predictive value of pretreatment metabolic activity measured by fluorodeoxyglucose positron emission tomography in patients with metastatic advanced gastric cancer: the maximal SUV of the stomach is a prognostic factor. Eur J Nucl Med Mol Imaging 2012;39:1107-1116.
23. Higashi T, Saga T, Nakamoto Y, et al. Diagnosis of pancreatic cancer using fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET) - usefulness and limitations in "clinical reality". Ann Nucl Med 2003;17:261-279.