Prognostic value of intratumoral heterogeneity of preoperative ^{18}F-FDG PET/CT in pancreatic cancer

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Abstract

Objective: The purpose of current study was to investigate the value of textural features used fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in predicting recurrence-free survival (RFS) and overall survival (OS) in patients with pancreatic cancer. **Subjects and Methods:** Seventy two patients with pancreatic cancer who underwent ^{18}F-FDG PET/CT prior to curative surgical treatment were enrolled. Conventional parameters, such as maximum standardize uptake value (SUVmax), metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were measured. Twenty-two textural features were extracted from PET images derived from first-order and 4 higher-order matrices: Grey level co-occurrence matrix (GLCM), neighborhood grey-level different matrix (NGLDM), grey-level run length matrix (GLRLM), and grey-level zone length matrix (GLZLM). Independent predictive factors for survival were determined using Cox proportional hazards regression models. **Results:** The SUVmax did not have prognostic values for RFS and OS. Median values of TLG and intratumoral heterogeneity parameter (kurtosis) were 63.95, and 3.15. High TLG and high kurtosis patients group showed shorter OS. Cox proportional hazards regression analysis revealed differentiation of the tumor, kurtosis and TLG were the significant predictive factors on OS. Besides, kurtosis presented no correlation with the conventional PET parameters, such as SUVmax, MTV and TLG. **Conclusion:** This study suggests that intratumoral heterogeneity and volumetric parameter induced by ^{18}F-FDG PET/CT could be significant prognostic surrogate markers in patients with pancreatic cancers.

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Introduction

Pancreatic cancer is a common cause of cancer-related death across the world [1]. Pancreatic cancer is the fourth leading cause of cancer death in the USA and fifth in South Korea [2, 3]. The only possible curative treatment of pancreatic cancer is surgery, yet only 20% patients are resectable status [4]. Besides, the recurrence rate after resection remains high and >50% of the patients may recur with 5-year survival rate of only 10%-20% [5, 6].

Several pathologic factors, such as lymphovascular invasion, peripancreatic lymph node (LN) metastasis, and perineural invasion, have been reported as prognostic markers in pancreatic cancer [7-10]. Prognostic values of aforementioned traditional factors are, however, nearly dependent on postoperative surgical specimens. Thus, evaluating preoperative prognostic parameters over traditional pathologic factors may have benefits for patient stratification with high risk disease.

Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is used as a tool for prognosis in the field of cancer. Maximum standardize uptake value (SUVmax), commonly-used imaging parameter of ^{18}F-FDG PET/CT, has been proposed a possible marker for prognostic predictor in pancreatic cancer [11, 12]. Furthermore, few studies have indicated that volume-based PET imaging parameters, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), are well associated with the survival of pancreatic cancer [13, 14].

Intratumoral heterogeneity has lately developed and contributed to the cancer studies related to the prognosis [15-17]. Meanwhile, there is emerging evidence that textural analysis is useful for quantifying intratumoral heterogeneity [18-21]. The textural features induced by PET have been reported to predict survival outcomes in esophageal, cervical, and lung cancer [22-24]. The relationship between the textural features measuring intratumoral heterogeneity and the prognostic potential in pancreatic cancer has not yet been researched sufficiently.

The present study interested in whether SUVmax, MTV, TLG and texture analysis of intratumoral heterogeneity in preoperative ^{18}F-FDG PET/CT image could be used as factors predicting recurrence-free survival (RFS) and overall survival (OS) in the patients with pancreatic cancer.

Subjects and Methods

Patient eligibility

Eighty-two consecutive patients with pancreatic cancer underwent ^{18}F-FDG PET/CT prior to surgery between September 2009 and December 2016. Among them, only 72 patients were included in the study. The exclusion criteria were: 1) if they had received neoadjuvant chemotherapy or radiation treatment 2) endocrine tumors based on histologic examination of resected specimens (n=4 patients) 3) metabolic volume after segmentation lower than 3.0mL (n=6 patients). This study was approved by our institutional review board and written informed consent was obtained from each patient.

^{18}F-FDG PET/CT imaging

Standard patient preparation included a fasting period of at least 6h and a serum glucose level lower than 6.7mmol/L (120mg/dL) before ^{18}F-FDG administration. Positron emission tomography/CT imaging was performed 60min after injection of ^{18}F-FDG (5MBq/kg of body weight). For attenuation correction, a low-dose CT scan was acquired. Whole-body CT was obtained without contrast agent and performed using a 40 slices spiral CT scanner with quality reference 170mAs w/Caredose 4D at a 120kV and 5.0mm slice thickness. The emission scan was performed after CT scan. The emission scan time per bed position was 3min and six bed positions were acquired.

The ^{18}F-FDG PET/CT data were obtained using a dedicated PET/CT scanner (BIOGRAPH 40 TruePonit w/TrueV; Siemens Medical Solutions). Positron emission tomography images were reconstructed using an iterative algorithm (TrueX, iteration 3, subset 21, zoom 1.2, No-filter) with image matrix size of 168x168.

Imaging analysis

Volume of interest (VOI) was drawn over the primary tumor uptake in the pancreas by using a threshold of SUVmax cut-off value of 2.5. In each VOI, 3 conventional indices (SUVmax, MTV, TLG) and 24 textural features were calculated. The textural analysis was performed on PET images. Voxel intensity was resampled with 64 grey levels and normalized by absolute resampling bounds between 0 and 20 SUV units. All parameters were extracted automatically by using LIFEx software (http://www.lifexsoft.org).

Maximum SUV is defined by the highest voxel value within VOI, MTV was determined as a volume of the tumor delineated by 2.5 of SUV. Total lesion glycolysis is derived by multiplying MTV and SUVmean. The intratumoral heterogeneity was represented by the textural features from the first-order and higher-order matrices. First-order textural features included skewness, kurtosis, entropy H and energy H based on intensity histogram. Eighteen textural features were extracted from higher-order matrices leading to 6 features (homogeneity, energy, contrast, correlation, entropy and dissimilarity) for grey level co-occurrence matrix, 2 (coarseness and contrast) for neighborhood grey-level different matrix, 5 (SRE, LRE, GLNU, RLNU, RP) for grey-level run length matrix, and 5 (SZE, LZE, GLNUz, ZLNU, ZP) for grey-level zone length matrix. The formula from texture features were demonstrated at previously published study [25].

Statistical analysis

To investigate any relationship between textural features with conventional indices such as SUVmax, TLG and MTV, the Spearman's rank correlation was used. The duration of RFS was decided as the time from the date of the pre-treatment ^{18}F-FDG PET/CT scan to the recurrence. The duration of OS was determined as the time from the date of the pre-treatment ^{18}F-FDG PET/CT scan to the death. The prognostic significances of variables for RFS and OS were assessed by univariate and multivariate analyses using Cox proportional hazards regression models. Survival curves were conducted using the Kaplan-Meier method, and differences between groups were carried out with log-rank tests. Survival curves stratified by median values of parameter. Statistical analysis was performed by MedCalc software (MedCalc, Mariakerke, Belgium).

Results

Patient characteristics

The patient characteristics are summarized in Table 1. Of 72 patients, the median age at the time of diagnosis was 65 years (range, 30-83 years). Fifty six patients (77.7%) were recurred and 18 patients (25.0%) were dead during the follow-up period. The median follow-up time of RFS and OS were 5.6 months (range, 0.5-64.0 months) and 12.5 months (range, 0.7-67.7 months), respectively.

Recurrence-Free survival analysis

We analyzed prognostic factors using univariate Cox proportional hazards regression analysis. Univariate analysis demonstrated that poor differentiation, perineural invasion, peripancreatic metastatic LN, high stage, high TLG, high GLNUz were significant predictors of poor prognosis. Multivariate analysis elucidated that only pathologic data such as poor tumor differentiation (HR 2.13; 95% CI 1.24-3.65; P=0.005) and existence of perineural invasion (HR 2.19; 95% CI 1.08-4.43; P=0.028) was only significant predictive factor associated with RFS in the cancer patients.

Overall survival analysis

On the univariate analysis, differentiation, stage, MTV, TLG, kurtosis, correlation, coarseness, GLNUz, ZLNU were significant predictors of OS. The multivariate Cox proportional hazard regression analysis showed that poor differentiation (HR 2.99; 95% CI 1.23-7.25; P=0.015), high TLG (HR 4.60; 95%

Table 1. Patient characteristics.

Characteristic	Value (range)
Sex	
Male	41
Female	31
Age	65 (30-83)
Tumor size	3.5 (1.5-11.5)
Differentiation	
Well	16
Moderate	47
Poor	9
Lymphovascular invasion	
Yes	6 (15.7)
No	3 (7.8)
Perineural invasion	
Yes	53
No	19
Metastatic lymph node	
Yes	51
No	21
CEA	4.15 (1.03-62.09)
CA 19-9	720.2 (2.0-10000.0)
pStage	
IIA	21
IIB	49
III	1
IV	1
Surgery	
PD	61
DP	9
TP	2

PD: pancreatoduodenectomy; DP: distal pancreatectomy; TP: total pancreatectomy

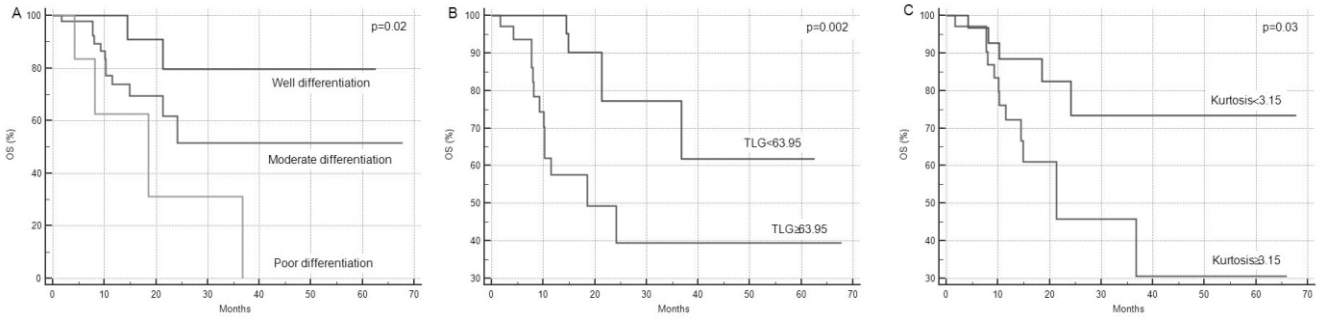

Figure 1. Overall survival stratified by (A) tumor differentiation (B) total lesion glycolysis and (C) kurtosis by Kaplan-Meier survival analysis.

CI 1.54-13.70; P=0.006) and high kurtosis (HR 3.98; 95% CI 1.36-11.61; P=0.011) were independent prognostic factors for the OS (Table 2). Kaplan-Meier survival analysis showing significant survival benefits of well differentiation tumor (x^2=7.54; P=0.023), low TLG (x^2=8.91; P=0.002) and low kurtosis (x^2=4.69; P=0.030) are illustrated in Figure 1.

Correlation between textural features and conventional PET indices

Figure 2 shows the relationship between textural feature and other PET parameters in patients with pancreatic can-cers. There was no correlation between kurtosis and SUVmax (r=0.06; P=0.575), MTV (r=-0.05; P=0.644) and TLG (r=-0.08;

Table 2. *Multivariate Cox proportional hazards analysis for overall survival.*

Variable	HR	95% CI	P
Differentiation (well/moderate/poor)	2.99	1.23-7.25	0.015
TLG (≤63.95/>63.95)	4.60	1.54-13.70	0.006
Kurtosis (≤3.15/>3.15)	3.98	1.36-11.61	0.011

HR: hazards ratio; CI: confidence interval TLG: total lesion glycolysis

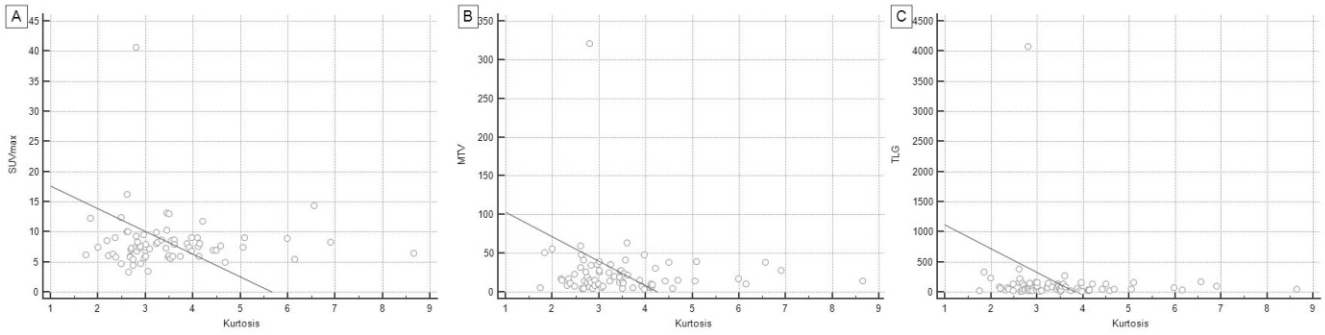

Figure 2. Correlation between kurtosis and conventional parameters from ^{18}F-FDG PET/CT. Kurtosis showed no association with (A) SUVmax, (B) metabolic tumor volume and (C) total lesion glycolysis.

P=0.462). We evaluated the relationship between tumor size and volumetric parameters of ^{18}F-FDG PET/CT. There was weak correlation between tumor size and MTV (r=0.51; P< 0.0001), and TLG (r=0.50; P<0.0001).

Discussion

This study focused on potential indices predicting tumor recurrence and survival in pancreatic cancer. The current study concluded that conventional indices of ^{18}F-FDG PET/CT such as SUVmax did not have prognostic potential. Volumetric parameter and intratumoral heterogeneity depicted by textural features were potent predictors for overall survival. The results of this study suggest that textural features of pretreatment ^{18}F-FDG PET/CT may be important prognostic factors in surgically resected pancreatic cancer.

Some studies have reported that conventional PET parameters can offer the prognostic information in pancreatic cancer. The SUVmax would be the most commonly applied index presenting prognostic value [11, 12]. However, there exist conflicting data in the use of SUVmax for prognosis prediction. Xu et al. (2014) reported that SUVmax was not predictive of RFS and OS [14]. Im et al. (2016) showed SUVmax was not independent predictor of RFS [13]. It is identical to our study as both studies conducted on the same resectable pancreatic cancer patient group. There was no association found between SUVmax and survival in this study. Maximum SUV may not serve as the surrogate parameter of pancreatic tumor behavior considering it only represents single-pixel intensity into the tumor.

It has been a debate over whether tumor size reflecting pathologic tumor volume would predict prognosis in cancer patients [26, 27]. We could not found any significance of the tumor size for the survival analysis. There, however, exist weak correlation between tumor size and volumetric parameter. This can be interpreted that tumor size could be inadequate to be used as a sole prognostic factor and it might be implied that volumetric parameters bear more than pathologic tumor burden.

Volumetric parameters of ^{18}F-FDG PET/CT are three-dimensional measurements that include total tumor volume and metabolic activity. Recent studies proposed volumetric parameters of ^{18}F-FDG PET/CT are reliable indicators of poor survival. Choi et al. (2014) showed the MTV is a strong independent prognostic factor for patient survival treated with chemoradiation therapy [28]. Im et al. (2016) and Xu et al. (2014) showed volumetric parameters were strong independent prognostic factors of RFS and OS [13, 14]. Current result showed the similar conclusion that TLG can function as a reliable prognostic parameter predicting OS in pancreatic cancer.

In current study, one textural feature, kurtosis from the first-order matrix, was independently associated with OS. The textural features were better surrogate marker for the survival prediction than conventional PET parameter, such as SUVmax.

Intratumoral heterogeneity can be influenced by assorted biological elements such as necrosis, vascularity, hypoxia, and proliferation, which are randomly distributed across tumor [29, 30]. These biological factors are associated with adverse prognosis [29-32]. A measure of intratumoral heterogeneity in analysis may reflect the prognostic potential. Textural analysis is a method to assess intratumoral heterogeneity using information about the relation between ad-

jacent pixels [23]. Few studies have investigated that this textural features to have a better role in predicting of survival or response to the therapy. Cook et al. (2013) showed that textural features of ^{18}F-FDG PET/CT, such as busyness, contrast, and coarseness, were related to poor prognosis and no response to chemoradiotherapy in patients with non-small cell lung cancer [22]. Tixier et al. (2011) represented textural features on the baseline ^{18}F-FDG PET/CT scan, such as coarseness, entropy and size variability, can predict response to combined chemoradiotherapy in esophageal cancer [23]. Yang et al. (2013) suggested that changes of intratumor heterogeneity characterized by textural features calculated from GLRLM and grey-level size zone matrix during chemoradiotherapy may serve as a reliable prognostic parameter in cervical cancer [24]. Yet, it is uncertain which textural feature is the most predictive of patient outcome for different tumor types. Further studies need to address to solve this problem.

Although textural features measuring intratumoral heterogeneity have prognostic information, they could bring similar information with conventional PET parameters [19, 20]. In the current study, we found no such correlation between kurtosis of first-order matrix and conventional indices, SUVmax, MTV, and TLG. This might represent that kurtosis has adding prognostic value over SUVmax and volumetric parameters in the pancreatic cancer.

Several drawbacks limited this study. First, this study had weakness originated from retrospective design. Second, method of detecting textural feature has yet been standardized. Third, the patients were pooled from a relatively small number of patients. These problems should be solved when a prospective study with a larger number of patients is conducted to validate studies.

In conclusion, conventional indices of pretreatment ^{18}F-FDG PET/CT might not have a prognostic value of patient outcome. Volumetric parameter and intratumoral heterogeneity measured by textural analysis of ^{18}F-FDG PET/CT was important independent prognostic predictors in patient with pancreatic cancer.

The authors declare that they have no conflicts of interest.

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