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The value of ^{18}F-FDG PET/CT and carbohydrate antigen 19-9 in predicting lymph node micrometastases of pancreatic cancer

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Abstract

Purpose This study aimed to assess the value of ^{18}F-FDG PET/CT and carbohydrate antigen 19-9 (CA 19-9) levels in predicting lymph node micrometastases in patients with pancreatic cancer.

Patients and methods A total of 160 patients with pancreatic carcinoma were included in the study from 2012 to 2017. All patients underwent surgical treatment and PET/CT scans as well as tests to measure CA 19-9 levels before surgery. The PET/CT scans were evaluated by 2 nuclear medicine physicians who were blinded to the clinical information and were compared to the postsurgical pathological findings. Logistic regression analysis was performed to determine the variables that could predict lymph node micrometastases. Receiver operating characteristic (ROC) curves were utilized to find the best cutoff value of the variables related to predicting lymph node micrometastases.

Results The maximum standardized uptake value (SUV_{max}) of the primary tumor and CA 19-9 level were potent predictors for determining the lymph node status. The best SUV_{max} and CA 19-9 cutoff values for predicting lymph node micrometastases were 7.05 (sensitivity = 71.2%, specificity = 76.6%) and 240.55 U/ml (sensitivity = 62.1%, specificity = 79.8%), respectively.

Conclusion Patients with pancreatic cancer with a tumor $SUV_{max} \geq 7.05$ or a CA 19-9 value ≥ 240.55 are likely to have lymph node micrometastases.

Keywords Pancreatic cancer · Lymph nodal micrometastases · ^{18}F-FDG PET/CT · CA19-9

Introduction

Pancreatic carcinoma is one of the most aggressive malignancies with a 5-year survival rate lower than 7%, which is partly due to delayed diagnoses since more than half of the patients are diagnosed at advanced stages (5-year survival rate is 2%) [1]. Presently, radical resection is still the only curative method for pancreatic carcinoma. Despite significant improvements to the operative technique, little progress has been made in the overall survival (OS) of patients with pancreatic carcinoma in the past 40 years. The majority of patients develop distant metastatic disease and up to 80% of patients develop local recurrent disease, with the majority of recurrences occurring within 1–3 cm of the resection margin [2]. Lymph node metastasis occurs frequently in pancreatic carcinoma patients [3] and is an independent negative prognostic factor for patients [4]. The use of neoadjuvant therapy has demonstrated effects on tumor regression in the lymph node and has improved the survival of pancreatic cancer patients [2, 5, 6]. Large regional lymph nodes in patients with pancreatic carcinoma have been proposed as one of the four high-risk factors for neoadjuvant therapy in the National Cancer Institute-designated National Comprehensive Cancer Network (NCCN) guidelines. The remaining three factors are highly elevated serum carbohydrate antigen 19-9 (CA-19-9) levels, large primary tumor, and excessive weight loss or extreme pain. Therefore, predicting the lymph node status before performing invasive procedures or providing treatment is important.

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The non-enhancement characteristics on magnetic resonance (MR) images appear to be linked with lymph node metastasis in pancreatic neuroendocrine tumors [7]. Diffusion-weighted MR imaging and perfusion MR imaging can differentiate between benign and malignant lymph nodes in patients with cancers of the mediastinum, neck, and pancreatobiliary region [8–10]. Positron emission tomography using 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG PET) is a noninvasive useful imaging modality for diagnosing and managing pancreatic carcinoma when combined with computed tomography (CT). PET/CT has been reported to improve the detection of distant metastases in patients with resectable pancreatic carcinoma, ultimately allowing these patients to avoid unnecessary surgery and complications [11–13]. However, not all postoperative pathological lymph nodal metastases, especially small metastases, can be visually detected by imaging before surgery. These pathologically positive lymph node metastases that appear negative with imaging were defined as lymph node micrometastases. No studies have investigated the use of ^{18}F-FDG PET/CT in detecting regional lymph node micrometastases of pancreatic carcinoma.

The tumor marker CA 19-9 is widely used in the management of pancreatic cancer, including early detection [14], predicting prognosis [15], monitoring treatment, and evaluating curative effects [16]. As reported, elevated CA 19-9 levels are found in approximately 60–80% of pancreatic carcinoma patients with locally advanced or metastatic disease [16]. The role of CA 19-9 in detecting regional lymph node micrometastases of pancreatic carcinoma has not been reported.

In this study, we performed a retrospective study of the risk factors for regional lymph node micrometastases in pancreatic cancer based on PET/CT and CA 19-9.

Materials and methods

Patients

We retrospectively reviewed all pancreatic cancer patients who underwent ^{18}F-FDG PET/CT imaging from January 2012 to Marth 2017 in our hospital. Patients who met the following criteria were included: (a) underwent PET/CT imaging; (b) were tested for CA 19-9 levels within 1 week of the ^{18}F-FDG PET/CT scan; and (c) underwent surgical resection within 1 week after the ^{18}F-FDG PET/CT scan. Patients who met the following criteria were excluded: (a) received chemotherapy or radiotherapy before the ^{18}F-FDG PET/CT scan and surgical operation; and (b) had evidence of distant metastasis.

This retrospective research was approved by the institutional review board.

Acquisition technique

All patients were imaged using a standard clinical PET/CT protocol. All patients fasted for at least 6 h before the examination. The serum glucose levels were measured before the radiotracer injection to exclude those with hyperglycemia (cutoff of 180 mg/dl). The patients received a weight-adjusted intravenous injection of 370–555 MBq (10–15 mCi) of ^{18}F-FDG. The images were acquired from the skull base to the upper thighs 60 min after the radiotracer injection using a CTI Biograph duo PET/CT scanner (GE Medical Systems, Waukesha, USA; United Imaging, Shanghai, China).

Image interpretation

The following two dedicated diagnostic PET/CT devices were employed: Discovery VCT unit (GE Medical Systems, Waukesha, USA) and uMI S-96R unit (United Imaging, Shanghai, China) with a 64/16-MDCT scanner. A low-dose registration CT and a whole-body PET scan were acquired from the head to the upper thighs. All PET/CT scans were displayed via a uWS-MI R001 workstation (United Imaging, Shanghai, China) with abdominal (window width, 350 HU; window level, 50 HU) window settings.

Two independent nuclear medicine physicians who were blinded to the clinical findings and pathology results evaluated all PET/CT scans. The maximum standardized uptake (SUV_{max}) values of the primary tumor and suspicious lymph nodes were automatically calculated after free-hand volume of interest segmentation. The SUV_{max} values were calculated using the attenuation-corrected images, adjusting for the amount of injected FDG, the body weight of each patient, and the cross-calibration factors between the PET scanner and the dose calibrator [17]. The short-axis diameters of all visible lymph nodes were determined on the axial images by each reviewer. Lymph nodes larger than 1 cm in the short-axis diameters on CT or had higher radiotracer uptake than the muscle background on PET were defined as positive.

Surgical procedures

The surgical procedures included standard pancreaticoduodenectomy for tumors of the head and uncinate process and distal pancreatectomy and splenectomy for tumors of the neck, body, and tail. Lymphadenectomy included the removal of the anterior and posterior pancreaticoduodenal, pyloric, and biliary ducts, superior and inferior pancreatic head and/or body, common hepatic artery, and celiac trunk lymph nodes, as well as lymph nodes along

the right side of the superior mesenteric artery, during pancreaticoduodenectomy and total pancreatectomy.

CA 19-9 testing and histologic analysis of lymph node metastases

The serum CA 19-9 levels were measured by automated electrochemical luminescence immunoassays. Lymph nodes were defined as positive when metastatic deposits of any size were detected by a light microscopy examination with only hematoxylin and eosin stain.

Statistical analyses

All numerical values are reported as the mean ± standard deviation (mean ± SD). Statistical differences between the continuous variables were analyzed with independent sample t-tests, and nominal variables were analyzed with χ^2 tests or Fisher's exact tests. To determine the variables that can predict lymph node micrometastases, a logistic regression analysis was performed. We utilized receiver operating characteristics (ROC) curves to find the best cutoff value of the variables related to differentiation. Data were analyzed by Statistical Package for Social Sciences (SPSS) 19.0 software. All analyses were two-sided. A P value less than 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 160 pancreatic cancer patients were included in this study. The characteristics of the patients and surgical pathology results are reported in Table 1. Of all study participants, 66 patients were pathologically proven to have peripancreatic lymph node metastases. Significant differences ($P < 0.05$) were observed in the age, tumor SUV_{max}, and serum CA 19-9 levels before surgery between patients with and without lymph node metastases; moreover, no differences in sex, tumor location, tumor size or tumor pathology existed. Patients with peripancreatic lymph node metastases seemed to have higher tumor SUV_{max} and CA 19-9 levels than those without peripancreatic lymph node metastases.

Lymph node positivity on ^{18}F-FDG PET/CT

Of the 160 subjects who underwent ^{18}F-FDG PET/CT scans, 34 (21.3%) patients had peripancreatic lymph node metastases according to the definition given above, which was inconsistent with the pathological results ($P < 0.001$, kappa = 0.333, Table 2). The sensitivity and specificity of ^{18}F-FDG PET/CT in diagnosing positive lymph nodes were 39.4% and 91.5%, respectively. A significant positive correlation was observed between lymph node size and lymph node SUV_{max} ($r = 0.637$, $P < 0.001$) on ^{18}F-FDG PET/CT images.

Table 1 Characteristics of pancreatic cancer patients

Characteristics	No lymphatic metastasis	Lymphatic metastasis	*P* value
Number, *n*	94	66	
Gender, *n* (%)			0.508
Men	59 (62.8%)	38 (57.6%)	
Women	35 (37.2%)	28 (42.4%)	
Age, years			0.041
Median (range)	66 (36–86)	62 (44–79)	
Tumor location, *n* (%)			0.819
Head of pancreas	55 (58.5%)	37 (56.1%)	
Body of pancreas	23 (24.5%)	19 (28.8%)	
Tail of pancreas	16 (17.0%)	10 (15.1%)	
Tumor size, mm			0.153
Mean ± SD (range)	28.5 ± 14.8 (4.6–104)	31.8 ± 14.2 (13–100)	
Tumor SUV_{max}			< 0.001
Mean ± SD (range)	5.5 ± 2.1 (1.8–9.9)	8.6 ± 3.2 (2.1–15.8)	
Serum CA 19-9, U/ml			< 0.001
Mean ± SD (range)	156 ± 221.7 (0.6–1484)	563.4 ± 628.7 (0.6–2733)	
Pathology, *n* (%)			0.082
Ductal adenocarcinoma	80 (85.1%)	62 (93.9%)	
Others	14 (14.9%)	4 (6.1%)	

Table 2 Comparison of lymph node positivity between ^{18}F-FDG PET/CT and pathological results in pancreatic cancer patients

Characteristics		No lymphatic metastasis	lymphatic metastasis	*P* value	Kappa
Lymph node in ^{18}F-FDG PET/CT	Positive	8	26	< 0.001	0.333
	Negative	86	40		

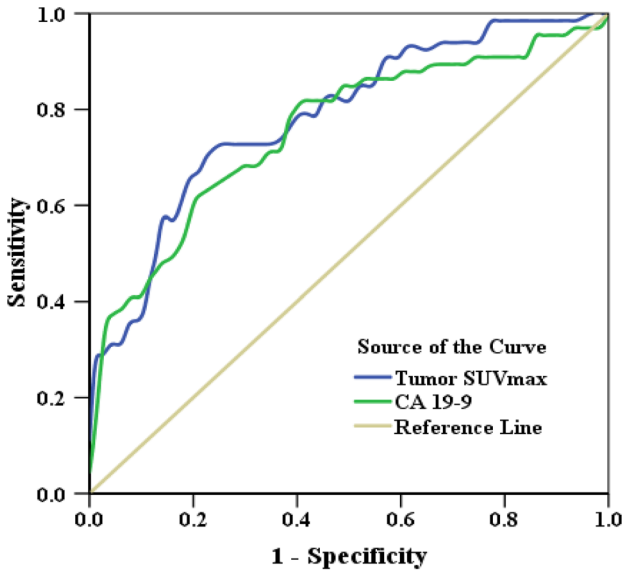

Fig. 1 The receiver operating characteristics curve analysis showing an area under the curve of 0.785 for the tumor SUV_{max} from the ^{18}F-FDG PET/CT scan ($P < 0.001$) and 0.756 for CA 19-9 levels ($P < 0.001$) in diagnosing the lymph node status in pancreatic cancer patients

SUV_{max} and CA19-9 in relation to lymph node status

Sex, age, tumor size, location, SUV_{max}, and pathology as well as CA 19-9 level were evaluated against lymph node metastases. After a logistic regression analysis of the various variables, tumor SUV_{max} and CA 19-9 levels were the potent predictors of lymph node status. The ROC curve showed an area under the curve of 0.785 for the tumor SUV_{max} from the ^{18}F-FDG PET/CT scan ($P < 0.001$) and 0.756 for CA1 9-9 levels ($P < 0.001$) in diagnosing the lymph node status in pancreatic cancer patients (Fig. 1). The best SUV_{max} and CA 19-9 cutoff values for predicting lymph node micrometastases were 7.05 (sensitivity = 71.2%, specificity = 76.6%, positive predictive value = 68.1%, negative predictive value = 79.1%) and 240.55 U/ml (sensitivity = 62.1%, specificity = 79.8%, positive predictive value = 68.3%, negative predictive value = 75.0%), respectively. A representative case is shown in Fig. 2.

Discussion

Lymph node status, especially the lymph node ratio, has been described as one of the most important prognostic factors for survival in patients with resected pancreatic cancer [18, 19]. The NCCN guidelines have proposed large regional lymph nodes as one of the factors for neoadjuvant therapy. Imaging evaluations of lymph node metastases mostly depend on the size, shape, density, and high radioactive uptake for visualization. Currently, the CT reporting standards for pancreatic disease indicate that CT is a reliable method [20]. However, true micrometastases are not expected to be visible on either CT or PET because of the inherent spatial resolution limitations of PET and the inability to discern normal lymph nodes from abnormal lymph nodes that are otherwise normal in size on CT. Our study was the first to assess the value of the primary

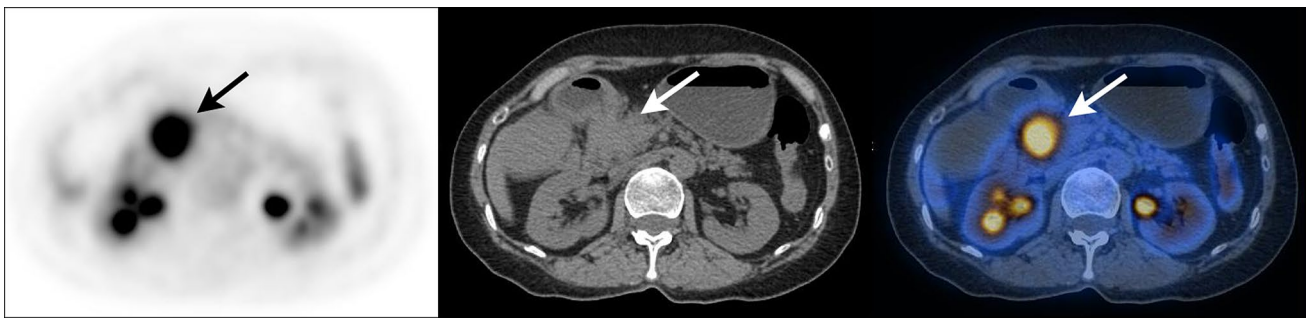

Fig. 2 ^{18}F-FDG PET/CT scan of a 59-year-old woman showing a 30.0-mm lesion with increased ^{18}F-FDG uptake at the head of pancreatic ($SUV_{max} = 13.8$), without suspicious lymph node. Her carbohydrate antigen 19-9 level was 1074 U/ml. Finally, it was confirmed to be pancreatic ductal adenocarcinoma with peripancreatic lymph node metastasis (1/6) by postoperative pathology

tumor SUV_{max} and CA 19-9 level in predicting lymph node micrometastases in patients with pancreatic cancer.

In this study, lymph node size was correlated with lymph node SUV_{max} ($r = 0.637$, $P < 0.001$) on ^{18}F-FDG PET/CT images. This finding indicates that small lymph nodes always manifest with low radioactive uptake and detecting lymph node status by observing the lymph nodes on ^{18}F-FDG PET/CT is inadequate. We demonstrated that two indirect parameters, primary pancreatic tumor SUV_{max} and CA 19-9 level, were indicators for lymph node micrometastases in patients with resectable pancreatic cancer. In fact, most studies have focused on the prognostic value of the tumor SUV_{max} for OS or recurrence-free survival, whereas the predictive role of this parameter for lymph node metastasis has been ignored. Im et al. [21] reported that the presence of lymph node metastasis was significantly associated with the primary pancreatic tumor SUV_{max} in 51 patients with resectable pancreatic cancer. The mean tumor SUV_{max} was 7.2 ± 2.6 in 24 patients with lymph node metastasis. In this study, we further revealed that the optimal tumor SUV_{max} cutoff for predicting nodal metastases was 7.05, with a sensitivity of 71.2% and a specificity of 76.6%. Although the sensitivity is not sufficiently high, the value is still much higher than the sensitivity of conventional ^{18}F-FDG PET/CT evaluations (39.4%) for predicting lymph node metastasis based on the size and SUV_{max} of the lymph node itself. In addition, the tumor SUV_{max} is an indirect factor for assessing lymph node status which may not have ideal sensitivity and specificity values.

Serum CA 19-9 levels are widely used as a prognostic or predictive factor in the management of pancreatic cancer [16]. Perioperative CA19-9 levels > 200 U/ml correlate with tumor burden, tumor spread, and early recurrence after resection in pancreatic adenocarcinoma [22–24]. Crippa S et al. [24] demonstrated that the median CA 19-9 value was 218 U/ml (range 414-1126 U/ml) in patients ($n = 47$) with celiac/para-aortic nodes compared to 47.7 U/ml (range 0.8-1805 U/ml) in patients without nodal metastasis ($n = 14$). In our study, a preoperative CA1 9-9 value ≥ 240.55 U/ml was a significant predictor of lymph node micrometastases in patients with pancreatic adenocarcinoma.

In comparison with the previous studies [24–26], we found that ^{18}F-FDG PET/CT had a limited role in assessing lymph node status, with a sensitivity of 39.4% and a specificity of 91.5%. Two possibilities exist. One possibility is that the lymph node metastases were at a too early stage to detect based on both anatomical structure and glucose metabolism. Another possibility is that the metastatic nodes were small and located close to the primary tumor and thus, these nodes were "hiding behind" the high metabolic activity of the primary tumor. Consequently, some indirect but effective indicators, such as the primary tumor SUV_{max} and CA1 9-9 level, are required to detect lymph node micrometastases in patients with pancreatic adenocarcinoma.

The retrospective design of the present study is a limitation. Because of the limited spatial resolution of PET/CT, the images of patients with small lymph nodes could be affected by partial-volume effects. The evaluation methods in this study were relatively simple. The use of a combination of other imaging modalities, such as MR imaging, may lead to the exploration of more valuable parameters. Further multicenter studies with large sample sizes are warranted to improve the data and elucidate the predictive value of the primary tumor SUV_{max} and CA 19-9 level.

In conclusion, our results showed that pancreatic cancer patients with a primary tumor $SUV_{max} \geq 7.05$ or CA1 9-9 value ≥ 240.55 are likely to have lymph node micrometastases, thereby contributing to the selection of patients who can benefit from neoadjuvant treatment.

Compliance with ethical standards

Conflict of interest The authors have declared that there are no conflicts of interest.

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