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Investigation of Association Between Borderline Pancreatic Head Cancer and Glucose Uptake by Using Positron-Emission Tomographic Studies

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Background: In the background of the well-known importance of positron-emission tomographic studies (PET) in the prediction of pancreatic oncologic problems, we designed and performed this investigation to study the link between borderline pancreatic head cancer and glucose uptake by using PET.

Material/Methods: We retrospectively investigated patients during the period of almost 4 years (May 2013 to December 2016). Patients underwent potentially curative resection for borderline exocrine pancreatic head adenocarcinoma without undergoing neoadjuvant therapy. We divided our PET protocol into 2 sets of methods as per renal calyces: 1) U-RC type in which renal calyx (RC) has relatively higher value than that of ^{18}F-fluoro-2-deoxyglucose (^{18}F-FDG) uptake and 2) S-RC type in which renal calyx has similar value than that of ^{18}F-FDG uptake.

Results: A total of 67 patients were enrolled after reclassification on the basis of majority-agreement. Among these patients, U-RC type was found in 22 patients (32.8%) while S-RC type was found in 45 patients (67.2%). Significant statistical differences were observed for each of the 2 types of pancreatic head cancer (U-RC type and S-RC type) in terms of adjusted cancer antigen 19-9 (CA 19-9), size of the tumor, tumor volume ($TV_{2.8}$), maximum standard uptake value (SUV↑), and lesion glycolysis (LG). A significantly longer disease-free survival time was shown by U-RC type (n=18) pancreatic cancer in comparison to S-RC type (n=42) (25.3 *vs.* 11.2 months). Additionally, U-RC type (n=4) had higher disease-free survival than did aS-RC type (n=3) (29.4 *vs.* 12.5 months).

Conclusions: Our PET protocol appears to be an indicator for estimation of recurrence of pancreatic head cancer and is as an indispensable asset to oncologists.

MeSH Keywords: Clinical Protocols • Pancreatic Neoplasms • Positron-Emission Tomography

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Background

Positron-emission tomographic (PET) study based upon ^{18}F-fluoro-2-deoxyglucose (^{18}F-FDG) is an imaging technology which may detect tumors with a high metabolic rate. This technology can also quantify the other metabolic activities, such as tumor volume (TV), maximum standard uptake value (SUV↑), and lesion glycolysis (LG); thus, it has become an essential part of clinical oncology [1,2]. Hexokinases and glucose transporters are sometimes overexpressed in cancer cells [3], which is why up-regulated surface glucose transporters take up ^{18}F-FDG and then are further phosphorylated by hexokinases. Additionally, in normal metabolic processes, FDG is dephosphorylated by glucose-6-phosphatase and eventually participates in it. On the other hand, we know that in comparison to many normal tissues, cancer cells have low expression of glucose-6-phosphatase and ^{18}F-FDG-phosphate accumulates in tumor cells [4–6]. In clinical oncology, PET based upon ^{18}F-FDG has been used as an assessment of treatment responses [7] during cancer staging [8] and diagnosis [9], and as an indicator of hidden metastasis.

The importance of PET based upon ^{18}F-FDG in the forecasting of pancreatic head cancer (PHC) has been shown in several reports [10–12]. In patients with locally advanced pancreatic cancer, LG and TV appear to be significant prognostic factors of overall survival [13]. Additionally, the basis of prediction of overall survival upon ^{18}F-FDG influx was established by quantitative and dynamic assessment of the key function of PET in pancreatic head cancer [14]. The usefulness of PET has been recently established, and it was reported that SUV↑ (>6.0) can predict early postoperative recurrence in resected pancreatic cancer [15]. In spite of all these reports and other relevant reports which have shown potential links between oncologic results and PET-based parameters, it might not be practical to calculate and document the individual PET-based parameters in clinical practice because it is very labor-intensive and time-consuming.

These and other studies have shown a potential association between oncologic results and image-based interpretation of tumors [16–18]. We performed qualitative assessment of FDG uptake in borderline pancreatic head cancer to investigate the potential association between them using PET results showing clinicopathological features.

Material and Methods

Patients

The institutional review board of Liaocheng People's Hospital has reviewed and approved our study. Our work was supported by Liaocheng Science and Technology Bureau of Shandong Province (Grant No. 2015-147). Written informed consent was obtained from the enrolled PHC patients before their inclusion in our study. In this study, we initially recruited 195 PHC patients who underwent pancreatectomy for exocrine pancreatic head adenocarcinoma between May 2013 and December 2016, but only those PHC patients who underwent surgical resection with preoperative PET based upon ^{18}F-FDG were included (67 patients). We excluded unresectable locally advanced (14 patients) and metastatic (48 patients) PHC patients and those who received neoadjuvant treatment (31 patients) and no preoperative PET (35 patients).

Clinicopathologic features

We retrospectively reviewed the variables with respect to clinicopathologic features such as gender, age, size of the tumor, its location, cancer antigen 19-9 (CA 19-9; as (A) actual preoperative serum CA 19-9 and (B) adjusted CA 19-9 calculated by dividing (A) with initial serum bilirubin), grade (with respect to well-, moderate-, poor-, and un-differentiated), tumor stage (T1, T2 or T3), node stage (N0 or N1), metastatic number of LNs, retrieved number of lymph nodes (LNs), lymph node ratio (LNR; ratio of metastatic LNs to retrieved LNs), lymphovascular invasion (LVI), recurrence (R0, R1 or R2), peri-neural invasion (PNI), tumor volume ($TV_{2.8}$), maximum standard uptake value (SUV↑) and lesion glycolysis (LG). For examination, a spherical-shaped volume (SSV) of each tumor was chosen and the value of the ratio of (ratio of decay-corrected activity to volume of the tissue) to (ratio of dose which was injected to the weight of the body) was considered as SUV↑ of SSV. Tumor volume with an SUV of ≥2.8 was denoted as $TV_{2.8}$ and its multiplication with mean SUV ($\overline{SUV}$) was considered as LG. Serum creatinine (Cr) levels and appraised glomerular filtration rate (aGFR) were also reviewed so that the possible effect of renal function on FDG uptake could be assessed.

Types of PET categorization

We divided our PET protocol into 2 sets of methods as per renal calyces by taking perceived signal intensity of ^{18}F-FDG in the renal calyceal system as a reference. The first one was categorized as U-RC type in which renal calyx (RC) had a relatively higher value than that of ^{18}F-fluoro-2-deoxyglucose (^{18}F-FDG) uptake, and the second one was categorized as S-RC type in which the renal calyx had a similar value to that of ^{18}F-FDG uptake (Figure 1). We categorized the types of PET (in our protocol) on the basis of majority-agreement of all 3 authors who were given the responsibility of categorization. For this purpose, we were not allowed to communicate regarding our interim results during the process of individual categorization. Eventually, if all authors (3 out of 3) determined a sample to be U-RC type (or S-RC type), the basis of majority-agreement

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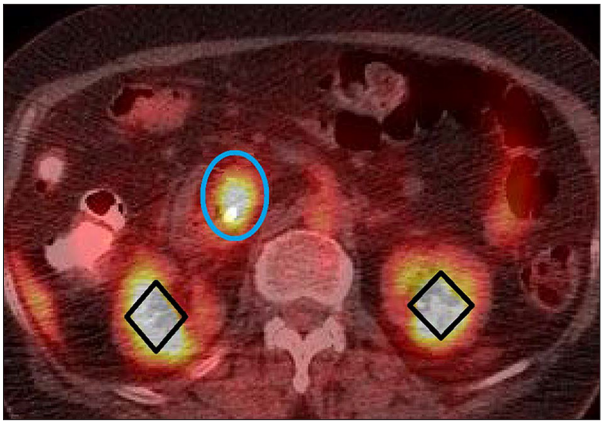

Figure 1. Determination of the S-RC type pancreatic head cancer using PET in which the perceived signal of FDG uptake type had similar intensity to that of the renal calyx (blue encircled section *vs.* black squared section).

decided that category of PET type would be U-RC type (or S-RC type). If 2/3 ratio was the majority criterion, then PET type was categorized as anU-RC type (or aS-RC type).

Statistical analysis

We used Student's t-test for the determination of typical variables (as frequency; in%) along with continuous variables (described as mean±standard deviation). As per a previous report [19], Cohen's Kappa and average agreement values were analyzed to estimate the inter-observer discrepancy. The results were defined as poor, fair, moderate, substantial, and excellent when we got values <0.2, 0.21–0.4, 0.41–0.6, 0.61–0.8, and 0.81–1, respectively. The Kaplan-Meier method was utilized for the calculation of cumulative disease-free survival and estimation of survival curves was performed. For all statistical analyses, SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was used. P-values <0.05 were considered as statistically significant.

Results

Demographic dividend of the patients

Out of 195 PHC patients chosen initially, 67 patients were included. The clinicopathological features of these patients (with respect to gender) are summarized in Table 1. The mean survival w.r.t. disease-linked and disease-freed situations were

Table 1. Clinicopathological features of borderline pancreatic head cancer patients (n=67).

Clinicopathological variables	Frequency (mean±standard deviation)	
	Male patients (n=37)	Female patients (n=30)
Age (years)	64.2±9.6	63.8±9.4
Tumor location (upper/middle/lower)	26/8/3	22/6/2
Size of the tumor (cm)	2.8±0.6	2.8±0.8
Cancer antigen 19-9 (U/mL)	514.2±1789.6	526.7±1677.9
Grade (well-/moderate-/poor- & un-differentiated	6/27/4	5/22/3
Tumor stage (T1/T2/T3)	2/2/33	2/2/26
Node stage (N0/N1)	17/20	14/16
Metastastic number of lymph nodes (LNs)	1.5±2.4	1.4±2.5
Retrieved number of LNs	19.4±8.3	19.1±8.2
Lymph node ratio	0.08±0.14	0.08±0.13
Lympho-vascular invasion (Yes/No)	13/24	11/19
Recurrence (R0/R1/R2)	37/0/0	30/0/0
Peri-neural invasion (Yes/No)	24/13	19/11
Tumor volume with an SUV of ≥2.8	4.1±3.9	4.2±4.0
Maximum standard uptake value (SUV↑)	5.9±3.1	5.8±3.3
Lesion glycolysis	17.4±21.2	17.6±21.8
Serum creatinine levels	0.83±0.22	0.81±0.21
Appraised glomerular filtration rate (mL/min/1.73 m^2)	92.7±19.4	92.4±19.8

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Table 2. Correlation between clinicopathological features of borderline PHCs as per clinical PET outcomes of individual authors.

Frequency (mean ± standard deviation) (n=67)		Clinicopathological variables				
		Actual preoperative serum CA 19-9 (U/mL)	Adjusted serum CA 19-9 (U/mL)	$TV_{2.8}$ (P<0.001)	SUV↑ (P<0.001)	LG (P<0.001)
Author1 (A1)	U-RC (n=22)	229.4±260.7	196.4±361.2	1.2±1.8	3.5±0.8	3.2±2.8
	S-RC (n=45)	689.3±1990.4	360.4±661.9	6.3±3.5	7.1±2.7	26.2±22.8
Author2 (A2)	U-RC (n=22)	202.9±246.0	94.8±146.5	1.1±1.6	3.5±0.8	3.8±4.8
	S-RC (n=45)	709.7±2019.9	455.4±59.9	6.2±3.8	7.1±2.7	26.7±22.4
Author3 (A3)	U-RC (n=22)	230.4±265.7	104.6±151.4	1.2±1.7	3.6±0.8	4.2±4.8
	S-RC (n=45)	697.4±2010.5	460.4±561.9	6.1±3.8	7.2±2.7	26.7±22.7

CA – cancer antigen; $TV_{2.8}$ – tumor volume; SUV↑ – maximum standard uptake value; LG – lesion glycolysis.

Table 3. Majority-agreement with 2/3 ratio for the categorization of PHC patients.

Authors	Patient						
	1	2	3	4	5	6	7
A1	S-RC type	S-RC type	S-RC type	U-RC type	U-RC type	U-RC type	S-RC type
A2	U-RC type	S-RC type	S-RC type	U-RC type	S-RC type	U-RC type	U-RC type
A3	S-RC type	U-RC type	U-RC type	U-RC type	U-RC type	S-RC type	U-RC type
Majority-agreement (as 2/3 ratio)	aS-RC type	anU-RC type	aS-RC type	anU-RC type	aS-RC type	anU-RC type	anU-RC type

32.3 months [95% CI: 26.3–38.7] and 21.2 months [95% CI: 16.1–27.1], respectively. Out of 67 patients, 18 patients (26.9%) and 42 patients (62.7%) had U-RC type and S-RC type, respectively. In the remaining 7 patients (10.4%), we reached a majority-agreement with 2/3 majority ratio (not as 3/3 majority ratio). We observed normal serum Cr levels in all patients. However, almost half of the patients (34) had lower aGFR value (mild to moderate lower) than the standard value 90 mL/min/1.73 m^2. We were unable to find any significant correlation between SUV↑ and aGFR in patients w.r.t. normal serum Cr levels (r=–0.121, P=0.439).

Correlation outcomes

Correlation between clinicopathological features and both types of PHC investigated by PET is shown in Table 2. We did not observe significant differences between U-RC type and S-RC type pHC w.r.t. of several clinicopathological features such as size of the tumor, its location, grade differentiation, tumor stage, node stage, metastatic number of LNs, retrieved number of LNs, LNR, LVI, recurrence, and PNI (P>0.05) (data not shown). The actual preoperative serum CA 19-9 level was higher in S-RC type PHC, but the difference was not significant (P>0.05) (Table 2). On the other hand, there were significantly different adjusted serum CA 19-9 levels among the 3 authors (A2: 94.8±146.5 *vs.* 455.4±59.9, *P*=0.006; and A3: 104.6±151.4 *vs.* 460.4±561.9, *P*=0.008, Table 2). Individual authors (A1–A3) determined that $TV_{2.8}$, SUV↑, and LG (P<0.001 in all 3 cases) had significantly different values between U-RC and S-RC type PHC.

Divergence analysis between authors

The average of pairwise agreement between different pairs (A1 & A2; A1 & A3; A2 & A3) was greater than 92%, having a pairwise Cohen's Kappa of 0.88. As per our basis of majority-agreement (both as 3/3 and 2/3 ratios) categorization, we found that 22 patients (32.8%) had U-RC type PHC and 45 patients (67.2%) had S-RC type PHC. Table 3 shows how we reached a 2/3 majority-agreement. A significant difference was observed between S-RC type and U-RC type of PHCs in terms of CA 19-9 (485.2±699.2 *vs.* 112.4±166.9, P=0.007), size of the tumor (2.8±0.6 *vs.* 2.3±0.8, P=0.028), $TV_{2.8}$ (6.2±4.9 *vs.* 1.3±1.9, P<0.002), SUV↑ (6.9±3.3 *vs.* 3.7±1.1, P<0.001), and LG (24.8±23.2 *vs.* 3.9±4.8, P<0.001).

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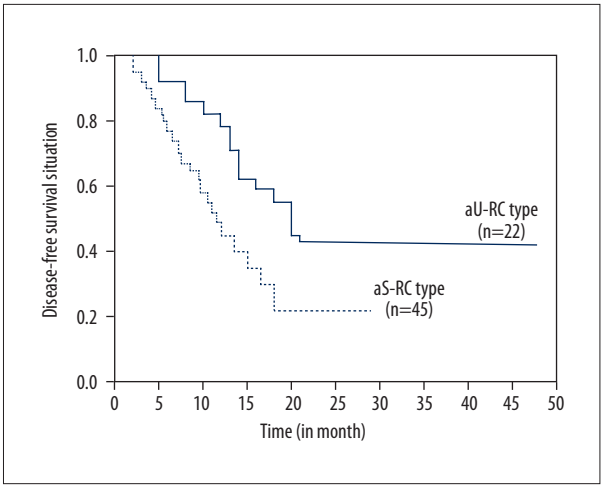

Figure 2. Disease-free survival situation outcomes for aU-RC and aS-RC type PHC patients.

Disease-free survival situation outcomes

We found significant differences in disease-free survival between individually determined anU-RC type and aS-RC type borderline PHCs as follows: For anU-RC type borderline PHC, the disease-free survival was found by A1-A5 as 24.7, 29.8, 29.7, 29.9, and 25.2 months (P<0.05), respectively, and for aS-RC type borderline PHC the disease-free survival was found by A1–A5 as 17.9, 11.5, 11.8, 17.4, and 11.6 months (P<0.05), respectively. Thus, our PET-based protocol is able to predict tumor recurrence even after radical pancreatectomy. However, by following basis of majority-agreement (2/3 or 3/3 ratio), we found that U-RC type PHC patients (N=18, mean disease-free survival time, 25.3 months [95% CI: 22.5–39.5], P=0.011) showed significantly delayed recurrence compared to S-RC type PHC patients (N=42, mean disease-free survival time, 11.2 months [95% CI: 9.3–14.3]). Similarly, for the remaining 7 patients having 2/3 favored majority-agreement basis, anU-RC type (n=4) showed higher disease-free survival to that of aS-RC type (n=3) (29.4 months [95% CI: 21.6–37.2], *vs.* 12.5 months [95% CI: 10.2–16.0], P=0.012) (Figure 2).

Effect of postoperative adjuvant chemotherapy

We offered the postoperative adjuvant chemotherapy (PAChemo) to all the patients after curative resection. We found no significant oncologic impact (in terms of disease-free survival) on U-RC type PHC patients (mean 27.4 months [95% CI: 14.7–45.2] *vs.* 23.2 months [17.3–29.1], P=0.670). However, it played an important role in disease-free survival of S-RC type PHC patients and resulted in an improvement (mean 6.2 months [95% CI: 3.9–8.3] *vs.* mean 13.2 months [95% CI: 9.1–15.6], P=0.041).

Discussion

To date, positron-emission tomography (PET) based upon ^{18}F-fluoro-2-deoxyglucose (^{18}F-FDG) has established itself as a tool for preoperative image modality since it can estimate tumor biology even in preoperative staging situations. Thus, it has emerged as an indispensable radiologic technique for the detection of metabolic and biologic properties of cancer [20,21]. In the background of the utility of PET, we established a correlation between the oncologic outcomes of borderline PHC with our novel PET type after defining it as a qualitative approach. For this, as per perceived signal intensity of PET based upon ^{18}F-FDG uptake compared to that shown in the renal calyces, we divided PHCs into U-RC type and S-RC type. We know that brain and myocardium can also be used as a reference organs for determining the signal of ^{18}F-FDG uptake, and in pancreatic cancer it is required to frequently move the axial section-field to the chest level or even the brain area but it very tedious to do so. Hence, we chose the renal calyx as a reference organ because it can be easily visualized due to its proximity to the pancreas. However, it might be possible to get different perceived intensity of FDG uptake in renal calyx among the PHC patients; even then, we derived PET types by comparing perceived intensity of renal calyx with patient PHC. We easily achieved this in a single image since we used the renal calyx as reference, which is in proximity to the pancreas.

We found that our defined PET types (U-RC and S-RC type) can successfully discriminate disease-free survival in borderline PHC (P<0.05, Figure 2). Our results are supported by an earlier report showing a link between SUV$\uparrow$ (>6.0) and early postoperative recurrence following resection of pancreatic cancer [22]. Since our work is based upon the perception of authors about ^{18}F-FDG uptake in the tumor by keeping the renal calyx as the reference signal, our work might not be reliable due to its subjective nature. But this is compensated for by the estimation of majority-agreement rate among 3 individual authors and it was found to be more than 92%, having a pairwise Cohen's Kappa value of 0.88, yielding an excellent inter-observer variability in our work. Inter-observer agreement for SUV$\uparrow$ has been reported to be 91–93% [23] and for $\overline{\text{SUV}}$ it has been reported to be only 17% [24]. Thus, it appears that our method can be reliably used as a detectable parameter for the estimation of tumor biology and glucose metabolism in clinical practice.

Our results show that PET type can predict tumor recurrence and may be developed as an indicator for prediction of recurrence before surgical intervention, even when there is no documented w.r.t. PET-based parameters. Based on an earlier report [25], it appears that the biological mechanism behind our results as that there is a link between poor oncologic result and loss of SMAD4 (Mothers against decapentaplegic

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homolog 4), which is directly associated with higher SUV↑, and we found supportive results in Table 2 showing that S-RC types have high SUV↑ values. This may explain the poor disease-free survival of aS-RC type patients. However, the role of PET imaging in prognosis of PHC needs further investigation.

There are several other advantages of our method: it is simple, easy to use, reproducible, and is a practical approach for the determination of PET type. Clinicians can easily estimate the oncologic results by examining the previous preoperative PET scan, even without any kind of specialized effort and equipment used for PET-based parameter measurements. We used subjective determination of the authors, and there appeared to be significant difference in PET-based parameters of SUV↑, $TV_{2.8}$, and LG between U-RC and S-RC type PHCs (Table 3). We achieved higher correlation value of preoperative actual CA 19-9 levels but with a less statistically significant difference. Nevertheless, observed correlation values of adjusted CA 19-9 levels with PET types for authors A2, A4, and A5 suggested that PET type can be a useful preoperative prognostic indicator for borderline PHC (Table 2). Hence, that in near future, it will be necessary to validate this potential relationship between PET type and serum CA 19-9 for a larger study volume.

We found that S-RC type PHC, a preoperatively-determined PET type, needed PAChemo after radical pancreatectomy, since our results (Figure 2) showed that PAChemo influenced disease-free survival of S-RC type PHC patients. However, there are several reports [26–28] which have evaluated the role of PET scans in monitoring the outcomes of patients with locally advanced pancreatic cancer treated with neoadjuvant treatment, but there are only a few reports in which the potential role of preoperative PET scan for the prediction of the oncologic advantages of PAChemo in borderline PHC was evaluated. Thus, our procedure is decisive w.r.t. PAChemo after radical pancreatectomy in borderline PHC. The main limitation to our approach is that it is not applicable in unresectable PHC patients, which is why further studies based on larger populations and including unresectable cases are needed.

Our study is retrospective in nature and avoid any selection bias, we excluded some patients with neoadjuvant treatment along with random exclusion of some patients before undergoing preoperative PET. Previous reports [29,30] found that PET parameters, especially SUV↑, can be influenced by size of the tumor; therefore, it might be tedious to discriminate between U-RC type and S-RC type in small pancreatic cancers, and our data supports this. We also found that 2/3 or 3/3 ratio-based majority-agreement in determination of PET type was significantly higher than 2/3 ratio-based majority-agreement (1.9±0.6 cm *vs.* 2.8±0.6 cm, P=0.002). Interestingly, when we limited ourselves to analyzing patients with tumors >2 cm, we found increased average majority-agreement rate (up to 94%) having pairwise Cohen's Kappa value of 0.843. Since ^{18}F-FDG is excreted through urine and we were unable to apply our PET type to all patients because impaired renal function and dehydration type, some clinical conditions should be taken into account [31]. However, FDG uptake in renal calyces is decreased in patients with impaired renal function due to reduced urine activity. Thus, in such cases, anecdotal clinician memory of the usual intensity of FDG uptake in the renal calyx should be used for the determination of PET types. Patients with impaired renal function were not included in our study. In spite of the limitations regarding the determination of PET type for patients having abnormal renal functions, we found that SUV↑ and normal serum Cr levels having mild-moderate decrease in aGFR are not correlated.

Conclusions

Our results reveal that PET type determined by our protocol can be utilized as an alternative indicator for estimation of recurrence of pancreatic head cancer. It is simple, easy to use, reproducible, and practical for the determination of PET type, and will establish itself as an indispensable asset to oncologists.

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