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Original article

Clinical correlations with ^{18}FDG PET scan patterns in solid pseudopapillary tumors of the pancreas: Still a surgical enigma?☆

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ABSTRACT

Background: There are limited numbers of PET studies of solid pseudopapillary tumors (SPT) of the pancreas.
Materials and methods: We reviewed the medical records of 37 patients who underwent resection of pancreatic SPT and had been preoperatively evaluated by ^{18}F-FDG PET or PET/CT scan. Immunohistochemical analysis of glucose transporter-1 (GLUT-1) and hexokinase II (HK-II) was performed.
Results: SPT could be categorized into five types according to the morphologic characteristics observed in PET images. Type I (hot FDG uptake in the entire tumor portion) was the most frequent (13, 34.2%), followed by type IV (focal uptake, 12, 31.6%), II (focal defect, 8, 21.1%), III (multiple and geographic uptake, 3, 7.9%), and V (total defective type, 1, 2.6%). The SUV_{max} in the solid portion of the SPT was 5.3 ± 4.1. The clinical pattern of FDG uptake in SPT was not associated with histopathologic features suggesting malignant potential. The SUV_{max} of SPT followed a pattern according to pattern of FDG uptake ($R^2 = 0.203$, $p = 0.055$), and was significantly associated with adjusted tumor volume ($p = 0.001$). GLUT-1 was not expressed in SPT, and only eight patients (12.3%) showed mild to moderate expression of HK-II, which was associated with the clinical pattern of SPT in PET images ($p < 0.05$).
Conclusion: SPT of the pancreas could be categorized according to the morphologic patterns observed in PET images. The clinical significance of FDG uptake, glucose metabolism, and clinical usefulness of PET scan in SPT need to be further investigated, and thus this tumor remains a surgical enigma.

Introduction

Solid pseudopapillary tumors (SPTs) are very rare pathologic tumors of the pancreas, accounting for only 1–2% of all exocrine pancreatic tumors [1]. This tumor is also known as Frantz's tumor [2], named after the author who first described its characteristics. Although various names have been used to describe this lesion, in 1996 it was finally included in the WHO classification of pancreatic tumors under the name of solid pseudopapillary tumor [3]. SPTs predominantly affect young female patients. Although SPTs are often large in size, most are well circumscribed and surgical resection usually shows an excellent prognosis. It was reported that approximately 10–15% of cases of SPTs are malignant, but complete surgical resection of these tumors can result in long-term survival even in cases of distant metastasis and peritoneal seeding [4]. Despite their clinical rarity, recognition of their importance in potential differential diagnosis has recently increased. However, the origin of SPT is still controversial, and its clinical course is known to be unpredictable because both pathological and biological prognostic factors are non-specific for metastasis and recurrence. Therefore, pancreatic SPTs have been called “surgical enigmas” [5–7]

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Positron emission tomography (PET) with 2-deoxy-2-[^{18}F] fluoro-D-glucose (^{18}F-FDG) is an evolving diagnostic modality for tumor detection and differentiation between benign and malignant lesions in staging work-up, therapeutic monitoring, and follow up of various malignant conditions. The enhanced glucose metabolism of cancer cells is the basic premise for clinical applications of PET scanning [8]. ^{18}F-FDG is transported into tumor cells by glucose transporters, and glucose transporter-1 (GLUT-1) has been identified as the principal glucose transporter [9]. Hexokinases (HKs), which are overexpressed in cancer cells, phosphorylate incorporated glucose, resulting in accumulation of phosphorylated ^{18}F-FDG. Malignant cells usually possess low glucose-6-phosphatase activity; therefore, as long as phosphorylated ^{18}F-FDG is not metabolized by glucose-6-phosphatase, it remains within the cells [10–12], giving a continuous signal that can be detected by the imaging system.

The clinical and biological significance of ^{18}F-FDG PET scanning has been investigated in many malignancies arising from the gastrointestinal tract [13–18], and recent several studies tried to evaluate clinical value of ^{18}F-FDG PET scan even in pancreatic cystic neoplasm [19–21]. However, there have only been a few studies on the appearance of SPT on ^{18}F-FDG PET or PET/CT.

In this study, we evaluated patients with SPT who had undergone ^{18}F-FDG PET or PET/CT for tumor characterization. We categorized the clinical pattern of ^{18}F-FDG uptake on PET or PET/CT scan of SPT and correlated this with clinicopathologic characteristics. In addition, we review the available literature reporting experiences of ^{18}F-FDG PET or PET/CT in SPT, and summarize the pattern of ^{18}F-FDG uptake in SPTs, thus indirectly validating our current observations.

Materials and methods

Review of medical records

We reviewed the medical records of 37 patients who underwent resection of pancreatic SPT and were preoperatively evaluated by ^{18}F-FDG PET or PET/CT scan from January 2005 to March 2013. The patients' clinicopathological characteristics, such as age, gender, clinical presentation, radiologically measured tumor size, proportion of FDG uptake noted in the tumor, SUV_{max} (standardized uptake value), operative outcomes, histopathological features suggesting malignant or benign potential, and follow-up data were reviewed and recorded. Institutional Review Board of Yonsei University College of Medicine approved this study protocol.

PET or PET/CT protocol

All patients fasted for at least 6 h before the study and rested for at least 1 h before PET/CT scanning. Blood glucose concentration was measured and confirmed to be less than 140 mg/dL before scanning. Approximately 5.5 MBq of ^{18}F-FDG per kilogram of body weight was administered intravenously, and the duration of the uptake phase was 60 min. Examinations were performed using a Discovery DSTe PET/CT scanner (Discovery DSTe, GE Medical Systems, Milwaukee, WI), with an axial field of view of 21.6 cm and a spatial resolution of 5 mm in full width at half maximum at 1 cm from the center. A low-dose CT scan for attenuation correction was first obtained, immediately followed by emission imaging from the neck to mid-thigh in three-dimensional mode at 3 min per bed position. PET data were reconstructed iteratively using an ordered-subset expectation maximization algorithm, with the low-dose CT datasets used for attenuation correction. For PET, patients fasted for at least 6 h before intravenous injection of ^{18}F-FDG, and scanning began 60 min later. Emission scans from the neck to the proximal thigh were obtained for 3 min per bed position in three-dimensional mode. The images were reconstructed using an ordered-subset expectation maximization with a matrix size of 128 × 128.

PET interpretation for analysis

The clinical pattern of FDG uptake in SPT of the pancreas was categorized based on characteristic morphologic conditions in each tumor condition. Visual grading of ^{18}F-FDG activity in GPs was performed without knowledge of the clinical pattern of FDG uptake in SPT of the pancreas; ^{18}F-FDG activity was scored <, = , or > if its activity was lower, similar to, or greater than liver parenchymal activity. For semi-quantitative analysis, a region of interest was drawn on each lesion in all axial sections, and the highest maximum standard uptake value (SUV) was recorded. Maximal SUV (SUV_{max}) was calculated using the formula SUV = Cdc/(di/w), where Cdc is the decay-corrected tracer tissue concentration (in becquerels per gram), di is the injected dose (in becquerels), and w is the patient's body weight (in grams).

Tissue microarray

Immunohistochemical analysis was performed using tissue microarray (TMA). In brief, tumor samples from patients with available paraffin-embedded tissue who underwent surgical resection from March 2000 to March 2013 were selected as donor blocks for tissue microarray (TMA). Using hematoxylin-eosin (H & E)-stained slides, representative regions were defined for each of the tumor samples. We punched out paraffin columns from the donor block using a tissue microarray apparatus with a 3-mm punch and set the paraffin columns into the pipes of a pre-made plastic TMA cassette with 30 pipes. After immersing the cassette in paraffin solution, we obtained a TMA paraffin block containing multiple vertically oriented tissue cores, which was cut at a thickness of 4 ㎛ for immunostaining.

Immunohistochemistry

Immunohistochemical analysis was performed using prediluted anti–GLUT-1 rabbit monoclonal antibody (clone SPM498, Abcam, Cambridge, MA) and anti-hexokinase II (C64G5) rabbit monocloncal antibody (Cell Signaling, catalog #2867) according to the manufacturer's instructions. Appropriate positive and negative control samples were used, including RBCs as an internal positive control. The area of GLUT-1 or HK-2 staining was evaluated as the percentage of cells with positive membranous staining among the total population of SPT cells using a semi-quantitative scoring scale from 0 to 2+ (0, no expression; 1+, <50% staining; and 3+, >51% staining).

Statistical analysis

Actual tumor volume was determined using the following formula; $V = 4/3\pi r^3$(where 'V' is volume, 'π' is 3.14, and 'r' is the radiologically measured semi-diameter). Adjusted tumor volume was calculated by multiplying by a co-factor representing the portion of FDG uptake (x 0.05 for <10%, x 0.2 for 10%–30%, x 0.4 for 30%–50%, x 0.6 for 50%–70%, x 0.8 for 70%–90%, and x 0.95 for > 90%). Continuous variables are expressed as the mean ± standard deviation and categorical variables are expressed as frequency (percent). The chi-square test, Fisher's exact test, and t-test were used for statistical assessment of the association between clinical pattern of FDG uptake in SPTs of the pancreas and their clinicopathological profiles. Changes in SUV_{max} according to pattern of FDG uptake in SPT and the correlation between tumor volume and SUV_{max} were estimated by regression analysis. The variables were considered significant when $p < 0.05$.