Prognostic Correlation of the expression of Glucose Transporter with Positron Emission Tomography in Gallbladder cancer

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Directed by Professor Dong Sup Yoon

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ABSTRACT

Prognostic Correlation of the expression of Glucose Transporter with Positron Emission Tomography in Gallbladder cancer

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The aim of the present study was to investigate whether the uptake level of 18-fluorodeoxyglucose (FDG) in PET/CT would correlate to the expression level of glucose transporter (GLUT1, GLUT4) and hexokinase (HK 1 and HK3) in GB cancers and its clinicopathological implication in tumor cell differentiation and prognosis for GB cancer. This study included a total of 90 patients with GB pathology (44 benign lesions and 46 GB cancer) who underwent 18-FDG PET-CT. The maximum standardized uptake value of the tumor (SUVmax) was calculated in the targeted lesion. The correlation was analyzed between clinicalpathological characteristics and SUVmax. Immunochemistry of GLUT1, GLUT4, HK 1 and HK3 was performed and analyzed in benign (n=10) and cancer (n=11) specimens, and the relation of their expression levels to SUV max in 18-FDG PET-CT was determined.

The clinical charateristics showed that the mean age was higher in GB cance than in benign GB lesions (66.1 vs. 57.3, p=0.036).

GLUT1 in cytoplasm and membrane were strongly expressed in cancer than in benign lesions. A GLUT1 score correlated positively to the SUVmax but the GLUT4, HK 1 and HK3 score did not. SUVmax was more elevated in poorly-differentiated or undifferentiated cell types than in well-differentiated or moderately-differentiated cells (9.62 ± 4.3 vs. 5.74 ± 3.1, p = 0.038) and was also more elevated in patients with advanced stages than in those with early stages (4.0 ± 2.3 in stage I and II vs. 7.2 ± 3.0 in stage III and IV, p = 0.016). When using a cut-off value of 4, we found that the progression-free survival rate was better in the low SUVmax (≤4) group than in the high SUVmax (>4) group (p = 0.0216; unadjusted Hazard ratio 3.13; 95% CI 1.18–8.29). In conclusion, the increased uptake of FDG in GB cancer was associated with elevated GLUT-1 expression, dedifferentiation, advanced stages, and a poor progression-free survival rate.

Key words : Gallbladder, Cancer; Glucose, Trasnporter; Positron, Emission, Tomography

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I. INTRODUCTION

Various imaging studies have been used to differentiate between benign and malignant gallbladder lesions to determine resectability and to monitor treatment response.[1-4] 18-fluorodeoxyglucose (FDG)-positron emission tomography-computed tomography (FDG-PET-CT) is an integrating imaging tool combining PET, a functional imaging technique, with CT for anatomical localization.[2,3,5,6] FDG-PET-CT helps detect metabolic rates due to the uptake of FDG by cells through glucose transporters. 18F-labeled glucose (FDG) is transported into tumor cells via GLUT-1, where it is phosphorylated by hexokinase to FDG-6-phosphate, resulting in the accumulation of FDG-6-phosphate in cells and subsequent visualization by PET.[7-9]

A number of tumors including gastric cancer,[10] colorectal cancer,[11] head and neck cancer, and pancreatic cancer,[12] have been shown to strongly express glucose transporter-1 (GLUT-1). Gallbladder cancer is also reported to be related to GLUT-1 expression, with an absence of GLUT-1 in normal GBs, a weak positive in GB hyperplasia or dysplasia, and a strong positive in GB cancer.[8 13]

A strong expression of GLUT-1 tends to show more invasiveness in

gastric cancer,[10] higher grade tumors in breast cancer,[14-17] more metastatic potential in oral squamous cell carcinomas,[18,19] and poor clinical outcomes in various cancers. Based on previous experimental and clinical observations, it is assumed that increased uptake of FDG in PET-CT may correlate to the expression levels of glucose transporters and represent more malignant features of cancer cells and may predict poor clinical outcomes in GB cancer.

We investigated if the expression levels of glucose transporters (GLUT1, GLUT4) and hexokinase (HK 1 and HK3) would correlate to the uptake level of 18-fluorodeoxyglucose (FDG) in PET/CT in GB cancers. We then found the clinicopathological implication of the FDG uptake in tumor cell differentiation and prognosis for GB cancer.

II. MATERIALS AND METHODS

1. A cohort of patients with GB pathology who underwent PET-CT scans

We used the clinical database registry system of Gangnam Severance Hospital, Yonsei University Health System, and the Ethics Committee approved the data collection and analyses of patients presenting between January 2005 and December 2011. A total of 90 patients underwent PET-CT scans for GB disease, and all of their records were transmitted to the electronic clinical database registry system and subsequently reviewed **(Figure 1)**.

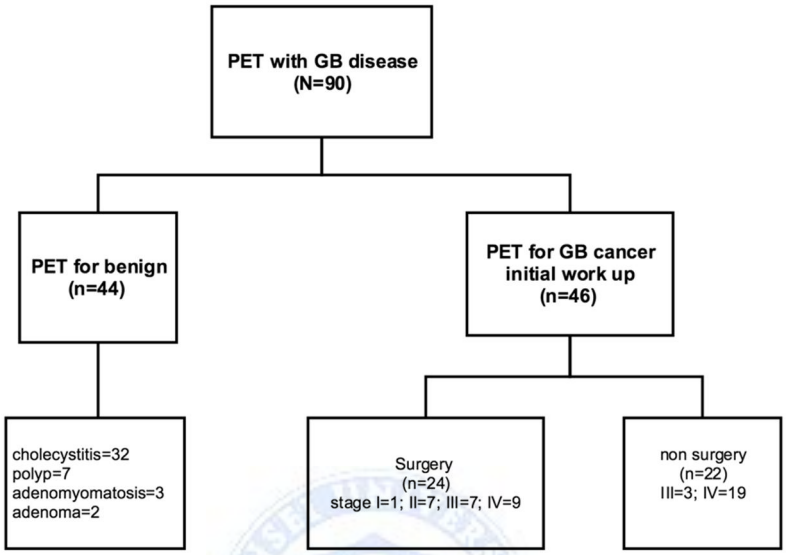


Figure 1. The patients cohort of undergoing PET scan with GB benign disease (n=44) and cancer (n=46)

Clinical information and pathology reports were obtained from the medical records stored in the electronic clinical database registry system. All primary GB cancer cases were staged clinically or pathologically according to the tumor, lymph node, and metastasis system of the 7th American Joint Commission on Cancer [20].

The histological classification of well-differentiated, moderately-differentiated, poorly-differentiated, and undifferentiated

types of GB adenocarcinomas was precisely performed by pathologists. The final pathological report was submitted to the electronic clinical database system.

All GB lesions were pathologically confirmed. Of a total of 46 except 3 advanced GB cancer patients (one with stage III and 2 with stage IV) who were diagnosed with imaging studies, 43 GB cancer samples with pathological confirmation, 39 samples were diagnosed with adenocarcinoma. Of these samples, 7 were well differentiated, 14 moderately differentiated, 8 poorly differentiated, and 2 undifferentiated. In the remaining samples (n=8), the precise histological data of cell differentiation degree were missing in our database system.

Surgeries in patients with non-disseminated disease included resection of liver segments IVB and V and regional lymph node dissection (cystic, pericoledochal, common hepatic artery, and aortocaval lymph nodes). The bile duct was resected when radical resection was necessary. After the surgery, most patients with stage III or IV cancer underwent adjuvant chemotherapy. Patients who had advanced unresectable disease or refused surgical treatment were treated with chemotherapy or radiation therapy.

Treatment responses were measured by adopting Modified Response

Evaluation Criteria in Solid Tumors (mRECIST) based on a uniform image acquisition protocol. [21] Overall response assessment included target lesion responses, non-target lesion responses, and new lesion formation. In this study, the time to progression reflected the time to progression and the time to recurrence after surgery based on the overall response using mRECIST.

2. ^{18}F-FDG PET-CT Method and image analysis

Patients were scanned using a whole body PET-CT camera (Biograph TruePoint40, Siemens Healthcare). Prior to PET imaging, all patients fasted for a minimum of 6 h, and blood glucose level was controlled so as to be lower than 150 mg/dl. Approximately 370 MBq 18F-FDG was injected intravenously, and scanning started 50–60 min after the injection. The area from the skull base to the upper thigh was imaged using the 3D mode. For semiquantitative evaluation, the maximum standardized uptake value of the tumor (SUVmax) was calculated by drawing the region of interest in the targeted hypermetabolic lesion.

Lesions of increased FDG uptake rather than physiological distribution were considered as pathological.[22] The lymph nodes on PET-CT images

that were interpreted as metastatic were based on focally increased FDG uptake. [1] In GB cancer patients, when PET-CT scanning showed metastatic lesions on lymph nodes around the portocaval, aortocaval, retrocaval, or paraaortic spaces or the mesentery, superior mesentery or celiac arteries, such cases were classified as stage IV.

3. Immunohistochemical Analysis of GLUT1, GLUT 4, HK1 and HK3

Formalin-fixed paraffin-embedded tissue samples were obtained from surgically resected tissues of 21 patients; benign (n=10) and cancer (n= 11) specimens were included. Tissues containing the representative tumor area were selected for immunohistochemical staining. Tissue sections 4 μm thick were heated in a microwave oven for 10 minutes in 10 mmol/L citrate buffer (pH 6.0) and then incubated with 0.5% hydrogen peroxide solution (Dako, Glostrup, Denmark) for 10 minutes to inhibit endogenous peroxide activity. After incubation for 90 minutes with primary anti-GLUT1 (1:200; Dako) and primary anti-GLUT4 (1:200; Dako) or anti-HK1 (1:100; Cell Signaling Technology, Danvers, Mass) antibodies and anti-HK3 (1:100; Cell Signaling Technology, Danvers, Mass) antibodies, a 30- minute polymer detection method was

performed by allowing the samples to react with anti–mouse or rabbit immunoglobulin G–poly–horseradish peroxidase antibodies (Dako). Staining results for both antibodies in cell membrane, cytoplasm, and nucleus were assigned scores of 0 to 3 (Figure 2) by the experienced pathologist who was uninformed of the patients' clinical status reported pathological results.

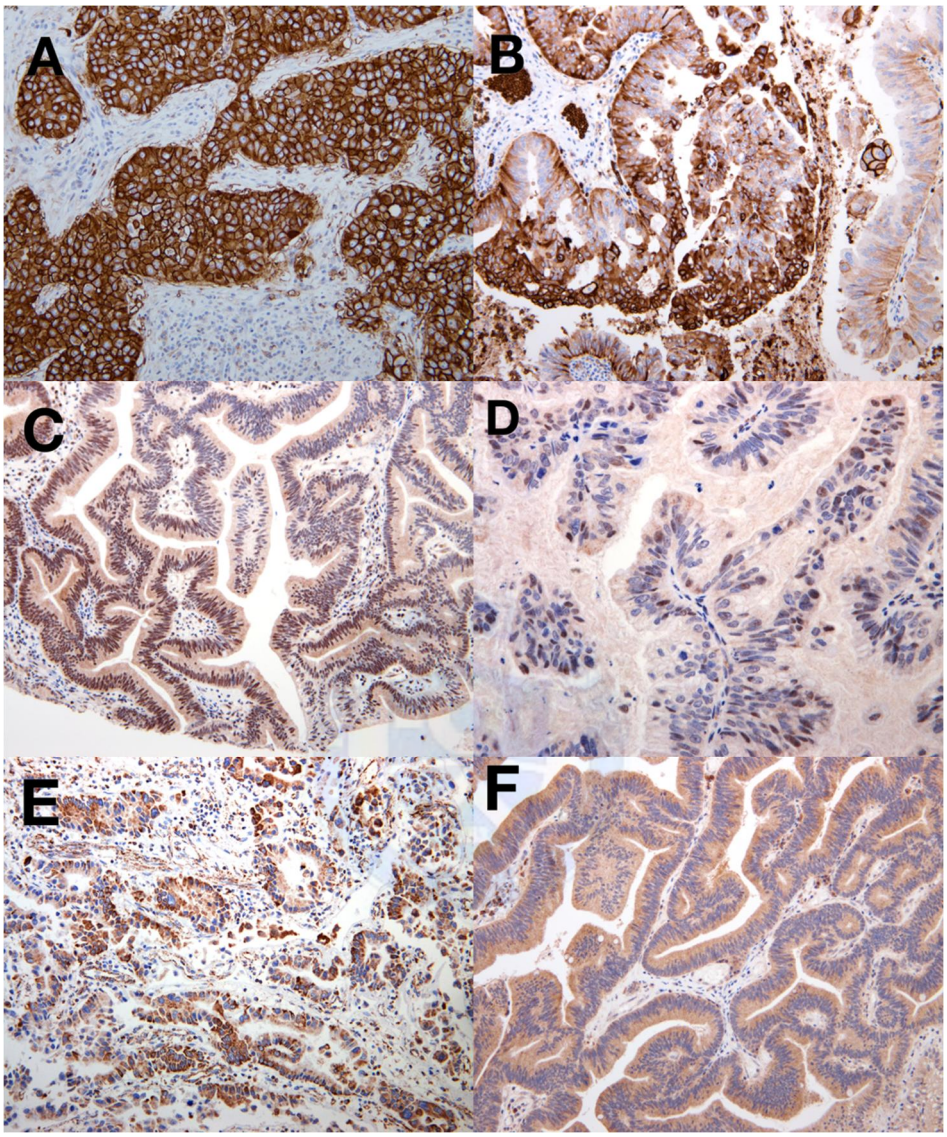


Figure 2. Immunohistochemistry grading of glucose transporters and he xokinases. Staining results for both antibodies in cell membrane, cytoplasm, and nucleus in GB cancer were assigned scores of 0 to 3 as follows: less than 10% cells stained, 0; 10% to 50%, 1; <50% strong or

>50% weak, 2; >50% strong to 100%, 3.

A: GLUT1 expression score (nuclear= 0; cytoplasm= 2; membrane=2)

B: GLUT1 expression score (nuclear= 0; cytoplasm= 1; membrane=2)

C: GLUT4 expression score (nuclear= 2; cytoplasm= 1; membrane=0)

D: GLUT4 expression score (nuclear= 1; cytoplasm= 1; membrane=0)

E: HK1 expression score (nuclear= 1; cytoplasm= 1; membrane=0)

F: HK3 expression score (nuclear= 2; cytoplasm= 3; membrane=1)

4. Statistical Analysis

Continuous variables (age, SUVmax) are expressed as the mean ± standard deviation for parametric variables. Comparison between the two groups was performed using Student's t-test for parametric variables (age, SUVmax), the Mann-Whitney test for non-parametric variables (GLUT1, GLUT4, HK1 and HK3 expression score), and the chi-square test or Fisher's exact test for categorical variables (sex). Calculating Kappa factor, Spearman's correlation coefficient, concordance and correlation were accessed between immunohistochemical results and SUV max. The post hog test was done for statistical power analysis of GLUT and HK expression between benign and GB cancer.

The predictive value of PET-CT for differentiating between benign and malignant lesions was determined by analysis of the area under the receiver operating characteristic (ROC) curve. The correlation of tumor differentiation grade with the SUVmax was assessed with a one-way analysis of variance and Tukey's B test. Survival curves between the high and low SUVmax groups were constructed using Kaplan-Meier estimates, and the unadjusted relationship of the high SUVmax to death or progression-free survival was assessed with a stratified log-rank test. Statistical analyses were performed using SPSS (SPSS, Inc., version 18, Chicago, IL, USA). A p value of <0.05 was considered statistically significant.

III. RESULTS

1. Clinical characteristics in patients with benign GB versus GB cancer pathologies

Clinical characteristics are described in Table 1. Of a total of 90 patients who underwent PET-CT, More than half of patients with GB cancer had advanced stage or metastatic lesions at the time of diagnosis (stage III or IV: n = 38, 82.6%; stage 1 or II: n = 8, 17.4%). (Table 1).

Table 1. Clinical characteristics between patients with benign and GB cancer

	Benign GB disease (n=44)	GB cancer (n=46)	P value
Age(mean)years	57.3±15.9	66.1±11.6	0.036*
Sex,	23:21	16:30	0.136†
Male:Female	(59%:41%)	(34.8:65.2%)	
Pathological confirmation	44 (100%)	43 (93.5%)	
Treatment			
Surgical resection	44 (100%)	24 (52.1%)	
Adjuvant chemotherapy		16 (34.8%)	
Stage			
Stage I		1 (2.2%)	
Stage II		7(15.2%)	
Stage III		10 (21.7%)	
Stage IV		28 (60.9%)	

* Student's t-test, † Fisher's exact test

2. GLUT1, GLUT4, HK 1 and HK3 expression

We first explored whether the glucose uptake activity measured with 18-FDG PET would be related to the expression levels of glucose uptake-related transporters. In all 11 cancer and 10 benign specimen, GLUT1 expression was generally found in cell membrane and to the lesser extent in the cytoplasm. Strong positive expressions of GLUT1 were seen in all 11 GB cancer specimens. GLUT1 in the cytoplasm and membrane were strongly expressed in cancer than in benign lesions. The GLUT1 score correlated positively to the SUVmax (R=0.623, P=0.017). However, GLUT4, HK1 and HK3 expression score were not different in cancer and benign lesions (Table 2). The GLUT4, HK 1 and HK3 score were not associated with SUVmax.

Table 2. GLUT and HK expression between benign and GB cancer

		Benign GB disease (n=10)	GB cancer (n=11)	P value*
GLUT-1				
	Nuclear	0.3±0.7	0.0±0.0	0.193
	Cytoplasm	1.4±0.7	2.0±0.0	0.02 [1]
	Membrane	1.4±0.9	2.5±0.5	0.009 [2]
GLUT-4				
	Nuclear	1.0±0.5	1.1±0.5	0.687
	Cytoplasm	0.1±0.3	0.1±0.3	0.947
	Membrane	0.0±0.0	0.0±0.0	1.000
HK-1				
	Nuclear	0.2±0.4	0.0±0.0	0.131
	Cytoplasm	0.6±0.7	1.0±0.8	0.231
	Membrane	0.1±0.3	0.0±0.0	0.343
HK-3				
	Nuclear	1.9±0.3	1.6±0.7	0.263
	Cytoplasm	1.9±0.3	1.9±0.5	0.963
	Membrane	1.7±0.5	0.6±0.8	0.002 [3]

* Student's t-test; GLUT, glucose transporter; HK, hexokinase

[1] post hog power was 0.675

[2] post hog power was 0.887

[3] post hog power was 0.948

3. PET-CT scan for the differential diagnosis between benign

and malignant lesions

The ROC curve demonstrated an area under the curve of 0.938 (95% CI [0.861 to 0.979]) (Figure 3) . This method provided the objective cut-off criterion for diagnosis of GB cancer based on the maximum standardized uptake value (SUVmax). An SUVmax of 3.9 was the best cutoff value for differentiating between benign and malignant lesions in patients with a GB pathology (sensitivity=86.05%, 95% CI [72.1 - 94.7]; specificity=94.59 %, 95% CI [81.8 - 99.3]).

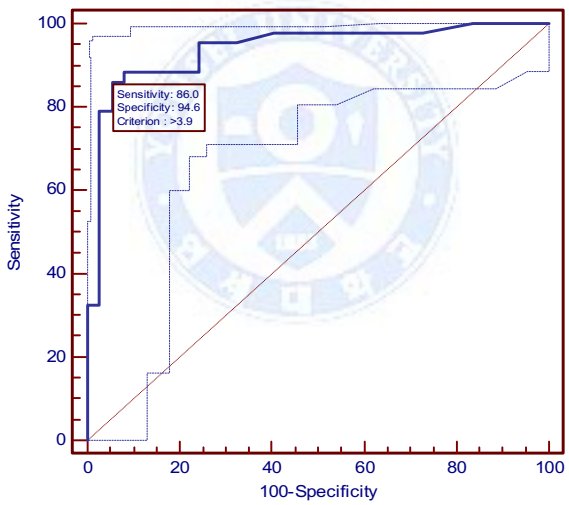
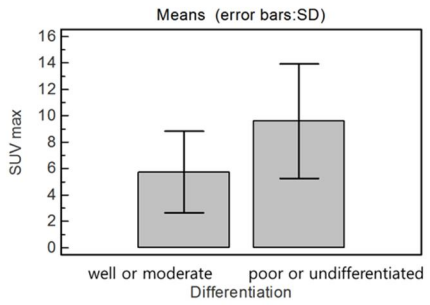


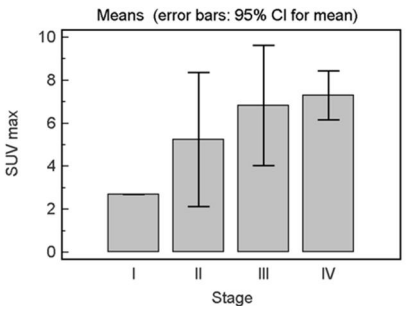
Figure 3. ROC curve of SUV max in PET scan for differential diagnosis between cancer and benign disease. ROC curve (*solid line*), 95% CI bounds (*dashed line*).

4. The relation of SUVmax in PET-CT to tumor cell differentiation and stages

We then investigated whether SUVmax would be associated with differentiation degrees of tumor cells or advanced stages. The SUVmax values were lower in tumor cells with well-differentiated and moderately-differentiated features (n = 21, 5.74 ± 3.1) than those with poorly-differentiated and undifferentiated features (n = 10, 9.62 ± 4.3; *p* = 0.038)(Figure 4A). SUVmax tended to correlate positively with advancing stages; the mean of SUVmax was 2.7 in stage I (n = 1), 4.95 in stage II (n = 7), 6.95 in stage III (n = 10) and 7.25 in stage IV (n = 28). The patients with more advanced stages showed the higher SUVmax levels (4.0 ± 2.3 in stage I and II; 7.2 ± 3.0 in stage III, and IV; p = 0.016) (Figure 4B).



(A)



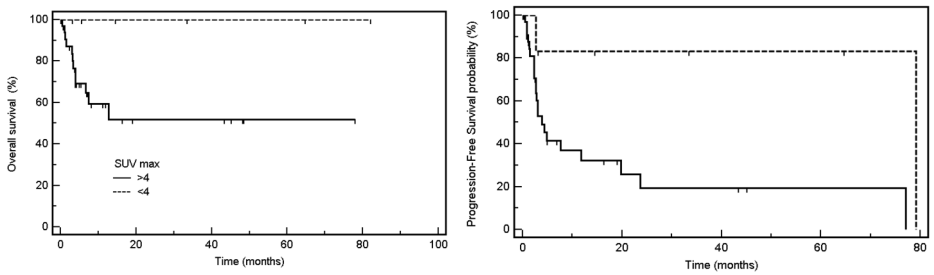
(B)

Figure 4. SUVmax correlates with tumor differentiations and stages.

The SUVmax values were lower in tumor cells with well to moderately-differentiated features than those with poorly or undifferentiated features(A) SUVmax correlated positively with advancing stages (B).

5. The predictive role of PET-CT in progression-free and overall survival

Poorly-differentiated and undifferentiated cell features as well as advanced stage are closely related to a bad prognosis in various cancers; thus, we next evaluated the predictive role of high SUVmax values to the progression-free and overall survival rates. When using a cut-off value of 4, we found that the progression-free survival rate was better in the low SUVmax (≤4) group than in the high SUVmax (>4) group (p = 0.0216; unadjusted Hazard ratio 3.1308; 95% CI 1.1828–8.2869)(Figure 5A.). The overall survival rate was also higher in the low SUVmax (≤4) group than in the high SUV max (>4) group with marginal significance (p = 0.0784)(Figure 5B.).



(A) (B)

Figure 5. Overall and progression-free survival according to SUVmax The progression-free and the overall survival were better in the low

SUVmax ($\leq$4) group than in the high SUVmax (>4) group

IV. DISCUSSION

This study showed that the increased uptake of FDG in PET-CT correlated positively to the expression level of glucose transpoter 1 (GLUT-1) .

The overexpression of glucose transporter has been found to correlate with poor prognosis in various cancers including esophageal cancer, gastric cancer[10], laryngeal cancer, and cervical cancer[23]. Some studies also reported that the strong positive expression of GLUT1 had a worse clinical outcome for GB cancer;[14] however, other studies did not find a strong connection to bad prognoses. [15]A general assumption can be made from the experimental and clinicopathological findings that as tumors grow aggressively, hypoxic conditions generated in large tumors induce hypoxia inducible factor-1 (HIF-1) and sequentially stimulate the expression of GLUT-1.

In the current study, the increased cell uptake of the FDG correlated to the high expression score of GLUT1 and was associated with cancer. These findings are consistent with the previous reports that the expression of GLUT-1 increased in tumors with larger sizes, more invasive features, and advanced stages in various cancers[21]. Previous

studies also reported that the elevated expression of GLUT1 was related to GB cancer and higher tumor degree, [20] whereas GLUT-1 was weakly detected with premalignant or benign GB lesions. [20] The current study is the first report to demonstrate the relation of the FDG uptake to the expression levels of GLUT-1 and malignant cell features in GB cancer.

This study showed that the SUVmax of PET-CT scans was significantly associated with histopathology of GB cancer and prognosis. A positive correlation between FDG uptake and the pathological grade of cancer has been reported in brain [21], lung, [9] and breast cancer, [8,13] as well as in soft tissue sarcomas. [5] In the current study, SUV max values were significantly higher in undifferentiated or poorly-differentiated cells than in well-differentiated or moderately-differentiated cells. The mean survival time of GB cancer patients with high FDG uptakes (SUVmax > 4) was shorter than of those with lower FDG (SUV max ≤ 4) uptakes. In the current study, PET-CT was useful in differentiating GB cancer from benign lesions. PET-CT scan was used for the initial diagnostic workup for differential diagnosis between benign and malignant lesions and resectability of GB cancer. Since early 2000s, FDG-PET-CT has been reported to differentiate malignant from benign disease, [24] though

the previous reports included the small number of patients verified with GB histopathology. By using SUV from dual time FDG-PET was reported helpful for the differentiation between malignant and benign lesions. [9] In recent reports, malignant or benign GB polyps of 1 - 2 cm were differentiated by modification of SUV.[7,25,26] In our study, the sensitivity was 86.05 % and the specificity was 94.59 % for differentiating between benign and malignant gallbladder lesions. Even PET-CT scan is helpful for differentiation, however it has been reported false-positive of PET for adenomyomatosis, inflammation and xanthogranulomatous cholecystitis.[27]

The current study has several limitations. First, we compared the expression levels of glucose transporters/hexokinases with the SUVmax in only 21 subjects. Further precise evaluation is needed in a large study population. Second, we could not compare the usefulness of PET-CT with other imaging modalities. Third, there may exist the potential for selection bias during Immunochemistry of available specimen.

V. CONCLUSION

In conclusion, FDG uptake in PET-CT scans correlated with the expression level of GLUT-1 in GB cancer and was associated with malignant features of tumor cells, advanced stages, and a bad prognosis.

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ABSTRACT(IN KOREAN)

담낭암에서 포도당 수송체 발현과 양전자 방출 단층촬영 결과가 예후에 미치는 영향

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본 연구의 목적은 PET / CT 의 18 fluorodeoxyglucose (FDG)의 섭취정도가 담낭암에서 포도당 수송 체의 발현 수준 (GLUT1, GLUT4) 및 헥소 키나제 (HK 1 HK3)에 상관 관계가 있을지 알아보고자 하였다. FDG 섭취정도가 종양 세포 분화 및 예후와 관련이 있는지 보고자 하였다. 18-FDG PET-CT 를 시행한 90 명의 담낭질환자(43 양성 병변,

46 담낭암)를 포함했다. GLUT1 GLUT4, HK1 HK3 를 이용해 양성(n = 10) 병변과 악성종양 (n = 11) 표본에 면역염색을 시행하고, 발현 수준은 염색 된 세포의 비율에 따라 0 에서 3 까지 점수화하였다. 종양의 표준화된 흡수 최대 값(SUVmax)은 표적 대사 활동을 활발 병변에서 계산하였다. 세포질과 세포막에서 GLUT1 가 양성 병변에 비해 악성병변에서 강하게 발현했다. SUVmax 는 GLUT1 염색 강도가 증가에 따라 증가하지만, GLUT4, HK 1, HK3 염색 정도와는 관련되지 않았다. SUVmax 는 분화가 좋지 않거나 미분화 세포 유형에서 분화도가 좋은 경우보다 증가되었다. (9.62 ± 4.3 vs. 5.74 ± 3.1, P = 0.038) 또한 조기보다 진행된 악성종양에서 증가되어 있었다. (1 또는 2 기암에서 4.0 ± 2.3 vs. 3 또는 4 기암에서 7.2 ± 3.0 , p = 0.016).). SUVmax 의 컷-오프 값을 4 기준으로 나누어, 낮은 SUVmax 군(≤4)이 높은 SUVmax 군(> 4)에 비해 무병 생존율이 더 나은 것을 발견했다. (P = 0.0216, HR 3.13; 95 % CI 1.18-8.29). 결론적으로, 담낭암에서 FDG 의 섭취 증가는 상승된 GLUT-1 발현, 악성세포의 분화도, 진행암 병기, 그리고 불량한 예후와 관련이 있었다.

핵심되는 말 : 담낭암 ; 포도당 수송체; 양전자 방출 단층촬영