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# Clinical and metabolic parameters for predicting disease progression of gallbladder adenocarcinoma

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***Objective*** **This study aimed to identify reliable predictors of disease progression in patients with gallbladder (GB) adenocarcinoma.**

***Patients and methods*** **A total of 54 patients with GB adenocarcinoma underwent preoperative F-18 fluorodeoxyglucose (FDG) PET/CT. Age, sex, clinical stage, and pathologic differentiation were collected. Tumor size and PET parameters such as $SUV_{max}$, $SUV_{mean}$, $SUV_{peak}$, metabolic tumor volume (MTV), and total lesion glycolysis were measured. Univariate and multivariate logistic regression analyses were performed to determine the utility of clinical values and PET parameters. Pearson bivariate correlation was used to evaluate the association between progression-free survival (PFS) and various parameters.**

***Results*** **No recurrence was found in 15 of 54 patients, while six showed recurrence and another 33 manifested disease progression. There were significant differences in size, stage, pathologic differentiation, and PET parameters between the groups with and without recurrence/progression. However, there was no difference in those parameters between the groups with recurrence and progression. The average PFS of the groups with no recurrence, recurrence, and progression groups was 33.1, 17.1, and 5.0 months, respectively. In univariate analysis, age, sex, clinical stage, pathologic differentiation, size, and PET parameters were correlated with PFS. In multivariate analysis, only clinical stage and MTV were statistically significant and MTV showed the highest odds ratio. Pearson correlation coefficients showed moderate negative correlations between PFS and clinical stage or MTV.**

***Conclusion*** **In GB adenocarcinoma, clinical stage and MTV are the most powerful parameters for predicting recurrence and disease progression. Based on clinical stage, MTV will represent a strong prognostic predictor.**


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**Keywords disease progression, F-18 FDG PET/CT, gallbladder adenocarcinoma, prognosis**

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## Introduction

Gallbladder (GB) adenocarcinoma is one of the common malignancies of the biliary tree and its incidence has been increasing in recent years [1]. Due to indolent onset and nonspecific clinical manifestations such as chronic abdominal pain and anorexia at an early stage, patients with GB adenocarcinoma often present with advanced disease when detected and manifest a poor 5-year survival rate of less than 5% [2,3].

Surgical resection is the major therapeutic option and the only curative treatment, which is indicated only in a small number of patients with T1 and T2 tumors without metastatic disease [4,5]. Despite an aggressive surgical approach, the majority of patients develop disease recurrence after curative resection [6]. Furthermore, as the majority of patients with GB adenocarcinoma present advanced disease by the time they are diagnosed, most inoperable patients manifest disease progression.

Currently, F-18 fluorodeoxyglucose (FDG) PET/computed tomography (CT) is a widely used functional imaging modality in the oncologic fields. It also has been used for differentiating malignant from benign GB wall thickening as well as the detection and staging of GB adenocarcinoma [7]. Because GB adenocarcinoma shows high glucose metabolism, F-18 FDG PET/CT has been used as a preoperative diagnostic algorithm to identify the surgical candidates [8–10]. However, evidence supporting the prognosis of GB adenocarcinoma using F-18 FDG PET/CT is scarce [10].

Because chemotherapy, with or without radiotherapy, improves survival of patients at an advanced stage [11,12], the prediction of disease progression and recurrence is essential for early and appropriate therapy, which has a great impact on patient outcomes.

Here, we investigated clinical, pathological, and metabolic parameters of prognostic value in determining disease progression in patients with GB adenocarcinoma.

## Patients and methods

### Patients

Patients with GB adenocarcinoma who underwent preoperative F-18 FDG PET/CT between July 2008 and July 2015 were screened. Only the patients who had histological diagnoses based on cholecystectomy or excisional biopsy of metastatic lesions were included. Patients with a history of other malignancies or having synchronous malignancies were excluded. Finally, 54 patients were included in the analysis.

Age, sex, clinical stage, and pathologic differentiation were collected from the electronic medical records. The classification of sex different clinical stages such as I, II, IIIA, IIIB, IVA, and IVB was based on the TNM stage of American Joint Committee on Cancer staging system (eighth edition) for GB cancer [13]. Based on pathologic differentiation, the cancer was categorized into three different types: well-differentiated, moderately differentiated, and poorly differentiated.

This study was reviewed and approved by the institutional review board at our hospital (CUH 2019-02-036), and the written informed consent was waived because of the retrospective nature of the study.

### F-18 FDG PET/computed tomography protocol

All patients fasted for at least 6 hours before intravenous injection of F-18 FDG and blood glucose levels of all patients were found to be below 126 mg/dl [14]. Approximately 5.5 MBq of F-18 FDG per kilogram of body weight was administered intravenously. Scanning was performed about 60 minutes after FDG administration. Images were obtained from the base of the skull to the proximal thigh using either a Biograph TruePoint 40 PET/CT scanner (Siemens Medical Solutions, Knoxville, Tennessee, USA) or a Biograph 16 PET/CT scanner (Siemens Medical Solutions). A CT scan was obtained first using a continuous spiral technique (120 kVp, 160 mA, 0.5 seconds rotation time). A PET scan was then acquired in a three-dimensional mode for 2.5 minutes in each bed position. The PET data obtained were reconstructed iteratively using an ordered-subset expectation maximization algorithm (128 × 128 matrix, 3.27 mm slice thickness, subset: 21, iterations: two). Acquisition and processing protocols of F-18 FDG PET/CT had not altered during the study duration. All F-18 FDG PET images were to be reported in compliance with the hospital's own reporting form.

### Imaging analysis and metabolic parameters

We reviewed preoperative FDG PET/CT images at a workstation (Syngo MI applications, Flexible Display 7.0.7.7; Siemens Medical Solutions, Erlangen, Germany). All PET images were expressed in standardized uptake value (SUV) units normalized to the patient's body weight using the formula: SUV (g/ml) = tissue activity (Bq/ml)/[injected dose (Bq)/body weight (g)], where the tissue activity was decay-corrected to account for the time elapsed between injection and acquisition [15]. We measured 5 different metabolic parameters: maximum SUV ($SUV_{max}$), mean SUV ($SUV_{mean}$), peak SUV ($SUV_{peak}$), metabolic tumor volume (MTV), and total lesion glycolysis (TLG). A volume of interest (VOI) was carefully drawn slightly large enough to include GB cancer in the axial, coronal, and sagittal planes. $SUV_{max}$, defined as the maximum SUV within the tumor, was calculated as follows: $SUV_{max}$ = concentration of highest tumor activity in the VOI (MBq/ml) × total body weight (kg)/injected radioactivity (g/MBq). $SUV_{mean}$, representing the average uptake of more than 2.5 SUV units, was calculated as the summed SUV more than 2.5 SUV units divided by the number of voxels within the contour. $SUV_{peak}$ was identified manually by moving a fixed 1 mL spherical VOI over GB cancer and identifying the focus that yielding the highest mean SUV value. A 1.2 cm spherical VOI yields in a volume of approximately 1 ml [15,16]. MTV represents the summed volume in cubic centimeters of the tumor and was measured using a fixed threshold method of SUV 2.5 by an SUV-based automated contouring program. The contour near the tumor margin inside the VOI was automatically delineated, and voxels presenting SUV > 2.5 were incorporated to define MTV [17]. TLG was calculated as the product of $SUV_{mean}$ by MTV, which includes both metabolic activity and tumor burden.

### Clinical follow-up

All patients were evaluated regularly via physical examination and imaging studies (chest CT or abdominal CT or FDG PET/CT). When suspected lesions were detected, further pathology or imaging studies were performed. Recurrence was defined as a new appearance of disease after at least 3 months of complete remission. Progressive disease was diagnosed based on the revised RECIST guidelines (version 1.1) for patients who did not reach complete remission [18]. Progression-free survival (PFS) was defined as the interval from the date of preoperative FDG PET/CT scan to the date detecting recurrence or progressive disease. If no event occurred, PFS was defined as the interval from the date of preoperative FDG PET/CT scan to the date of the last follow-up. All follow-up evaluations ended on 30 April 2017.

### Statistical analysis

Statistical analysis was performed using MedCalc software (version 12.2.1.0). Continuous variables such as age, size, and various PET parameters were compared using the Mann–Whitney *U* test. Categorical variables such as sex, stage, and pathologic differentiation were evaluated

using Pearson's chi-square test. Receiver operating characteristic curve (ROC) analysis was used to determine the optimal cutoff values. Univariate and multivariate logistic regression analyses were performed to determine the utility of clinical values and FDG PET/CT parameters. Comparison of PFS between different groups was performed using the log-rank test in univariate analysis. The Cox proportional hazards regression model using forward conditional stepwise selection was performed to validate prognostic parameters in multivariate analysis. Hazard ratio (HR) with a 95% confidence interval (95% CI) was also presented. Pearson bivariate correlation was used to evaluate the correlation between PFS and various parameters. PFS curves were produced by the Kaplan–Meier method. Statistical significance was defined as a *P*-value less than 0.05.

## Results

### Patient characteristics

A total of 54 patients (M:F = 22:32, 68.1 ± 10.9 years) were included in the analysis. Based on preoperative FDG PET/CT, 30 patients manifested regional or distant lymph node metastasis; 22 patients had hematogenous metastasis to the lung, liver, or adrenal glands; and three patients showed peritoneal carcinomatosis. The number of patients at the clinical stages I, II, IIIA, IIIB, IVA, and IVB were four, eight, three, seven, one, and 31, respectively. Well-differentiated, moderately differentiated, and poorly differentiated GB adenocarcinoma was detected in eight, 24, and 8, respectively. Differentiation of GB adenocarcinoma of the other 14 patients was not provided in the pathologic reports.

Eight patients underwent curative cholecystectomy alone, whereas 13 patients received adjuvant chemotherapy after cholecystectomy and two of them underwent neoadjuvant chemotherapy before cholecystectomy. Ten patients received cisplatin-based systemic chemotherapy without cholecystectomy and one of them underwent local hyperthermia therapy as well. A single patient underwent local hyperthermia only. Another two patients underwent palliative cholecystectomy alone, whereas the other 20 patients did not receive any therapy. None of the patients received external radiation therapy. Patient characteristics are summarized in Table 1.

**Table 1 Characteristics of patients ($n = 54$)**

| Characteristics | Number (%) |
|---|---|
| Age (mean ± SD, years): 68.1 ± 10.9 | |
| Sex | |
| Male | 22 (40.7%) |
| Female | 32 (59.3%) |
| Metastasis | |
| Lymph node | 30 (55.6%) |
| Liver | 15 (27.8%) |
| Lung | 10 (18.5%) |
| Peritoneum | 3 (5.6%) |
| Adrenal gland | 2 (3.7%) |
| Stage | |
| I | 4 (7.4%) |
| II | 8 (14.8%) |
| IIIA | 3 (5.6%) |
| IIIB | 7 (13.0%) |
| IVA | 1 (1.9%) |
| IVB | 31 (57.4%) |
| Pathologic differentiation | |
| Well-differentiated | 8 (14.8%) |
| Moderately differentiated | 24 (44.4%) |
| Poorly differentiated | 8 (14.8%) |
| Unknown | 14 (25.9%) |
| Treatment protocol | |
| Curative cholecystectomy only | 8 (14.8%) |
| Cholecystectomy + adjuvant chemotherapy | 11 (20.4%) |
| Neoadjuvant chemotherapy + cholecystectomy + adjuvant chemotherapy | 2 (3.7%) |
| Chemotherapy only | 9 (16.7%) |
| Local hyperthermia only | 1 (1.9%) |
| Chemotherapy + local hyperthermia | 1 (1.9%) |
| Palliative cholecystectomy | 2 (3.7%) |
| None | 20 (37.0%) |

### Groups with no recurrence, recurrence, and progression

Complete response was seen in 21 out of 54 patients. Among them, 15 patients showed no recurrence and persisted for more than 6 months. The remaining six patients showed recurrence during the follow-up period including three patients with a relapse of liver metastasis, two showing GB bed recurrence with peritoneal seeding, and the remaining patient reporting new metastases to the lung, pleura, and multiple lymph nodes. Disease progression was recorded in the other 33 of 54 patients; 24 patients showed new or increased number of metastatic nodules in the liver; 23 patients showed markedly increased size of GB cancer; 18 patients reported increased size and number of metastatic lymph nodes; two patients had new peritoneal carcinomatosis; another two showed increased size and number of metastatic lesions in the lung; and one patient had a new metastatic nodule in the psoas muscle in addition to new peritoneal seeding. Most patients had metastatic lesions involving more than two sites. None of the patients maintained stable disease or partial response until the last follow-up. The mean follow-up period was 14.17 ± 17.28 months (range, 1.4–74.7 months). The shortest interval from pretreatment F-18 FDG PET/CT scan to detection of disease progression was 43 days and to recurrence was 4.3 months.

### Clinical/metabolic parameters and progression-free survival

There were significant differences in size, clinical stage, pathologic differentiation, and various FDG PET parameters between the groups with no recurrence and recurrence/progression groups. However, there was no difference in those parameters between the groups with recurrence group and progression group. Median PFS in groups with no recurrence, recurrence, and progression group was 25.9, 16.4, and 3.2 months, respectively. Tumor

size and various metabolic parameters for each group are summarized in Table 2.

In ROC analyses, optimal cutoff values for age, clinical stage, pathologic differentiation, and size were > 56 years, > IIIB, > well-differentiated, and > 3.5 cm, respectively. The optimal cutoff values for metabolic parameters were $SUV_{max}$ > 7.96, $SUV_{mean}$ > 3.88, $SUV_{peak}$ > 4.98, MTV > 24.88 $cm^3$, and TLG > 117.72 $cm^3$. In univariate analysis, age, sex, clinical stage, pathologic differentiation, size, and various FDG PET parameters were correlated with PFS (Fig. 1). In multivariate analysis, only clinical stage and MTV were statistically significant risk factors and MTV showed the highest odds ratio with the lowest *P*-value (*P* = 0.003, HR = 5.57, 95% CI = 1.82–17.04) (Table 3). Figure 2 presents the difference in PFS of two patients at the same stage IIIB but different MTV. Pearson correlation coefficients showed moderate negative correlations between PFS and clinical stage or MTV.

## Discussion

GB adenocarcinoma is epithelial in origin and accounts for 90% of GB malignancies [2]. Although it is an uncommon malignancy of the gastrointestinal tract, it is one of the common biliary tract malignancies, accounting for more than 70% of all such cancers. It is also considered the most aggressive cancer with a median survival of less than 6 months [2,3]. Histologically, the normal GB wall does not contain muscularis mucosa or submucosa, and the connective tissue of GB along the hepatic surface is continuous with the interlobular tissue of the liver [2]. These anatomical factors promote early local invasion to the liver and adjacent structures, resulting in unresectable or metastatic disease with a poor prognosis.

It is well known that histologic type, histologic grade, and tumor stage are important prognostic factors in GB cancer. However, GB cancer histology and grade can be determined only after cholecystectomy in a small proportion (10%) of operable patients. Although tumor characteristics can be investigated via biopsy of a metastatic lesion, it is difficult to conclude that they reflect the histologic properties of primary GB cancer and other metastatic sites because the tumor may show heterogeneity. Therefore, to predict a prognosis, a noninvasive imaging test that can be used in all patients with GB cancer, regardless of their stage, is an appropriate modality for evaluation. Unlike other imaging tests, F-18 FDG PET/CT can survey the whole body in a single test and provides information about tumor glucose metabolism as well as the anatomical characteristics.

Several studies have investigated GB cancer using F-18 FDG PET/CT. Most of them reported that F-18 FDG PET/CT plays a potential role in staging work-up and distinguishing the benign or malignant nature of the GB wall thickening [8,19,20]. A few studies evaluated the prognostic parameters using F-18 FDG PET/CT. One of them revealed that high $SUV_{max}$ is independently associated with poor overall survival [21] and another study reported that total tumor burden, such as total MTV, which is the sum of the MTVs of both GB cancer and metastatic lesions, facilitates the determination of overall survival [22]. They both focused on overall survival as a factor determining the prognosis. As far as we know, no studies have evaluated PFS of GB adenocarcinoma with F-18 FDG PET/CT.

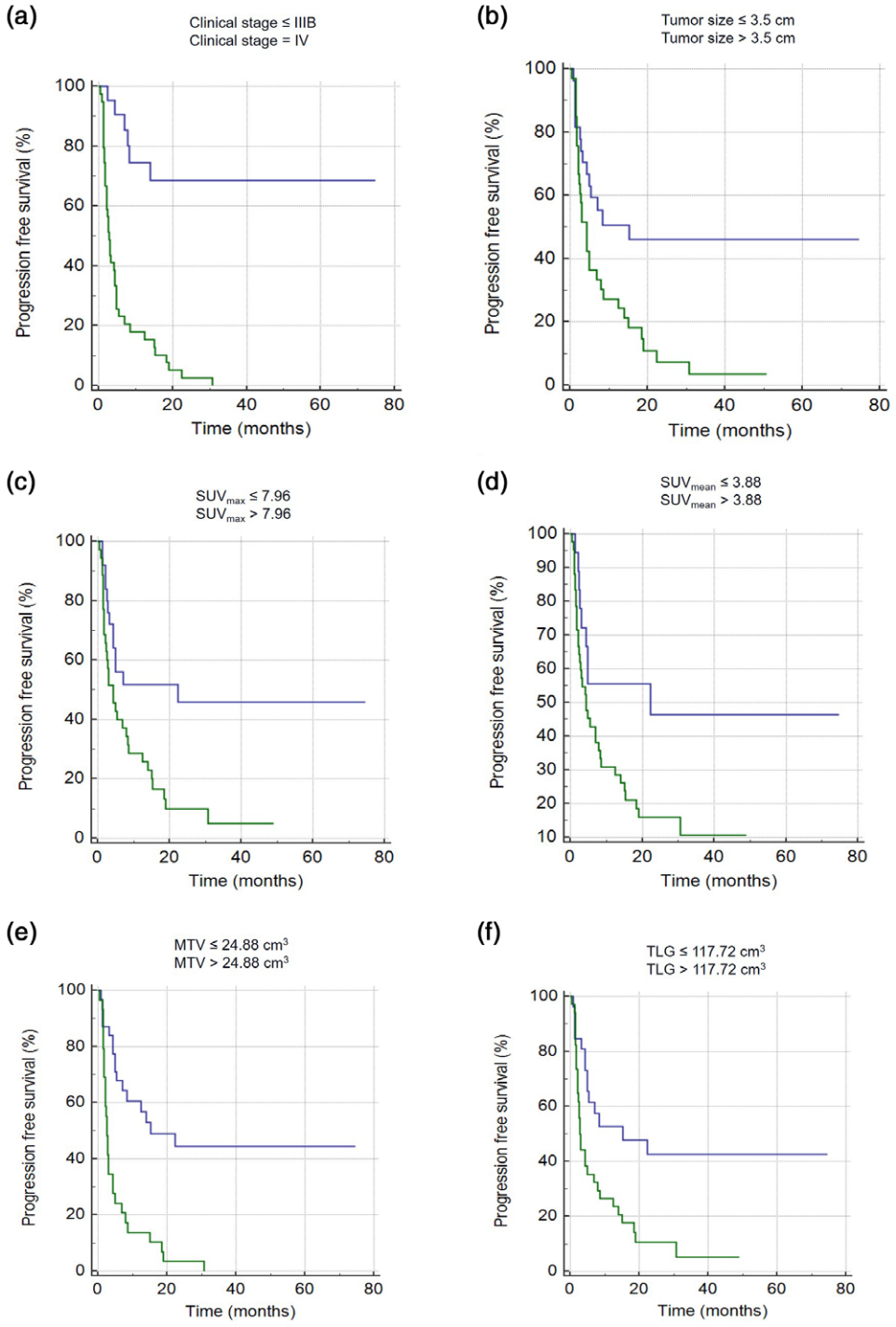
One of the meaningful findings in the present study is that 28.6% of patients with CR (six of 21 patients), which is a substantial number, showed recurrence. Tumor size and various metabolic parameters of patients in the groups with no recurrence and recurrence differed with statistical significance. Unlike many studies dealing with a tumor at a similar clinical stage, such as locally advanced GB cancer [22], we included GB adenocarcinoma of all clinical stages to determine the increased risk of recurrence due to high MTV even in early clinical stages. Conversely, it was found that the likelihood of recurrence was minimal when MTV was low even at an advanced clinical stage. A patient in the recurrence group at an early clinical stage II but with high MTV (28.28 $cm^3$) relapsed as new liver metastasis, while four patients in the group with no recurrence and low MTV (8.68 ± 8.79 $cm^3$) did not show recurrence despite the advanced clinical stages of IIIA and IIIB. Therefore, aggressive treatment modalities and closed follow-up are required even in patients with complete remission but a high MTV.

**Table 2 Tumor size, metabolic parameters, and progression-free survival of each group**

| | | | | *P*-value | | | |
|---|---|---|---|---|---|---|---|
| Group | No recurrence group | Recurrence group | Progression group | No recurrence vs. recurrence group | No recurrence vs. progression group | No recurrence vs. recurrence/progression group | Recurrence vs. progression group |
| Tumor size (cm) | 2.43 ± 0.97 | 5.22 ± 2.43 | 5.34 ± 2.68 | 0.000 | 0.000 | 0.000 | 0.985 |
| $SUV_{max}$ | 6.73 ± 4.46 | 10.26 ± 2.84 | 10.28 ± 4.19 | 0.045 | 0.003 | 0.002 | 0.690 |
| $SUV_{peak}$ | 4.68 ± 3.00 | 7.34 ± 2.46 | 7.03 ± 2.94 | 0.066 | 0.004 | 0.003 | 0.412 |
| MTV ($cm^3$) | 8.09 ± 8.94 | 64.12 ± 73.28 | 114.53 ± 128.29 | 0.002 | 0.000 | 0.000 | 0.556 |
| TLG ($cm^3$) | 10.02 ± 51.05 | 282.25 ± 297.62 | 515.09 ± 573.69 | 0.003 | 0.000 | 0.000 | 0.481 |
| PFS (months) | 25.9 ± 21.9 | 16.4 ± 9.1 | 3.2 ± 4.0 | 0.045 | 0.000 | 0.000 | 0.212 |

PFS, progression-free survival; TLG, total lesion glycolysis.

**Fig. 1**




In ROC analyses, the optimal cutoff values of clinical stage, size, and metabolic parameters were >IIIB, >3.5 cm, $SUV_{max}$ > 7.96, $SUV_{mean}$ > 3.88, $SUV_{peak}$ > 4.98, MTV > 24.88 $cm^3$, and TLG > 117.72 $cm^3$ respectively. In univariate analysis, those parameters were correlated with PFS. PFS, progression-free survival; ROC, receiver operating characteristic curve; TLG, total lesion glycolysis.

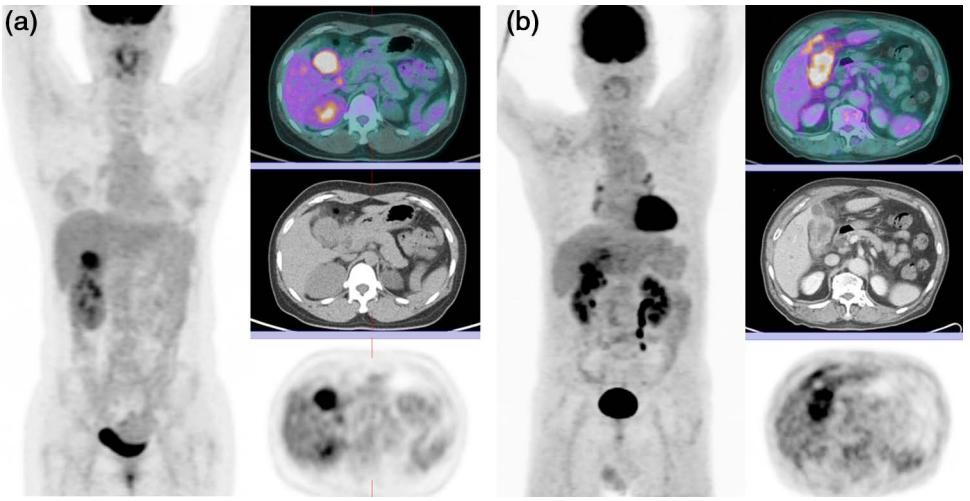
This study has several limitations. First, because of the retrospective design, the treatment method could not be randomly controlled and various treatment protocols might affect the patients′ prognosis. Second, the clinical stage of the patients was uneven. More than 57% of patients belonged to clinical stage IVB, thus reflecting the nature of GB adenocarcinoma, which is usually found in the advanced stage and may have contributed to the

**Table 3 Univariate and multivariate analyses**

| Univariate analysis | Hazard ratio | *P*-value | Multivariate analysis | Hazard ratio | *P*-value |
|---|---|---|---|---|---|
| Sex = male | 2.12 | 0.0231 | Sex = male | 2.84 | 0.075 |
| Age > 56 years | 2.32 | 0.0481 | Age > 56 y | 2.05 | 0.242 |
| Stage > IIIB | 7.47 | <0.0001 | Stage > IIIB | 4.72 | 0.013 |
| Pathologic differentiation > WD | 11.29 | 0.0180 | Pathologic differentiation > WD | 5.28 | 0.125 |
| Size > 3.5 cm | 3.45 | 0.0006 | Size > 3.5 cm | 0.92 | 0.884 |
| SUVmax > 7.96 | 3.25 | 0.0023 | | | |
| SUVpeak > 4.98 | 3.22 | 0.0036 | | | |
| SUVmean > 3.88 | 2.17 | 0.0520 | | | |
| MTV > 24.88 $cm^3$ | 6.13 | <0.0001 | MTV > 24.88 $cm^3$ | 5.57 | 0.003 |
| TLG > 117.72 $cm^3$ | 5.27 | <0.0001 | | | |

TLG, total lesion glycolysis; WD, well-differentiated.

**Fig. 2**




Two patients at the same clinical stage IIIB but different MTV show different PFS rates. (a) MTV of gallbladder cancer in a 45-year-old woman was 16.58 $cm^3$. Her PFS was 23.0 months. (b) MTV of gallbladder cancer in a 72-year-old man was 60.69 $cm^3$. His PFS was only 7.8 months. MTV, metabolic tumor volume; PFS, progression-free survival.

evaluation of the prognostic predictive ability. Further, although all patients were diagnosed with GB adenocarcinoma by biopsy, not all the biopsies were obtained from GB. In some patients, tissues were obtained from metastatic lesions. Differentiation of metastatic lesions may differ from that of primary GB cancer. Nevertheless, this is one of the very rare studies evaluating various parameters in predicting the prognosis of GB adenocarcinoma.

In conclusion, clinical stage and MTV are the most powerful parameters for predicting recurrence and disease progression of GB adenocarcinoma. In addition to clinical stage, MTV, which is one of the volume-based metabolic parameters, is a strong prognostic indicator. Additional larger-scale studies are necessary to validate the results.

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### Conflicts of interest

There are no conflicts of interest.

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