# Prospective Evaluation of the Clinical Implications of the Tumor Metabolism and Chemotherapy-Related Changes in Advanced Biliary Tract Cancer

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Tumor metabolism measured by $^{18}$F-FDG PET has a diagnostic and prognostic role in several cancers. The clinical implication of tumor metabolism in biliary tract cancer (BTC) has not been studied well. Therefore, we evaluated the prognostic value of tumor metabolism and chemotherapy-related changes in advanced BTC patients. **Methods:** We prospectively enrolled advanced BTC patients before the initiation of palliative chemotherapy. Using $^{18}$F-FDG PET, we assessed the baseline $SUV_{max}$ and monitored the changes in $SUV_{max}$ during chemotherapy. We analyzed the associations between $SUV_{max}$, and clinicopathologic factors and clinical outcomes. **Results:** Seventy-five patients were enrolled. All patients received gemcitabine/cisplatin as first-line chemotherapy. Primary tumor site, histologic differentiation, molecular characteristics, laboratory findings, and disease extent were associated with the metabolic characteristics. The high-metabolism group showed worse survival outcome (hazard ratio [HR] = 4.09, $P$ = 0.001 for progression-free survival; HR = 2.61, $P$ = 0.019 for overall survival [OS]) than the low-metabolism group. The lesser reduction of $SUV_{max}$ was also associated with worse outcome (HR = 3.35, $P$ = 0.002 for progression-free survival; HR = 1.96, $P$ = 0.082 for OS). When both baseline tumor metabolism and its chemotherapy-related changes were considered, patients with a low metabolism and more reduction in metabolism obtained the best OS (20.7 vs. 6.2 mo, $P$ = 0.013). **Conclusion:** Tumor metabolic activity and the chemotherapy-related changes in the metabolism are associated with prognosis in advanced BTC patients.

**Key Words:** biliary tract neoplasm; carcinoma; positron-emission tomography; metabolism; prognosis

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Biliary tract cancers (BTCs), which include gallbladder cancers, intrahepatic cholangiocarcinomas (IHCCs), extrahepatic cholangiocarcinomas (EHCCs), and ampulla of Vater (AoV) cancer, are heterogeneous diseases with diverse histologic and biologic characteristics (*1*). These malignancies have poor prognoses because many patients are diagnosed at an inoperable stage and have only limited options for palliative chemotherapy (*2*). Although systemic chemotherapy has improved the overall survival (OS) and quality of life, there are still huge unmet medical needs to be addressed in BTC (*3,4*). Efforts to target several interesting therapeutic targets such as isocitrate dehydrogenase 1 and fibroblast growth factor receptor fusion have been ongoing. However, until today, no therapeutic targets for BTCs have been clinically validated (*5,6*). More insights on biology should be discovered in BTC. Cancer cell metabolism differs from that of normal cells in ways that support highly active proliferation, which is achieved through various genetic alterations. In addition, metabolic heterogeneity is observed among different tumor types. Recently, there have been many efforts to target cancer metabolism as an anticancer strategy (*7*). In PET performed with the radiolabeled glucose analog $^{18}$F-FDG, the uptake of $^{18}$F-FDG serves as a measure of glycolysis, thereby reflecting cancer cell metabolism, and is actively used in the diagnosis, detection of recurrence, and assessment of therapeutic response for several types of cancer (*8*). Even though many studies have shown the role of $^{18}$F-FDG PET in the prediction of treatment response and prognosis of several malignancies, the clinical values of tumor metabolism evaluated by $^{18}$F-FDG PET differ between tumor types (*9–11*).

Studies focusing on the tumor metabolism of BTCs are limited, and a small number of the studies are mostly retrospective data and have some barriers to the clinical application (*12–16*). We previously reported that the tumor metabolism of BTC assessed by $^{18}$F-FDG PET before chemotherapy had a prognostic value identified by retrospective analysis (*17*). Therefore, the purpose of this prospective study was to validate the clinical implications of the assessment of tumor metabolism before chemotherapy and to evaluate the prognostic value of metabolic changes after chemotherapy using $^{18}$F-FDG PET in patients with advanced BTC.

## MATERIALS AND METHODS

### Patients and Data Collection

We conducted a prospective cohort study to evaluate the role of tumor metabolism through $^{18}$F-FDG PET in patients with gastric cancer, pancreatic cancer, and BTCs who were planned to receive palliative chemotherapy. We enrolled patients in the study starting in October 2013 at Seoul National University Hospital (Seoul, Republic of Korea), with the data cutoff for this analysis in October 2015. The inclusion criteria were histologically confirmed unresectable or recurrent cancer, planned palliative chemotherapy, and informed consent.

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Among the patients enrolled in the study, only the patients with BTC were included in the present analysis. Data on age, sex, primary tumor site, performance status, histologic findings including immunohistochemistry and molecular profiling, laboratory findings including carcinoembryonic antigen and carbohydrate antigen 19-9, chemotherapy regimens and their schedules, chemotherapeutic response according to RECIST 1.1 using contrast-enhanced CT scanning, PFS, and OS were collected (*18*). The response evaluation based on RECIST 1.1 was done by 2 independent readers to secure inter- and intrareader reproducibility. The 2 independent readers for RECIST 1.1 evaluation were not masked to clinical information in a nonrandomized fashion. If there was discrepancy between 2 readers, repeated evaluation and discussion was done to obtain final consensus.

### $^{18}$F-FDG PET/CT

Before the initiation of palliative first-line chemotherapy, tumor metabolism in patients was evaluated using $^{18}$F-FDG PET/CT. Follow-up $^{18}$F-FDG PET/CT was performed with corresponding contrast-enhanced CT scanning at the first response evaluation timing, which was after the administration of 2 cycles of chemotherapy. Henceforth, $^{18}$F-FDG PET/CT was performed at every response evaluation time point if possible.

Dedicated PET scanners (Biograph True-Point, Biograph mCT 40, and Biograph mCT 64; Siemens) were used in the acquisition of the $^{18}$F-FDG PET images. Patients fasted at least 6 h and had regulated blood sugar levels less than 210 mg/dL before the injection of $^{18}$F-FDG (5.18 MBq/kg). $^{18}$F-FDG PET/CT was performed 1 h after the injection of $^{18}$F-FDG. Images were reconstructed using ordered-subset expectation maximization (2 iterations and 21 subsets; gaussian filter of 3 and 5 mm for the Biograph True-Point and Biograph mCT scanners, respectively). Images were analyzed using a commercialized software package (syngo.via; Siemens Medical Solution). For the quantitative analysis of the $^{18}$F-FDG uptake, a region of interest was placed over the most intense area of $^{18}$F-FDG accumulation. The activity concentration within the region of interest was determined and expressed as the SUV calculated according to the formula radioactivity concentration in region of interest (Bq/mL)/injected dose (Bq) per body weight (g). The $SUV_{max}$, defined as the pixel with the highest SUV within the region of interest, was measured and recorded for the focal areas of uptake. The $SUV_{max}$ values were standardized according to the injected dose and patient weight.

We assessed the $SUV_{max}$ for both the primary and the metastatic lesions, as well as for the organs and lesions with a significant $^{18}$F-FDG uptake. In addition, serial changes in $SUV_{max}$ of the same patient during chemotherapy were assessed. PET $SUV_{max}$ measurement was done by 2 readers, followed by review and confirmation by an independent additional reader.

### Statistical Analysis

Continuous variables were expressed as median (with range), and categoric variables were expressed as percentages. The Student *t* test and 1-way ANOVA were used to analyze the continuous variables, whereas the Pearson $\chi^2$ test or Fisher exact test was used to analyze the categoric variables. The log-rank test was used to find the appropriate initial $SUV_{max}$ and the associated cutoff value of reduction to predict PFS and OS.

The PFS was calculated as the period from the first day of palliative chemotherapy to the day of documented disease progression or death of any cause, and the OS was calculated as the period from the first day of palliative chemotherapy to the day of death. The Kaplan–Meier method and log-rank test were used to analyze the differences in PFS and OS depending on the clinical variables. After univariate analysis was performed, multivariate analysis was performed with Cox regression analysis using backward selection to identify the predictive impact of $SUV_{max}$ and its changes over time. A *P* value of 0.05 or less was considered statistically significant. All statistical analyses were performed using SPSS software version 21 for Windows (IBM SPSS).

### Ethics

The study protocol was reviewed and approved by the institutional review board of the Seoul National University Hospital (no. H-1307-132-508). The study was conducted according to the recommendations of the Declaration of Helsinki for biomedical research.

## RESULTS

### Patients

Seventy-five 75 patients were enrolled, and their characteristics are shown in Table 1. The median age was 64 y (range, 46–83 y), and 43 (57.3%) patients were men. Twenty-eight (37.3%) patients had gallbladder cancer, 22 (29.3%) had IHCC, 19 (25.3%) had EHCC, and 6 (8.0%) had AoV cancer. The Eastern Cooperative Oncology Group performance status was 0 in 20 (26.7%) patients. Moderately differentiated adenocarcinoma was identified to be the most common pathology (38 patients, 50.7%). Immunohistochemistry showed positive expression of c-Myc in 12 (30.0%) patients among the 40 patients who were analyzed. Thirty-five (46.7%) patients had initially unresectable diseases, and the remaining (53.3%) had recurrent disease. All patients received gemcitabine/cisplatin as first-line palliative chemotherapy. The median follow-up duration was 6.8 mo (range, 1.0–27.2 mo). The median PFS was 5.6 mo (95% confidence interval [CI], 4.4–6.8), and the median OS was 13.2 mo (95% CI, 7.1–19.3). There were 4 cases with discrepancies between 2 readers. All cases were evaluated as stable disease by the first reader and progressive disease by the second reader. Three cases were finally determined as stable disease (based on tumor sum) and 1 case as progressive disease (based on a new lesion) after repeated evaluation and discussion.

### $SUV_{max}$ Distribution at Baseline and Its Changes During Chemotherapy

The distribution of the median $SUV_{max}$ at baseline among all lesions (combined primary and metastatic lesions), primary lesions, and metastatic lesions were 8.6 (range, 1.0–20.5), 3.9 (range, 1.0–20.5), and 5.8 (range, 1.0–15.2), respectively. The median $SUV_{max}$ reductions among all lesions at the best metabolic response and during the initial evaluation were 9.5% (range, −162.5%–88.8%) and 5.2% (range, −162.5%–85.3%), respectively. The median number of organs and lesions with $^{18}$F-FDG uptake were 2 (range, 0–5) and 2 (range, 0–41), respectively (Supplemental Table 1 [supplemental materials are available at http://jnm.snmjournals.org]; Figs. 1A and 1B). Seventy patients had $^{18}$F-FDG–avid tumors. In terms of primary tumors, the median $SUV_{max}$ values at baseline among all lesions were 9.9, 7.5, 5.4, and 9.5 in gallbladder cancer, IHCC, EHCC, and AoV cancer, respectively (Fig. 1C).

### Cutoff Value of Initial $SUV_{max}$ and Degree of Metabolic Reduction During Chemotherapy

The most optimal $SUV_{max}$ cutoff values for predicting PFS and OS were determined by the log-rank test to be 9.0 and 10.0, respectively (Supplemental Table 2). On the basis of these results, we selected the $SUV_{max}$ values as the discriminating values, respectively.

All cutoff values for $SUV_{max}$ reduction at the best metabolic response were associated with PFS, and 20.0% were optimal cutoff values for predicting OS (Supplemental Table 2). On the basis of these results, we selected a $SUV_{max}$ reduction of 20% as the discriminating value.

**TABLE 1**
Baseline Characteristics of Patients

| Characteristic | Value ($n$ = 75) |
|---|---|
| Women ($n$) | 32 (42.7%) |
| Median age (y) | 64.0 (range, 46.0–83.0) |
| Median BMI (kg/m$^2$) | 23.4 (range, 15.8–30.0) |
| ECOG performance-status score ($n$) | |
| 0/1 to 2 | 20 (26.7%)/55 (73.3%) |
| Primary tumor site ($n$) | |
| Gallbladder cancer | 28 (37.3%) |
| IHCC | 22 (29.3%) |
| EHCC | 19 (25.3%) |
| AoV cancer | 6 (8.0%) |
| Pathologic differentiation ($n$) | |
| WD/MD/PD | 3 (4.0%)/38 (50.7%)/12 (16.0%) |
| HER 2 immunohistochemistry ($n$) | |
| Negative to 1+ | 33 (44.0%) |
| 2+ to 3+ | 10 (13.3%) |
| HER 2 FISH ($n$) | |
| Negative/positive | 5 (6.7%)/3 (4.0%) |
| c-MET cytoplasm immunohistochemistry ($n$) | |
| Negative to 1+ | 36 (48.0%) |
| 2+ to 3+ | 7 (9.3%) |
| c-MET membrane immunohistochemistry ($n$) | |
| Negative to 1+ | 16 (21.3%) |
| 2+ to 3+ | 27 (36.0%) |
| c-Myc | |
| Negative/positive | 28 (37.3%)/12 (16.0%) |
| Median CEA (ng/mL) | 2.6 (range, 0.5–182.9) |
| Median CA 19-9 (U/mL) | 133 (range, 2.0–36,000.0) |
| Median WBC (μL) | 6,300 (range, 2,890–16,330) |
| Median total bilirubin (mg/dL) | 0.6 (range, 0.3–3.3) |
| Median albumin (mg/dL) | 3.9 (range, 3.3–4.7) |
| Curative/palliative operation ($n$) | 40 (78.4%)/11 (21.6%) |
| Unresectable/recurrent disease ($n$) | 35 (46.7%)/40 (53.3%) |
| Best response ($n$) | |
| PR/SD/PD | 12 (16.7%)/45 (62.5%)/15 (20.8%) |
| Median follow-up duration (mo) | 6.8 (1.0–27.2) |
| Median PFS (mo) | 5.6 (95% CI, 4.4–6.8) |
| Median OS (mo) | 13.2 (95% CI, 7.1–19.3) |

BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; WD = well differentiated; MD = moderately differentiated; PD = poorly differentiated; HER 2 = human epidermal growth factor receptor 2; FISH = fluorescent in situ hybridization; CEA = carcinoembryonic antigen; CA 19-9 = carbohydrate antigen 19-9; WBC = white blood cell; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

**Comparison of Patient Characteristics Between High- and Low-Metabolism Groups**

We divided the patients into high- and low-metabolism groups using the $SUV_{max}$ cutoff value of 9.0 (Table 2). Gallbladder cancer was more common in the high-metabolism group, and EHCC was more common in the low-metabolism group. Poorly differentiated carcinoma and c-Myc–positive tumors were more frequently observed in the high-metabolism group. Initial metastatic disease was more frequent than recurrent disease in the high-metabolism group. The high-metabolism group showed high leukocytes and had more lesions and organs with $^{18}$F-FDG uptake. Age, sex, performance status, body mass index, carcinoembryonic antigen,

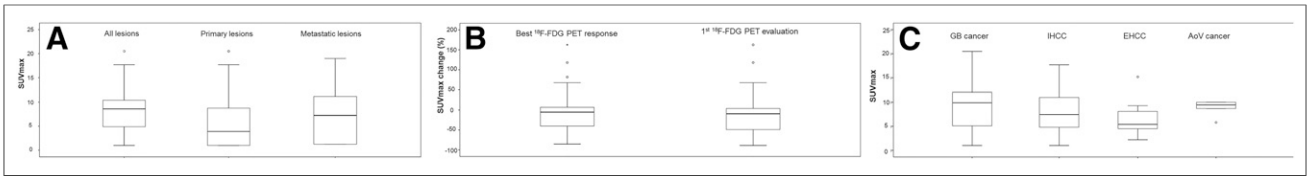


**FIGURE 1.** (A) Distribution of initial $SUV_{max}$. (B) $SUV_{max}$ reduction at best metabolic response and at first $^{18}$F-FDG PET evaluation. (C) Distribution of initial $SUV_{max}$ according to primary tumor origin.

carbohydrate antigen 19-9 levels, total bilirubin, albumin level, and treatment response did not differ between the 2 groups. The evaluation of metabolic activities according to patient characteristics showed similar findings (Supplemental Table 3).

### Prognostic Implications of Initial $SUV_{max}$ and Degree of Metabolic Reduction During Chemotherapy

The PFS was significantly shorter in patients of the high-metabolism group (3.8 vs. 7.0 mo; $P = 0.002$, respectively; Fig. 2A) and in the lesser $SUV_{max}$ reduction group at the best metabolic response (3.9 vs. 8.8 mo, $P < 0.001$; Fig. 2B). Primary tumor origin, initial $SUV_{max}$, and the degree of $SUV_{max}$ reduction were identified as independent prognostic factors for PFS in multivariate analysis (Table 3). Patients in the high-metabolism group (hazard ratio [HR], 4.09; 95% CI, 1.73–9.66; $P = 0.001$) and those with lesser reduction of $SUV_{max}$ had worse outcomes (HR, 3.35; 95% CI, 1.55–7.20; $P = 0.002$).

Patients with high metabolic activity had significantly worse OS (10.9 vs. 19.1 mo, $P = 0.003$; Fig. 2C). Patients with a lesser reduction of $SUV_{max}$ at the best metabolic response showed a trend of worse OS (13.2 vs. 20.7 mo, respectively, $P = 0.074$; Fig. 2D). The initial $SUV_{max}$ was identified as an independent prognostic factor for OS in multivariate analysis. Although statistically insignificant, $SUV_{max}$ reduction and organs with $^{18}$F-FDP uptake were potentially associated with clinical outcome. Patients with high metabolic activity (HR, 2.61; 95% CI, 1.18–5.81; $P = 0.019$) and lesser $SUV_{max}$ reduction (HR 1.96, 95% CI 0.91–4.20, $P = 0.082$) had worse OS (Table 4).

After the patients were divided into 4 groups depending on the initial $SUV_{max}$ values and their changes at the best metabolic response, patients having high metabolic tumors who achieved lesser $SUV_{max}$ reduction showed the worst survival outcomes, whereas those having low metabolic tumors who achieved greater $SUV_{max}$ reduction showed the best survival outcomes (2.8 vs. 11.5 mo, $P < 0.001$ for PFS; 6.2 vs. 20.7 mo, $P = 0.013$ for OS; Fig. 3).

The analysis of the relationship between metabolic changes in $SUV_{max}$ and their tumor response according to RECIST 1.1 showed that all patients who achieved partial response had reduced $SUV_{max}$ values (Supplemental Fig. 1). However, the reduction of $SUV_{max}$ was also observed in many of the patients who achieved stable disease status.

### Prognostic Value of Initial $SUV_{max}$ and Degree of Metabolic Reduction During Chemotherapy in Patients Who Achieved Disease Control According to RECIST 1.1

In patients who achieved disease control (complete response + partial response + stable disease) according to RECIST 1.1, patients in the high-metabolism and lesser $SUV_{max}$ reduction groups had

**TABLE 2**
Comparison of Patient Characteristics Between High-/Low-Metabolism Groups

| Characteristic | Low-metabolism group, $SUV_{max} \leq 9.0$ ($n = 46$) | High-metabolism group, $SUV_{max} > 9.0$ ($n = 29$) | *P* |
|---|---|---|---|
| Primary tumor site (*n*) | | | 0.013 |
| Gallbladder cancer | 12 (26.1%) | 16 (55.2%) | |
| IHCC | 14 (30.4%) | 8 (27.6%) | |
| EHCC | 17 (37.0%) | 2 (6.9%) | |
| AoV cancer | 3 (6.5%) | 3 (10.3%) | |
| Histologic differentiation (*n*) | | | 0.034 |
| WD | 1 (2.6%) | 2 (13.3%) | |
| MD | 31 (81.6%) | 7 (46.7%) | |
| PD | 6 (15.8%) | 6 (40.0%) | |
| c-Myc, positive | 3 (12,5%) | 9 (56.2%) | 0.005 |
| Initial presentation at enrollment (*n*) | | | <0.001 |
| Metastatic disease | 14 (30.4%) | 21 (72.4%) | |
| Recurrent disease | 32 (69.6%) | 8 (27.6%) | |
| Mean WBC (μL) | 5,980.4 ± 1,857.4 | 7,473.1 ± 3,032.8 | 0.010 |
| Mean no. of organs with $^{18}$F-FDG uptake | 1.5 ± 1.1 | 2.3 ± 1.0 | 0.004 |
| Mean no. of lesions with $^{18}$F-FDG uptake | 2.9 ± 3.5 | 7.0 ± 7.9 | 0.012 |

WD = well differentiated; MD = moderately differentiated; PD = poorly differentiate; WBC = white blood cell.

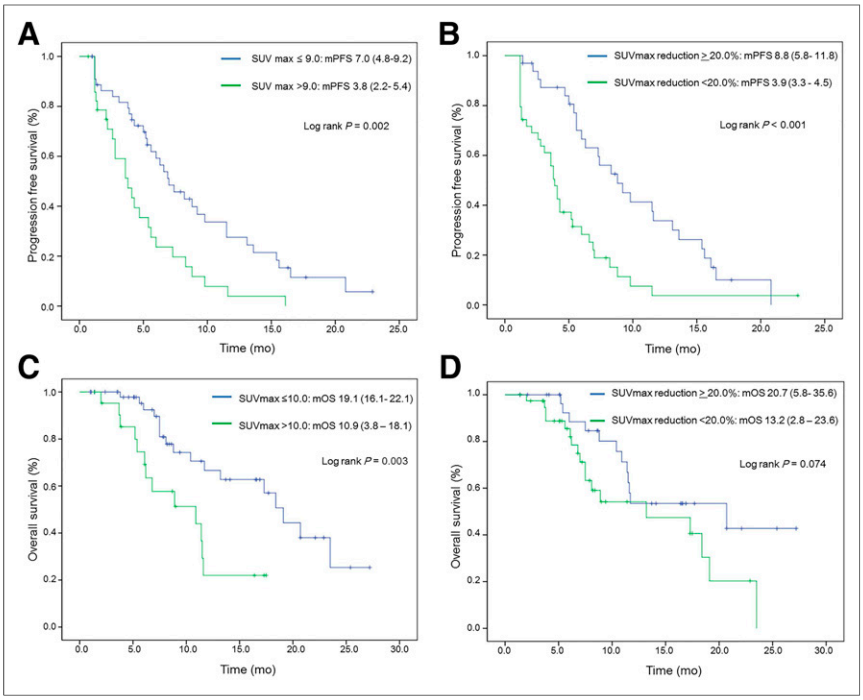


**FIGURE 2.** PFS according to initial $SUV_{max}$ (A) and $SUV_{max}$ reduction at best metabolic response (B). OS according to initial $SUV_{max}$ (C) and $SUV_{max}$ reduction at best metabolic response (D).

worse PFS than those in the low-metabolism (4.7 vs. 8.8 mo, $P = 0.003$; Supplemental Fig. 2A) and higher $SUV_{max}$ reduction (5.3 vs. 9.2 mo, $P = 0.013$; Supplemental Fig. 2B) groups. Patients in the high-metabolism group had significantly worse OS (10.9 vs. 19.1 mo, $P = 0.01$; Supplemental Fig. 2C), and patients in the group with lesser metabolic rate reduction potentially showed worse OS (13.2 vs. 20.7 mo, $P = 0.156$; Supplemental Fig. 2D).

## DISCUSSION

In this prospective study, we found that the metabolic characteristics of BTCs were associated with clinicopathologic heterogeneity. Tumor metabolism before chemotherapy and metabolic changes that occurred during chemotherapy were independent prognostic factors in BTC.

It has been reported that metabolic characteristics assessed using $^{18}$F-FDG PET reflect the clinical, histologic, and molecular diversity in several cancers, as well as intratumoral heterogeneity (*19,20*). In our previous retrospective study, we reported that metabolic activity differed according to tumor origin, pathologic differentiation, and tumor marker levels. In the present study, we prospectively validated our previous findings, showing that tumor metabolic activity differed based on the molecular characteristics of the BTCs. In a preclinical study, c-Myc activation was related to high $^{18}$F-FDG uptake and proliferative index (*21*). Although immunohistochemistry was done in some patients, c-Myc–positive tumors were more frequently found in the high-metabolism group in our study. Therefore, our study provides the clinical evidence supporting this preclinical hypothesis.

**TABLE 3**
Analysis of Prognostic Factors of PFS

| Variable | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | Median PFS (mo) | 95% CI | *P* | HR | 95% CI | *P* |
| Primary tumor origin | | | 0.013 | | | 0.003 |
| Gallbladder cancer | 5.3 | 2.8–7.8 | | 0.476 | 0.17–1.32 | |
| IHCC | 8.3 | 5.0–11.6 | | Ref | | |
| EHCC | 5.0 | 2.2–7.8 | | 2.31 | 0.83–6.50 | |
| AoV cancer | 1.3 | 0.7–1.9 | | 3.26 | 0.83–12.85 | |
| c-Myc | | | 0.044 | | | |
| Negative | 7.0 | 2.5–11.5 | | | | |
| Positive | 3.8 | 0.4–7.2 | | | | |
| Initial $SUV_{max}$ | | | 0.002 | 4.09 | 1.73–9.66 | 0.001 |
| ≤9.0 | 7.0 | 4.8–9.2 | | | | |
| >9.0 | 3.8 | 2.2–5.4 | | | | |
| $SUV_{max}$ reduction (at best $^{18}$F-FDG PET response) | | | <0.001 | 3.35 | 1.55–7.20 | 0.002 |
| ≥20.0% | 8.8 | 5.8–11.8 | | | | |
| <20.0% | 3.9 | 3.3–4.5 | | | | |
| Organs with $^{18}$F-FDG uptake (*n*) | | | 0.134 | | | |
| 0–2 | 6.3 | 4.8–7.9 | | | | |
| ≥3 | 3.9 | 2.2–5.6 | | | | |

**TABLE 4**
Analysis of Prognostic Factors of OS

| Variable | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | Median OS (mo) | 95% CI | *P* | HR | 95% CI | *P* |
| Age (y) | | | 0.094 | | | |
| ≤65 | 19.1 | 9.8–28.4 | | | | |
| >65 | 8.9 | 6.0–11.8 | | | | |
| CEA (ng/mL) | | | 0.062 | | | |
| ≤5.0 | 18.4 | 15.8–21.0 | | | | |
| >5.0 | 8.9 | 4.7–13.1 | | | | |
| Initial $SUV_{max}$ | | | 0.003 | 2.61 | 1.18–5.81 | 0.019 |
| ≤10.0 | 19.1 | 16.1–22.1 | | | | |
| 10.0 | 10.9 | 3.8–18.1 | | | | |
| $SUV_{max}$ reduction (at best $^{18}$F-FDG PET response) | | | 0.074 | 1.96 | 0.91–4.20 | 0.082 |
| ≥20.0% | 20.7 | 5.8–35.6 | | | | |
| 20.0% | 13.2 | 2.8–23.6 | | | | |
| Organs with $^{18}$F-FDG uptake (*n*) | | | 0.039 | 2.08 | 0.95–4.57 | 0.068 |
| 0–2 | 18.4 | 10.3–26.5 | | | | |
| ≥3 | 8.9 | 2.3–15.5 | | | | |

CEA = carcinoembryonic antigen.

Tumor metabolism indicated by $^{18}$F-FDG PET was a prognostic factor in various cancers (*9–11*). In BTCs, studies about the issues are limited. Preoperative metabolic activity in BTCs was associated with recurrence risk and survival outcome (*12,13*). In the metastatic setting, Kitamura et al. showed that $SUV_{max}$ was associated with OS; however, this study included only patients with EHCC and evaluated only the metabolism at the primary tumor site (*14*). In our previous study, we reported that patients with high tumor metabolism had worse clinical outcomes (*17*). To the best of our knowledge, the present study is the first prospective study on the prognostic impact of metabolic activity in BTCs. Metabolic activity was associated not only with OS but also with PFS. The $^{18}$F-FDG uptake had strong correlations with cancer cell counts, glucose tranporter-1 expression, and proliferation rate (*22*). Thus, higher $^{18}$F-FDG uptake might represent higher tumor burden, resulting in poor outcome. In support of this view, we found that patients in the high-metabolism group had the tendency to present with initially metastatic status and had higher $^{18}$F-FDG uptake at organs and lesions.

In the present study, another intriguing finding was that the metabolic changes during chemotherapy were also important prognostic factors. This is the first report, to our knowledge, on the metabolic response to chemotherapy as a prognostic factor of advanced BTC based on prospective design. Camacho et al. reported that $^{18}$F-FDG PERCIST predicts OS in IHCC patients. However, this study included only 9 patients treated with radioembolization that was not widely used for IHCC (*15*). Sahani et al. reported that the reduction of $SUV_{max}$ was a better predictor of survival outcome than morphologic changes in 28 advanced BTC patients. However, this study was a small retrospective analysis (*16*). In some BTC cases, those with the tumor spreading alongside the bile duct only without mass formation, determining the tumor extent and measuring the size of tumor lesions are difficult. In such cases, assessing the metabolic response might become a prominent alternative method. The prognostic significance of metabolic response was also maintained in patients who achieved disease control via RECIST 1.1 in our study. This further supports the clinical implications of tumor metabolism assessed by $^{18}$F-FDG PET in BTCs.

Recently, PET/MRI has been shown to have potential advantage over PET/CT in better anatomic division, simultaneous procedure, and less radiation exposure. In BTC, there have been little data of PET/MRI.

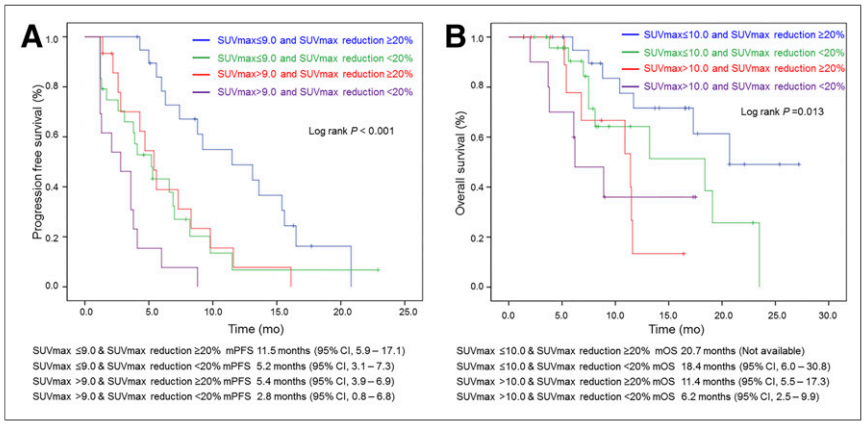


**FIGURE 3.** PFS (A) and OS (B) after patients were divided into 4 groups by initial $SUV_{max}$ and its response.

Some studies showed the superiority of PET/MRI for the evaluation of liver metastasis so it seems that PET/MRI has also potential role in BTC (*23*). However, longer scanning time, large volume of data, motion artifacts due to respiration or bowel movements, and contraindication of the procedure in patients with metal prosthesis are limitations of PET/MRI. Further study will be needed to define the potential role of PET/MRI in BTC.

In this prospective study, all patients were assessed using $^{18}$F-FDG PET before first-line chemotherapy and after first response evaluation. However, the follow-up $^{18}$F-FDG PET was not performed as scheduled in some patients lost to follow-up. Thus, best other than first metabolic response may have some potential biases. However, most participants (86.7%) followed scheduled $^{18}$F-FDG PET evaluation (at every response evaluation time point during progression) and best metabolic response may more accurately represent the effect of chemotherapy including delayed response. In the present study, the $SUV_{max}$ cutoff values determined for PFS and OS were 9 and 10, respectively. Various $SUV_{max}$ cutoff values are used to predict survival outcome in different tumor types (*11,14,17*). Because SUV is a semiquantitative index and has study performance variability across centers, further efforts for the standardization of the metrics are required for determining the most appropriate cutoff value. False positivity due to inflammation around the bile duct system is an important factor to consider when we analyze the tumor metabolism in BTC (*24*). However, patients enrolled in our study were evaluated with $^{18}$F-FDG PET/CT just before the initiation of first-line chemotherapies; therefore, they were clinically stable and had no evidence of active infection. Most of the patients had reference range of leukocytes and total bilirubin level. So, we assumed that the inflammatory effect was minimal to evaluate tumor metabolism using PET in our population. However, we should always be cautious in interpreting $SUV_{max}$, taking into consideration the possibility of false positivity due to inflammation.

## CONCLUSION

Metabolic characteristics of advanced BTCs differ depending on the tumor primary site of origin and molecular characteristics. Metabolic activity and changes that occur during chemotherapy were identified as useful prognostic factors for advanced BTC patients.

## DISCLOSURE

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