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

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ABSTRACT

Purpose

Tumor metabolism measured by ^{18}F-fluorodeoxy-D-glucose (^{18}F-FDG) positron emission tomography (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.

Materials and Methods

We prospectively enrolled advanced BTC patients before the initiation of palliative chemotherapy. Using ^{18}F-FDG PET, we assessed the baseline maximum standardized uptake value (SUVmax) and monitored the changes of SUVmax during chemotherapy. We analyzed the associations between SUVmax, and clinicopathologic factors and clinical outcomes.

Results

A total of 75 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 (PFS); HR=2.61, p=0.019 for overall survival (OS)] than the low metabolism group. The lesser reduction of SUVmax was also associated with worse outcome

(HR=3.35, p=0.002 for PFS; HR=1.96, p=0.082 for OS). Considering both baseline tumor metabolism and its chemotherapy-related changes, patients with a low metabolism and a more reduction in metabolism obtained the best OS (20.7 months versus 6.2 months, 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

INTRODUCTION

BTCs, which include gallbladder cancers, intrahepatic cholangiocarcinomas (IHCCs), extrahepatic cholangiocarcinomas (EHCCs), and ampulla of Vater (AoV) cancer, are heterogeneous diseases with diverse histological and biological 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 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, fibroblast growth factor receptor fusion, etc. 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 cell 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, as well as the 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 METHOD

Patients and Data Collection

We have 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 have enrolled patients in the study since October 2013 at Seoul National University Hospital (Seoul, Republic of Korea) and the data cut-off for this analysis was done at October 2015. The inclusion criteria were: histologically confirmed unresectable or recurrent cancer; planned palliative chemotherapy; informed consent.

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 (CEA) and carbohydrate antigen (CA) 19-9; chemotherapy regimens

and their schedules; chemotherapeutic response according to the RECIST 1.1 criteria using contrast-enhanced CT scan; PFS, and OS were collected *(18)*. The response evaluation based on RECIST 1.1 was done by two independent readers to secure inter- and intra- reader reproducibility. The two independent readers for RECIST 1.1 evaluation were not blinded to clinical information in a non-randomized fashion. If there was discrepancy between two readers, repeated evaluation and discussion was done to seek for final conclusion.

^{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 scan 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, Erlangen, Germany) were used in the acquisition of the ^{18}F-FDG PET images. Patients were fasted at least 6 hours and regulated blood sugar levels less than 210 mg/dL before the injection of 5.18 MBq/kg ^{18}F-FDG. ^{18}F-FDG PET/CT was performed 1 hour after the injection of ^{18}F-FDG. Images were reconstructed using ordered-subset expectation maximization (2 internations and 21 subsets; gaussian filter of 3mm and 5mmin Biograph True-Point and Biograph mCTs, respectively). Image analysis was performed using a commercialized software package (syngo.via, Siemens Medical Solution, Knoxville, TN, USA). 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 standardized uptake value (SUV) calculated according to the formula: SUV = 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 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 SUVmax measurement was done by two readers, followed by review and confirmation by independent another reader.

Statistical Analyses

Continuous variables were expressed as median (range) and categorical variables were expressed as percentages. Student's t-test and one-way analysis of variance were used to analyze the continuous variables, whereas Pearson chi-squared test or Fisher's exact test was used to analyze the categorical variables. The log-rank test was used to find the appropriate initial SUV_{max} and the associated cut-off 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 performing univariate analysis, 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 ≤ 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software version 21 for Windows (IBM SPSS, Somers, NY).

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

A total of 75 patients were enrolled and their characteristics are shown in Table 1. The median age was 64 (46–83) years 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 that 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 (range, 1.0–27.2) months. The median PFS was 5.6 months (95% confidence interval [CI]: 4.4–6.8) and the median OS was 13.2 months (95% CI: 7.1–19.3). There are four cases with discrepancies between 2 readers. All cases were evaluated as stable disease (SD) by first reader and progressive disease (PD) by second readers. Three cases were finally determined as SD (based on tumor sum), and one case as PD (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 uptakes were 2 (range, 0–5) and 2 (range, 0–41), respectively (Supplemental Table 1 and Fig. 1A and 1B). Seventy patients had 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).

Cut-off Value of the Initial SUV_{max} and the Degree of Metabolic Reduction during Chemotherapy

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

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

Comparison of Patient Characteristics between the High and Low Metabolism Groups

We divided the patients into high and low metabolism groups using the SUV_{max} cut-off value of 9.0 (Table 2). Gallbladder cancer was more common in the high metabolism group while 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 in the high metabolism group compared to recurrent disease. The high metabolism group showed high leukocyte and had more lesions and organs with ^{18}F-FDG uptake. Age, sex, performance status, body mass index, CEA, CA19-9 levels, total bilirubin, albumin level, and treatment response did not differ between the two groups. The evaluation of metabolic activities according to patient characteristics showed similar findings (Supplemental Table 3).

Prognostic Implications of the Initial SUV_{max} and Degree of Metabolic Reduction during Chemotherapy

The PFS was significantly shorter in patients of the high metabolism group (3.8 versus 7.0 months; p=0.002, respectively; Fig. 2A) and in the lesser SUV_{max} reduction group at the best metabolic response (3.9 versus 8.8 months, 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 ration (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 versus 19.1 months, 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 versus 20.7 months, 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 uptakes 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 dividing the patients 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 versus 11.5 months, $p<0.001$ for PFS; 6.2 versus 20.7 months, $p=0.013$ for OS; Figure 3).

The analysis of the relationship between metabolic changes in SUV_{max} and their tumor response according to the RECIST 1.1 showed that all patients who achieved partial response had reduced SUV_{max} values (Supplemental Figure 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 the RECIST 1.1 Criteria

In patients who achieved disease control (complete response+partial response+stable disease) according to the RECIST 1.1 criteria, patients in the high metabolism and lesser SUV_{max} reduction groups had worse PFS than those in the low metabolism (4.7 versus 8.8 months, $p=0.003$; Supplemental Fig. 2A) and higher SUV_{max} reduction (5.3 versus 9.2 months, $p=0.013$, Supplemental Fig 2B) groups. Patients in the high metabolism group had significantly worse OS (10.9 versus 19.1 months, $p=0.01$, Supplemental Fig. 2C), and patients in the group with lesser metabolic rate reduction potentially showed worse OS (13.2 versus 20.7 months, $p=0.156$; Supplemental Fig. 2D).

DISCUSSION

In this prospective study, we found that the metabolic characteristics of BTCs were associated with clinicopathological 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, histological, 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.

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. Pre-operative 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 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 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 PET Response Criteria for Solid Tumor (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 very 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 criteria in our study. This further supports the clinical implications of tumor metabolism assessed by ^{18}F-FDG PET in BTCs.

Recently, PET/Magnetic resonance imaging (MRI) has been shown potential advantage over PET/CT in better anatomical division, simultaneous procedure and less radiation exposure. In BTC, there have been a little data of PET/MRI. Some studied showed the superiority of the PET/MRI for 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 and/or bowel movements and contraindication of the procedure in patients with metal prosthesis are limitations of the PET/MRI. Further study will be needed to define 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 of participants (86.7%) follow 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} cut-off values determined for PFS and OS were 9 and 10, respectively. Various SUV_{max} cut-off values are used to predict survival outcome in different tumor types.*(11, 14, 17)* Because SUV is a semi-quantitative index and has study performance variability across centers, further efforts for the standardization of the metrics are required for determining the most appropriate cut-off value. False positivity due to inflammation around 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 normal range of leukocyte 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 $SUV_{max.}$ considering possibility of false positivity due to inflammation.

CONCLUSION

In 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

Nothing to declare.

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REFERENCES

1. Hezel AF, Deshpande V, Zhu AX. Genetics of biliary tract cancers and emerging targeted therapies. *J Clin Oncol*. 2010;28:3531-3540.

2. Hezel AF, Zhu AX. Systemic therapy for biliary tract cancers. *Oncologist*. 2008;13:415-423.

3. Glimelius B, Hoffman K, Sjoden PO, et al. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann Oncol*. 1996;7:593-600.

4. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*. 2010;362:1273-1281.

5. Geynisman DM, Catenacci DV. Toward personalized treatment of advanced biliary tract cancers. *Discov Med*. 2012;14:41-57.

6. Schweitzer N, Vogel A. Systemic therapy of cholangiocarcinoma: From chemotherapy to targeted therapies. *Best Pract Res Clin Gastroenterol*. 2015;29:345-353.

7. Vander Heiden MG. Targeting cancer metabolism: A therapeutic window opens. *Nat Rev Drug Discov*. 2011;10:671-684.

8. Larson SM, Schwartz LH. 18F-FDG PET as a candidate for "qualified biomarker": Functional assessment of treatment response in oncology. *J Nucl Med*. 2006;47:901-903.

9. Wahl RL, Zasadny K, Helvie M, Hutchins GD, Weber B, Cody R. Metabolic monitoring of breast cancer chemohormonotherapy using positron emission tomography: Initial evaluation. *J Clin Oncol*. 1993;11:2101-2111.

10. Spaepen K, Stroobants S, Dupont P, et al. Prognostic value of positron emission tomography (PET) with

fluorine-18 fluorodeoxyglucose ([18F]FDG) after first-line chemotherapy in non-hodgkin's lymphoma: Is [18F]FDG-PET a valid alternative to conventional diagnostic methods? *J Clin Oncol*. 2001;19:414-419.

11. Downey RJ, Akhurst T, Gonen M, et al. Preoperative F-18 fluorodeoxyglucose-positron emission tomography maximal standardized uptake value predicts survival after lung cancer resection. *J Clin Oncol*. 2004;22:3255-3260.

12. Lee EJ, Chang SH, Lee TY, et al. Prognostic value of FDG-PET/CT total lesion glycolysis for patients with resectable distal bile duct adenocarcinoma. *Anticancer Res*. 2015;35:6985-6991.

13. Song JY, Lee YN, Kim YS, et al. Predictability of preoperative 18F-FDG PET for histopathological differentiation and early recurrence of primary malignant intrahepatic tumors. *Nucl Med Commun*. 2015;36:319-327.

14. Kitamura K, Hatano E, Higashi T, et al. Prognostic value of (18)F-fluorodeoxyglucose positron emission tomography in patients with extrahepatic bile duct cancer. *J Hepatobiliary Pancreat Sci*. 2011;18:39-46.

15. Camacho JC, Kokabi N, Xing M, Schuster DM, Kim HS. PET response criteria for solid tumors predict survival at three months after intra-arterial resin-based 90Yttrium radioembolization therapy for unresectable intrahepatic cholangiocarcinoma. *Clin Nucl Med*. 2014;39:944-950.

16. Sahani DV, Hayano K, Galluzzo A, Zhu AX. Measuring treatment response to systemic therapy and predicting outcome in biliary tract cancer: Comparing tumor size, volume, density, and metabolism. *AJR Am J Roentgenol*. 2015;204:776-781.

17. Cho KM, Oh DY, Kim TY, et al. Metabolic characteristics of advanced biliary tract cancer using 18F-fluorodeoxyglucose positron emission tomography and their clinical implications. *Oncologist*. 2015;20:926-933.

18. Schwartz LH, Bogaerts J, Ford R, et al. Evaluation of lymph nodes with RECIST 1.1. *Eur J Cancer*. 2009;45:261-267.

19. Koo HR, Park JS, Kang KW, et al. 18F-FDG uptake in breast cancer correlates with immunohistochemically defined subtypes. *Eur Radiol*. 2014;24:610-618.

20. Fathinul F, Nordin AJ, Lau WF. 18[F]FDG-PET/CT is a useful molecular marker in evaluating tumour aggressiveness: A revised understanding of an in-vivo FDG-PET imaging that alludes the alteration of cancer biology. *Cell Biochem Biophys*. 2013;66:37-43.

21. Alvarez JV, Belka GK, Pan TC, et al. Oncogene pathway activation in mammary tumors dictates FDG-PET uptake. *Cancer Res*. 2014;74:7583-7598.

22. Bos R, van Der Hoeven JJ, van Der Wall E, et al. Biologic correlates of (18)fluorodeoxyglucose uptake in human breast cancer measured by positron emission tomography. *J Clin Oncol*. 2002;20:379-387.

23. Buchbender C, Heusner TA, Lauenstein TC, Bockisch A, Antoch G. Oncologic PET/MRI, part 1: Tumors of the brain, head and neck, chest, abdomen, and pelvis. *J Nucl Med*. 2012;53:928-938.

24. Andersen JB, Spee B, Blechacz BR, et al. Genomic and genetic characterization of cholangiocarcinoma identifies therapeutic targets for tyrosine kinase inhibitors. *Gastroenterology*. 2012;142:1021-1031.e15.

Figure with Legends

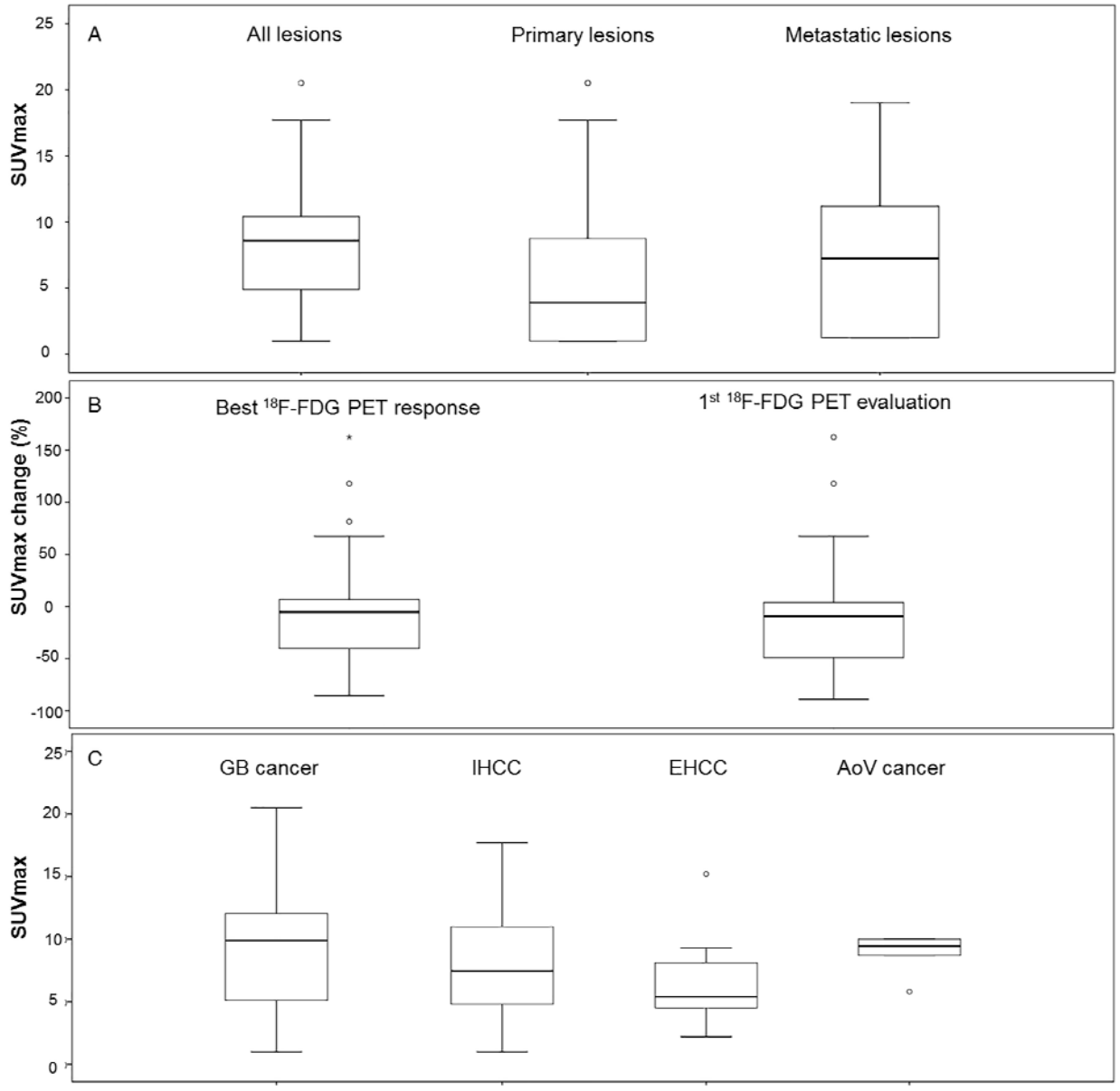


FIGURE 1. Distribution of initial SUV_{max} (A). SUV_{max} reduction at best metabolic response and at first ^{18}F-FDG PET evaluation (B). The distribution of initial SUV_{max} according to primary tumor origin (C)

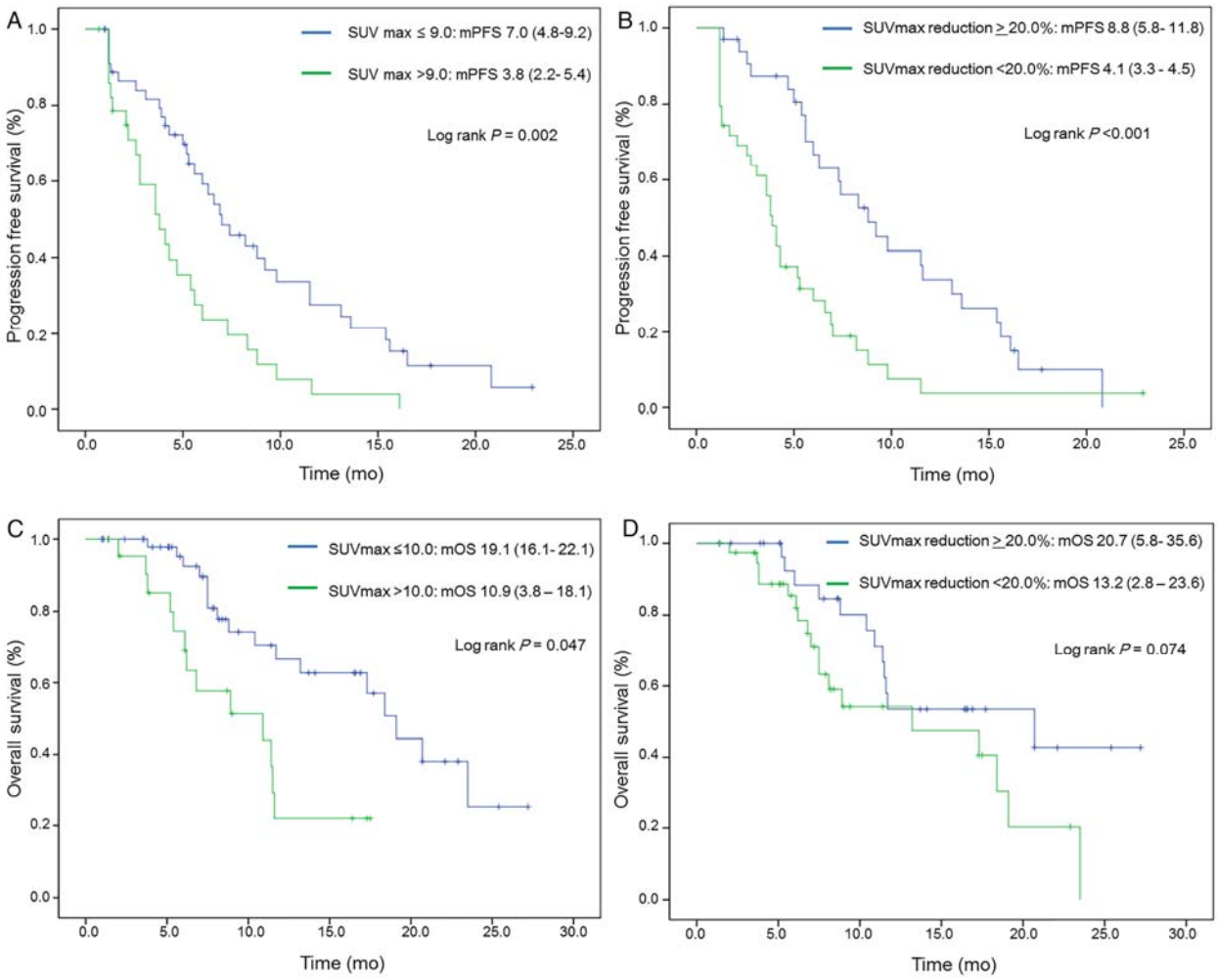
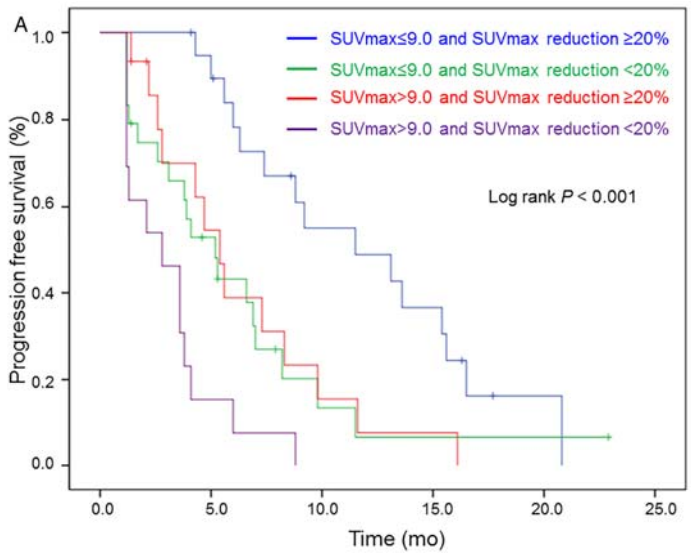
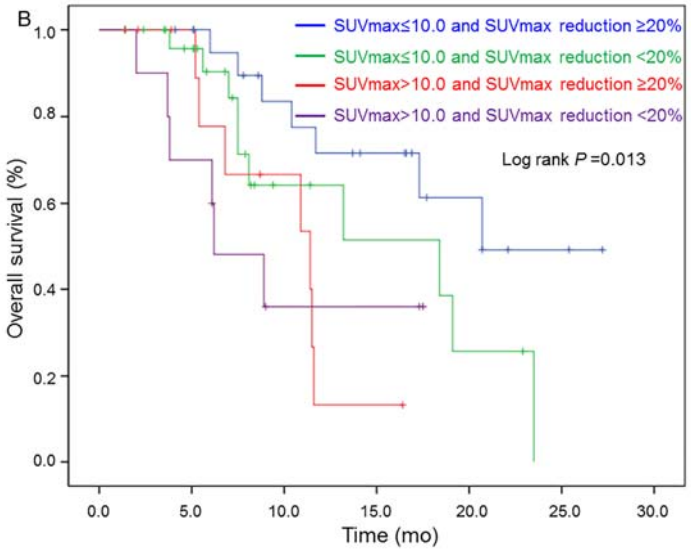


FIGURE 2. Progression free survival according to initial SUV_{max} (A) and SUV_{max} reduction at best metabolic response (B). Overall survival according to initial SUV_{max} (C) and SUV_{max} reduction at best metabolic response (D)



SUVmax ≤9.0 & SUVmax reduction ≥20% mPFS 11.5 months (95% CI, 5.9 – 17.1)
SUVmax ≤9.0 & SUVmax reduction <20% mPFS 5.2 months (95% CI, 3.1 – 7.3)
SUVmax >9.0 & SUVmax reduction ≥20% mPFS 5.4 months (95% CI, 3.9 – 6.9)
SUVmax >9.0 & SUVmax reduction <20% mPFS 2.8 months (95% CI, 0.8 – 6.8)



SUVmax ≤10.0 & SUVmax reduction ≥20% mOS 20.7 months (Not available)
SUVmax ≤10.0 & SUVmax reduction <20% mOS 18.4 months (95% CI, 6.0 – 30.8)
SUVmax >10.0 & SUVmax reduction ≥20% mOS 11.4 months (95% CI, 5.5 – 17.3)
SUVmax >10.0 & SUVmax reduction <20% mOS 6.2 months (95% CI, 2.5 – 9.9)

FIGURE 3. Progression-free survival (A) and overall survival (B) after dividing the patients into 4 groups by initial SUV_{max} and its response.

1 **TABLE 1. Baseline Characteristics of Patients**

Characteristics	Patients (n=75)
Women, no. (%)	32 (42.7%)
Median age, y (range)	64.0 (46.0–83.0)
BMI, kg/m^2 median (range)	23.4 (15.8–30.0)
ECOG performance-status score, no. (%)	
0 / 1 to 2	20 (26.7%) / 55 (73.3%)
Primary tumor site, no. (%)	
GB cancer	28 (37.3%)
IHCC	22 (29.3%)
EHCC	19 (25.3%)
AoV cancer	6 (8.0%)
Pathologic differentiation, no. (%)	
WD / MD / PD	3 (4.0%) / 38 (50.7%) / 12 (16.0%)
HER 2 IHC, no. (%)	
Negative to 1+	33 (44.0%)
2+ to 3+	10 (13.3%)
HER 2 FISH, no. (%)	
Negative / positive	5 (6.7%) / 3 (4.0%)
c-MET cytoplasm IHC, no. (%)	
Negative to 1+	36 (48.0%)
2+ to 3 +	7 (9.3%)
c-MET membrane IHC, no. (%)	
Negative to 1+	16 (21.3%)
2+ to 3+	27 (36.0%)
c-Myc	
Negative / positive	28 (37.3%) / 12 (16.0%)
CEA, ng/mL median (range)	2.6 (0.5–182.9)
CA 19-9, U/mL median (range)	133 (2.0–36,000.0)
WBC, /μL median (range)	6300 (2890–16330)
Total bilirubin, mg/dL median (range)	0.6 (0.3–3.3)
Albumin, mg/dL median (range)	3.9 (3.3–4.7)
Curative / palliative operation, no. (%)	40 (78.4%) /11 (21.6%)
Unresectable / Recurrent disease, no. (%)	35 (46.7%) / 40 (53.3%)
Best response, no. (%)	
PR / SD / PD	12 (16.7%) / 45 (62.5%) / 15 (20.8%)
Median follow-up duration, months (range)	6.8 (1.0–27.2)
Median PFS, months (95% CI)	5.6 (4.4–6.8)

Median OS, months (95% CI)	13.2 (7.1–19.3)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ECOG, Eastern Cooperative Oncology Group; GB, gall bladder; IHCC, intrahepatic cholangiocarcinoma; EHCC, extrahepatic cholangiocarcinoma; AoV, Ampulla of Vater; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; HER-2, human epidermal growth factor receptor 2; 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; PFS, progression free survival; CI, confidence interval; OS, overall survival.

TABLE 2. Comparison of Patient Characteristics between the 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* value
Primary tumor site, no (%)			**0.013**
GB 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, no (%)			**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			**0.005**
Pos	3 (12,5%)	9 (56.2%)	
Initial presentation at enroll, no (%)			**<0.001**
Metastatic disease	14 (30.4%)	21 (72.4%)	
Recurrent disease	32 (69.6%)	8 (27.6%)	
WBC (/μL)			**0.010**
Mean	5980.4 ± 1857.4	7473.1 ± 3032.8	
Number of organs with FDG uptake, no			**0.004**
Mean	1.5 ± 1.1	2.3 ± 1.0	
Number of lesions with FDG uptake, no			**0.012**
Mean	2.9 ± 3.5	7.0 ± 7.9	

Abbreviations: SUV, standardized uptake value; GB, gall bladder; IHCC, intrahepatic cholangiocarcinoma; EHCC, extrahepatic cholangiocarcinoma; AoV, Ampulla of Vater; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiate; WBC, white blood cell; FDG, fluorodeoxyglucose.

TABLE 3. Analysis of Prognostic Factors of Progression Free Survival

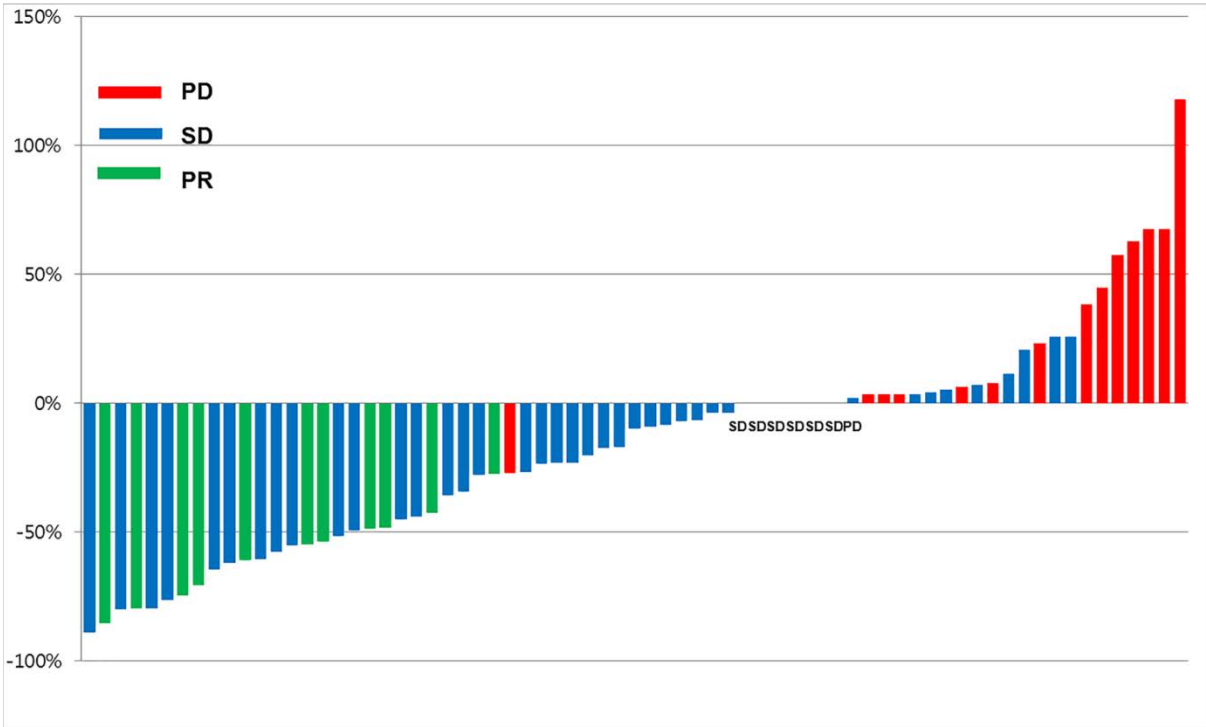
Variable	Univariate analysis			Multivariate analysis		
	Median PFS (Month)	95% CI	P value	HR	95% CI	P value
Primary Tumor Origin			**0.013**			**0.003**
GB cancer	5.3	2.8–7.8		0.476	0.17–1.32	
IHCC	8.3	5.0–11.6		Ref		
EHCC	5.0	2.2–7.8		2.31	0.83–6.50	
AoV cancer	1.3	0.7–1.9		3.26	0.83–12.85	
c-Myc			**0.044**			
neg	7.0	2.5–11.5				
Pos	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 FDG uptake (n)			0.134			
0 to 2	6.3	4.8–7.9				
≥3	3.9	2.2–5.6				

Abbreviations: PFS, progression free survival; CI, confidence interval; GB, gall bladder; IHCC, intrahepatic cholangiocarcinoma; EHCC, extrahepatic cholangiocarcinoma; AoV, Ampulla of Vater; SUV, standardized uptake value; FDG, fluorodeoxyglucose; PET, positron emission tomography.

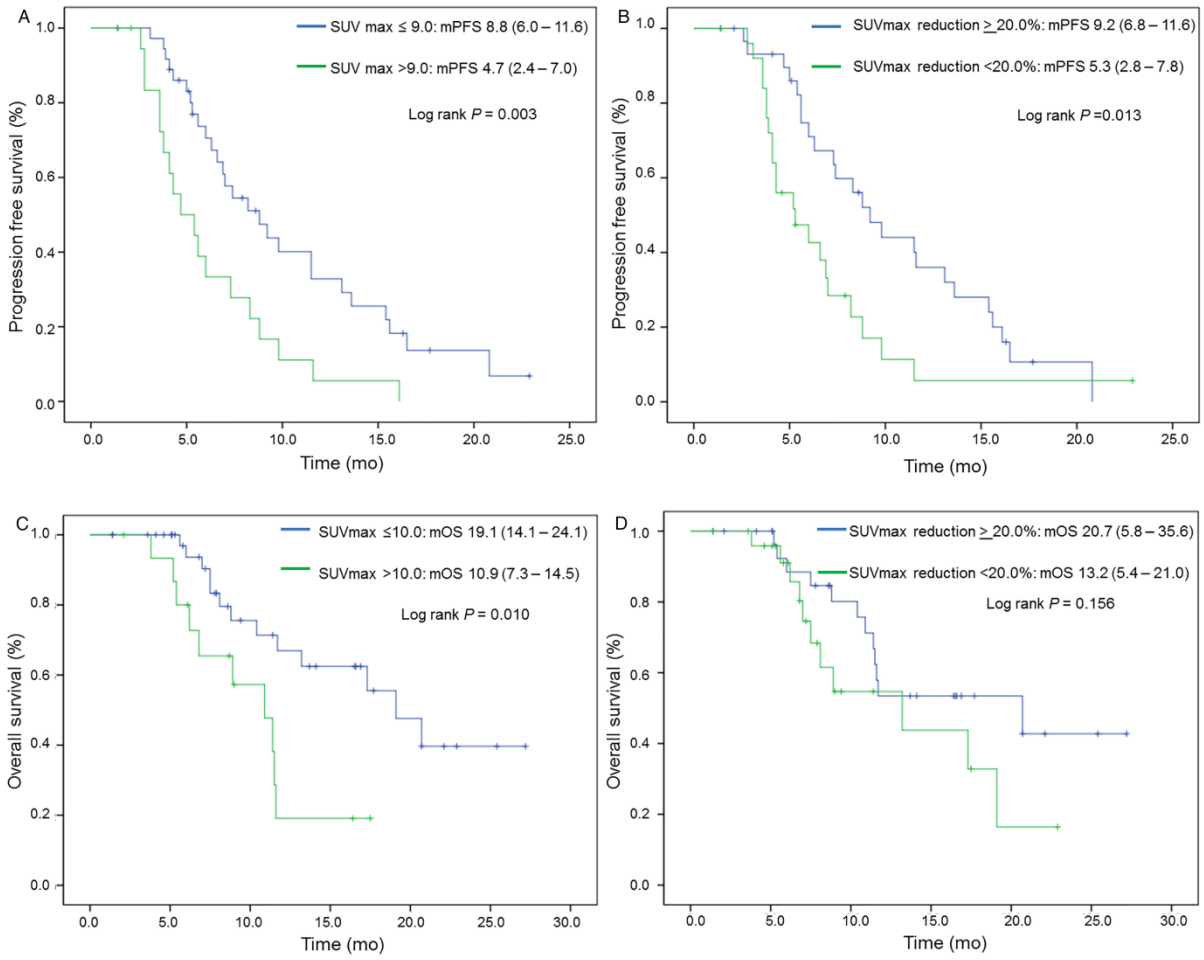
TABLE 4. Analysis of Prognostic Factors of Overall survival

Variable	Univariate analysis			Multivariate analysis		
	Median OS (Month)	95% CI	P value	HR	95% CI	P value
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 FDG uptake (n)			**0.039**	**2.08**	**0.95–4.57**	**0.068**
0 to 2	18.4	10.3–26.5				
≥3	8.9	2.3–15.5				

Abbreviations: OS, overall survival; CI, confidence interval; CEA, carcinoembryonic antigen; SUV, standardized uptake value; FDG, fluorodeoxyglucose.



Supplemental FIGURE 1. Waterfall plot according to change in SUVmax and disease response according to RECIST 1.1 using the corresponding contrast-enhanced computed tomography method.



Supplemental FIGURE 2. Progression-free survival and overall survival according to the initial SUV_{max} (A and C) and SUV_{max} reduction at best metabolic response (B and D) among patients who achieved disease control.

Supplemental table 1. Distribution of Initial SUV_{max} and ^{18}F-FDG PET Response

Initial SUV_{max}	
Among all lesions, median (range)	8.6 (1.0–20.5)
Among primary lesions, median (range)	3.9 (1.0–20.5)
Among metastatic lesions, median (range)	5.8 (1.0–15.2)
SUVmax reduction among all lesions at	
Best ^{18}F-FDG PET response (%), median (range)	9.5% (-162.5–88.8%)
1st ^{18}F-FDG PET evaluation (%), median (range)	5.2% (-162.5–85.3%)
Initial number of organs with FDG uptake	
Median (range)	2 (0–5)
Initial number of lesions with FDG uptake	
Median (range)	2 (0–41)

Abbreviations: SUV, standardized uptake value; FDG, fluorodeoxyglucose; PET, positron emission tomography.

Supplemental Table 2. Initial SUV_{max} and SUV_{max} Reduction Cut-off to Predict PFS and OS

Initial SUV_{max}	*P* value for PFS	*P* value for OS	SUV_{max} reduction at best ^{18}F-FDG PET response	*P* value for PFS	*P* value for OS
5	0.201	0.12	≥-10.0%	**<0.001**	0.921
6	0.171	0.106	≥0.0%	**<0.001**	0.146
7	0.057	0.077	≥10.0%	**0.001**	0.156
8	**0.032**	0.12	≥20.0%	**<0.001**	**0.074**
9	**0.002**	**0.047**	≥30.0%	**0.005**	0.096
10	**0.007**	**0.003**	≥40.0%	**0.005**	0.08
11	0.065	**0.016**	≥50.0%	**0.029**	0.119

Abbreviations: SUV, standardized uptake value; PFS, progression free survival; OS, overall survival; FDG, fluorodeoxyglucose; PET, positron emission tomography.

Supplemental Table 3. Comparison of Initial SUV_{max} According to Patient Characteristics

Characteristics	No.	Mean SUV_{max} ± SD	*P* value
Age, y			0.893
≤ 65	43	8.0 ± 4.8	
> 65	32	8.2 ± 3.4	
Sex			0.811
Women	32	8.2 ± 4.0	
Men	43	8.0 ± 4.4	
Primary tumor origin			0.120
GB cancer	28	9.1 ± 4.9	
IHCC	22	8.1 ± 4.3	
EHCC	19	6.2 ± 3.0	
AoV cancer	6	8.9 ± 1.6	
Histologic Differentiation			0.233
WD	3	8.8 ± 4.5	
MD	38	6.4 ± 3.6	
PD	12	8.1 ± 3.4	
HER2 IHC			0.150
Neg to 1+	33	7.8 ± 3.6	
2 to 3+	10	9.8 ± 4.6	
c-MET IHC (cytoplasm)			0.875
Neg to 1+	36	8.1 ± 4.1	
2+ to 3+	7	7.9 ± 4.0	
c-MET IHC (membrane)			0.690
Neg to 1+	16	7.8 ± 3.4	
2+ to 3+	27	8.3 ± 4.4	
c-Myc			**0.017**
Neg	28	7.0 ± 3.2	
Pos	12	10.4 ± 5.2	
Initial presentation at enroll			**0.001**
Recurrent disease	40	6.6 ± 3.3	
Unresectable disease	35	9.8 ± 4.6	
CEA, ng/mL			0.089
≤5.0	53	7.5 ± 4.2	
>5.0	20	9.4 ± 4.2	
CA 19-9, U/mL			0.540
≤37.0	27	7.7 ± 4.3	
>37.0	46	8.3 ± 4.2	
WBC, /μL			**0.001**

≤10,000	69	7.6 ± 3.9	
>10,000	6	13.6 ± 4.3	
Total bilirubin, mg/dL			0.136
≤1.2	64	8.4 ± 4.2	
>1.2	11	6.3 ± 3.8	
Albumin, mg/dL			0.794
≤3.9	44	8.0 ± 4.4	
>3.9	31	8.2 ± 4.1	
Organs with FDG uptake			**<0.001**
0 to 2	56	7.1 ± 3.9	
≥3	19	11.0 ± 3.8	
Lesions with FDG uptake			**<0.001**
0 to 2	41	6.6 ± 4.0	
≥3	34	9.9 ± 3.8	
Objective response			0.414
Yes	12	9.1 ± 4.3	
No	60	8.0 ± 4.2	
Disease control			0.149
Yes	57	7.8 ± 4.1	
No	15	9.6 ± 4.2	

Abbreviations: SUV, standardized uptake value; SD, standard deviation; GB, gall bladder; IHCC, intrahepatic cholangiocarcinoma; EHCC, extrahepatic cholangiocarcinoma; AoV, Ampulla of Vater; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; HER-2, human epidermal growth factor receptor 2; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; WBC, white blood cell; FDG, fluorodeoxyglucose.