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Preoperative FDG-Positive Lymph Nodes Predict the Postoperative Prognosis in Resectable Biliary Tract Cancers

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ABSTRACT

Background. F-18 fluorodeoxyglucose-positron emission tomography (FDG-PET) has been used to diagnose and stage various cancers. In regard to biliary tract cancer (BTC), due to cholangitis it is difficult to evaluate FDG uptake caused by cancer. We previously showed that FDG-positive lymph nodes (LNs) of resectable BTC had a possibility of predicting postoperative prognosis.

Objective. This study aimed to validate the usability of FDG-PET for LNs using another cohort and to investigate in detail the relationship between FDG-positive LNs and the prognosis of BTC.

Methods. We measured the preoperative maximum standardized uptake value (SUV_{max}) at each of the 190 surgically dissected LN areas in 67 patients and investigated the prognosis using our previously determined SUV_{max} cut-off values of ≥ 2.8.

Results. Regarding the prognosis of patients with resectable BTC, a LN $SUV_{max} \geq 2.8$ [PET N (+)] was a poor prognostic factor for recurrence-free survival (RFS) compared with a LN $SUV_{max} < 2.8$ [PET N (−)]. It was confirmed that the hazard ratio forest plot [PET N (+)/PET N (−)] for RFS indicated a similar tendency among subcategories. Moreover, we investigated patients with pN0

disease and demonstrated that the PET N (+) group also had a significantly worse RFS outcome compared with the PET N (−) group. Recurrence of the PET N (+) group has significantly occurred more often in LNs than that of the PET N (−) group.

Conclusion. High LN SUV_{max} was confirmed to be the preoperatively diagnosed prognostic risk factor for RFS in resectable BTC and could be helpful for clinical decision making regarding the perioperative treatment strategy.

Biliary tract cancer (BTC) is a fatal neoplasm with a poor prognosis. Despite the development of several examination methods or treatments, 5-year survival rates range from approximately 20–60% after curative resection,[1] and 30–40% for perihilar lesions. Furthermore, it was reported that perihilar cholangiocarcinoma (extrahepatic bile duct cancer) patients with R0 and N0 disease had a 5-year survival rate of 67.1%.[2] It has been demonstrated that a high-quality preoperative diagnosis, neoadjuvant chemotherapy, and surgery could improve critical cancer prognosis.

F-18 fluorodeoxyglucose-positron emission tomography (FDG-PET) has been used to predict the prognosis of various cancers, including gastrointestinal cancers and pancreatic cancer; a preoperative maximum standardized uptake value (SUV_{max}) >6.0 predicted early postoperative recurrence and poor survival of patients with pancreatic cancer.[3] Moreover, another study reported that high preoperative SUV_{max} of regional lymph nodes (LNs) was an independent prognostic factor for recurrence-free survival (RFS) and overall survival (OS) in patients with gastric

cancer.[4] However, in relation to BTC, the usability of SUV_{max} for primary cancer is still controversial.[5–11] Due to the accompanying cholangitis, it is difficult to distinguish FDG uptake caused by cancer or inflammation; therefore, in our previous study,[12] we focused on the role of FDG-PET in the preoperative diagnosis of LN metastasis in BTC. In that study, we demonstrated a possibility that FDG-PET-positive LNs using an SUV_{max} cut-off value of 2.8 correlated with prognosis in 36 patients. Moreover, multivariate analysis identified that FDG-PET-positive LNs ($SUV_{max} \geq 2.8$; hazard ratio 3.597, $p = 0.0230$) and curative resection were significant and independent prognostic factors. The limitation of this previous study was the small number of patients and the lack of validation.

The present study aimed to validate the usability of these FDG-PET-positive LNs by using an SUV_{max} cut-off value of 2.8 as the predictive factor in 67 BTC patients. For this purpose, we first evaluated clinicopathological features, including LN SUV_{max}, and divided patients into two groups ($SUV_{max} \geq 2.8$ or < 2.8). Second, we analyzed the postoperative prognosis between the two groups. Moreover, we investigated in detail the relationship between FDG-PET-positive LNs and the prognosis of BTC.

PATIENTS AND METHODS

Rules for the Classification of Biliary Cancer

In this study, we used the Union for International Cancer Control (UICC) general rules for the classification of biliary cancer to stage BTC, classify the LN area, and define curative resection described in detail in our previous report.[13]

Patients, Surgery, and Lymph Nodes (LNs)

The analysis was conducted in all 67 patients who underwent preoperative FDG-PET and were intended to treat with surgical resection from 2011 to 2015 at our institution. The average length of duration between preoperative FDG-PET and surgery was 38.8 ± 23.8 days. The results of FDG-PET did not affect the number of patients because the high LN SUV_{max} does not always indicate LN metastasis. Patients with neoadjuvant therapy were excluded because they had already been included in the other clinical trial. As almost all of the current BTC patients underwent neoadjuvant therapy, these patients within this time period were not enrolled in this current study. Seven patients (10.4%) had gall bladder cancer (GBC), 57 patients (85.1%) had biliary duct cancer (BDC; including intrahepatic bile duct cancer, perihilar extrahepatic bile duct cancer, and distal extrahepatic bile duct

cancer), and 3 patients (4.5%) had cancer of the papilla of Vater (PVC) (Table 1). LN stations dissected were 2, 3, 5, 6, 8a, 8p, 9, 12a, 12b, 12c, 12h, 12p, 13a, 13b, 14a, 14v, 16a2, 16b1, and 17. Among these patients, 36 (53.7%) underwent adjuvant chemotherapy; 10 patients received gemcitabine, 7 patients received S-1, 13 patients received gemcitabine and cisplatin, 5 patients received gemcitabine and S-1, and 1 patient received gemcitabine, cisplatin, and S-1 (GCS). Ethical approval was obtained from the Human Ethics Review Committee of the Graduate School of Medicine, Osaka University, and written informed consent was obtained from each of the patients.

Pathological Diagnosis

Pathological diagnosis of LNs was based on the Japanese Society of Biliary Surgery (JSBS) classification.[14] For histopathological examination, 6 μm paraffin-embedded sections were prepared from each LN. Pathological diagnosis was retrospectively compared with the diagnosis established based on FDG-PET imaging.

F-18 Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) Imaging and Maximum Standardized Uptake Value (SUV_{max}) Measurement of Each Primary Tumor and LN Area

FDG-PET/computed tomography (CT) was routinely performed using a three-dimensional (3D) mode PET/CT scanner (Gemini GXL 16; Philips, Amsterdam, The Netherlands; or SET-3000 GCT/X; Shimadzu, Kyoto, Japan), as a preoperative check of metastasis using standard methods as per our previous study.[12] The Gemini GXL 16 scanner was replaced with a Discovery PET/CT 710 scanner (GE Healthcare Japan, Tokyo, Japan) in April 2015; eight patients (11.9%) underwent FDG-PET using this new scanner. Additionally, one patient (1.5%) underwent FDG-PET using a Discovery ST scanner (GE Healthcare Japan), and two patients (3.0%) underwent FDG-PET using a Discovery ST Elite scanner (Discovery STE, GE Healthcare Japan, Tokyo, Japan) in two other hospitals. The long axial field of view (FOV) of the PET component was 157 mm in all these Discovery series. The intrinsic transverse and axial spatial resolution was 4.70 mm full width at half maximum (FWHM) and 4.74 mm FWHM in Discovery PET/CT 710, 5.63 mm FWHM and 5.74 mm FWHM in Discovery ST, and 5.97 mm FWHM and 6.11 mm FWHM in Discovery STE, respectively. Reconstruction methods were 3D ordered subset expectation maximization (OSEM) with time of flight (TOF) and point spread function (PSF; subsets = 8, iterations = 3) in Discovery PET/CT 710, and 3D OSEM in Discovery ST/STE. Injection dose of FDG and scan protocol were the

TABLE 1 Comparison of clinicopathological features in patients with biliary tract cancers, divided by FDG-PET SUVmax of lymph nodes

Factors	FDG-PET SUV$_{max}$ of lymph nodes		P-value
	< 2.8 (n = 47)	≥ 2.8 (n = 20)	
Age (mean ± SD), years	69 ± 10	68 ± 10	0.7601
Gender			
Male	27 (57.4%)	13 (65.0%)	0.5621
Female	20 (42.6%)	7 (35.0%)	
Tumor location			
Intrahepatic bile duct cancer	7 (14.9%)	2 (10.0%)	0.2943
Perihilar extrahepatic bile duct cancer	15 (31.9%)	5 (25.0%)	
Distal extrahepatic bile duct cancer	19 (40.4%)	9 (45.0%)	
Gall bladder cancer	3 (6.4%)	4 (20.0%)	
Cancer of the papilla of Vater	3 (6.4%)	0 (0.0%)	
CEA (mean ± SD), ng/mL	21.4 ± 125.8	17.1 ± 62.2	0.8844
CA19-9 (mean ± SD), U/mL	767.1 ± 3258.9	672.7 ± 1233.7	0.9006
UICC, cT			
1	8 (17.0%)	3 (15.0%)	0.6147
2	14 (29.8%)	4 (20.0%)	
3	19 (40.4%)	10 (50.0%)	
4	6 (12.8%)	3 (15.0%)	
UICC, cN			
0	37 (78.7%)	12 (60.0%)	0.1212
1	10 (21.3%)	8 (40.0%)	
UICC, cStage			
I	11 (23.4%)	3 (15.0%)	0.8824
II	20 (42.6%)	9 (45.0%)	
III	12 (25.5%)	6 (30.0%)	
IV	4 (8.5%)	2 (10.0%)	
FDG-PET SUV$_{max}$ of primary tumor (mean ± SD)	4.87 ± 3.03	6.64 ± 3.59	0.0404
Intraoperative blood loss (mean ± SD), mL	900.2 ± 645.3	1078.5 ± 805.6	0.3409
Total operation time (mean ± SD), min	552.9 ± 126.1	593.2 ± 115.2	0.2245
Tumor size (mean ± SD), mm	28.5 ± 15.0	31.6 ± 20.8	0.5117
Histology			
G1	8 (17.0%)	6 (30.0%)	0.0158
G2	29 (61.7%)	14 (70.0%)	
G3	10 (21.3%)	0 (0.0%)	
Number of dissected lymph nodes (mean ± SD)	22.0 ± 2.2	24.8 ± 3.4	0.4957
UICC, pT			
1	9 (19.2%)	1 (5.0%)	0.4473
2	19 (40.4%)	9 (45.0%)	
3	17 (36.2%)	9 (45.0%)	
4	2 (4.3%)	1 (5.0%)	
UICC, pN			
0	25 (53.2%)	6 (30.0%)	0.0778
1	22 (46.8%)	14 (70.0%)	
UICC, pStage			
I	7 (14.9%)	1 (5.0%)	0.3453
II	24 (51.1%)	8 (40.0%)	
III	9 (19.2%)	7 (35.0%)	
IV	7 (14.9%)	4 (20.0%)	

TABLE 1 continued

Factors	FDG-PET SUV$_{max}$ of lymph nodes		P-value
	< 2.8 (n = 47)	≥ 2.8 (n = 20)	
Residual tumor classification (UICC-8)			
R0	43 (91.5%)	17 (85.0%)	0.6728
R1	2 (4.3%)	1 (5.0%)	
R2	2 (4.3%)	2 (10.0%)	
Adjuvant chemotherapy			
Not performed	20 (42.5%)	11 (46.3%)	0.3500
Performed	27 (57.5%)	9 (53.7%)	

Values are expressed as mean±SD or number (%)

CA19-9 carbohydrate antigen 19-9, *CEA* carcinoembryonic antigen, *FDG-PET* F-18 fluorodeoxyglucose-positron emission tomography, *SUV* standard uptake value, *UICC* Union for International Cancer Control

same in the additional PET/CT scanners. FDG-PET images were viewed using Centricity PACS (GE Healthcare Japan), and SUV$_{max}$ was measured at each LN area according to the JSBS classification. We classified these according to an SUV$_{max}$ cut-off of 2.8, determined by mean + 2 standard deviations (SDs) of uptakes at pathological metastasis negative LNs.[14]

Statistical Analysis

Continuous variables were expressed as mean ± SDs. Categorical variables were compared using the Chi-square or Fisher's exact tests, as appropriate, and continuous variables were compared using Student's *t*-test. RFS and OS rates were constructed using the Kaplan–Meier method. The log-rank test compared differences in LN metastasis by FDG-PET diagnosis. Univariate and multivariate analysis using Cox's proportional hazard model were conducted to assess RFS and OS prognostic factors. All variables considered a clinical risk factor for survival rates in univariate analysis were included in the multivariate analysis. A *p*-value < 0.05 was considered statistically significant. Statistical analyses were performed using JMP software version 14.0 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient Characteristics

Overall, 67 BTC patients were eligible for this study. In this series, the mean age was 68 years; 40 patients were male and 27 patients were female. The median preoperative carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 levels were 20.1 ng/mL and 738.9 U/mL, respectively. UICC clinical and pathological TN classification and stage are described in Supplementary Table S1. The mean intraoperative blood loss was 953.4 mL, the mean total operation time was 564.9 min, and the mean tumor size was 29.4 mm. In regard to histology, 14 specimens were G1, 43 were G2, and 10 were G3. The mean number of dissected LNs was 23. R0 resection was achieved in 89.6% of patients, while R1 and R2 resection was achieved in 4.5 and 6.0% of patients, respectively. Adjuvant chemotherapy was performed in 36 patients (53.7%) (Supplementary Table S1).

Clinicopathological Features between FDG-PET-Positive and -Negative LNs

We evaluated preoperative FDG uptake in LNs and compared them with perioperative factors. We graded the 67 patients into two groups, based on the SUV$_{max}$ value at each LN area, as follows: PET N (+) group (SUV$_{max}$ ≥ 2.8; n = 20) and PET N (−) group (SUV$_{max}$ < 2.8; n = 47). The preoperative clinicopathological features of each group were summarized in Table 1. Analyses of the relationships between PET N (+/−) and preoperative clinicopathological features show that PET N (+) significantly correlated with SUV$_{max}$ of the primary tumor (p = 0.0404). Table 2 shows the postoperative clinicopathological features of each group. Analyses of the relationships between PET N and postoperative clinicopathological features show that the PET N (−) group possessed histology (G3) more often than the PET N (+) group. The PET N (+) group tended to include pN1 compared with the PET N (−) group. Regarding the prediction ability of PET N for pN1, the sensitivity, specificity, accuracy, and positive predictive value were 39%, 81%, 58%, and 70%, respectively. These percentages were a little worse than those reported in our previous study.[12]

TABLE 2 Univariate and multivariate analysis of recurrence-free survival in patients with biliary tract cancers

		Univariate			Multivariate		
		HR	95% CI	P	HR	95% CI	P
Age, years	≥ 69/< 69	1.14	0.63–2.11	0.6788			
Gender	Male/Female	1.79	0.95–3.52	0.0708			
CEA, ng/mL	≥ 6/< 6	1.54	0.58–3.40	0.3517	1.24	0.42–3.24	0.676
CA19-9, U/mL	≥ 38/< 38	1.56	0.85–2.88	0.1494	1.19	0.61–2.31	0.6151
UICC, cT	3 + 4/1 + 2	1.5	0.82–2.82	0.1875	1.47	0.77–2.86	0.2469
UICC, cN	1/0	1.78	0.92–3.28	0.0804			
UICC, cStage	III + IV/I + II	1.44	0.77–2.64	0.2508			
FDG-PET SUV_{max} of primary tumor	≥ 4.1/< 4.1	1.39	0.77–2.59	0.2752	1.38	0.69–2.82	0.3659
FDG-PET SUV_{max} of lymph nodes	≥ 2.8/< 2.8	2.64	1.40–4.86	0.0034	2.18	1.09–4.28	0.0284
Adjuvant chemotherapy	Not performed Performed	0.96	0.52–1.75	0.8839			

Values are expressed as mean±SD or number (%)

CA19-9 carbohydrate antigen 19-9, *CEA* carcinoembryonic antigen, *FDG-PET* F-18 fluorodeoxyglucose-positron emission tomography, *SUV* standard uptake value, *UICC* Union for International Cancer Control

Survival Rates After Surgery in FDG-PET-Positive and -Negative LN Metastasis

We then analyzed the relationship between PET N and the postoperative course. The mean follow-up times were 2.0 ± 1.6 years for patients with RFS and 2.9 ± 1.6 years for patients with OS. The survival analysis revealed that the PET N (+) group had a significantly worse outcome than the PET N (−) group in relation to RFS ($p = 0.0014$) (Fig. 1a); however, there was no significance between the two groups in relation to OS ($p = 0.1779$) (Fig. 1b). Moreover, we confirmed that the hazard ratio forest plot [PET N (+)/PET N (−)] for RFS indicated a similar tendency among subcategories (Fig. 1c). In 60 patients with BDC and PVC, which are strongly affected by cholangitis, the tendency of RFS was similar to that of the 67 patients included in this study ($p = 0.0081$) (Supplementary Fig. S1). We performed univariate and multivariate analyses to identify preoperative significant prognostic factors for RFS (Table 2) and OS (Table 3). In the univariate and multivariate analyses, PET N (+) was the only preoperative factor associated with RFS; however, in this study, no preoperative factors were associated with OS. On the other hand, preoperative clinical evaluation for tumor, LNs, and stage were underpowered in these analyses. Moreover, adjuvant chemotherapy was not a prognostic factor, the reason for which might be that those patients who received the therapy had advanced-stage disease and poor prognosis compared with patients who did not receive the therapy. These results suggest that PET N (+) was the only preoperative prognostic factor for RFS.

Investigating the Cause of FDG-PET-Positive LN Metastasis Correlating to Recurrence-Free Survival

As indicated by PET N (+) associated with RFS, we investigated the cause in detail. At first, we evaluated the prognosis of patients with or without pathological LN metastasis. In patients with pN0 disease, the survival analysis revealed that the PET N (+) group had a significantly worse outcome than the PET N (−) group in relation to RFS ($p = 0.0001$) (Fig. 2a). We compared the background of the PET N (+) group with that of the PET N (−) group (Supplementary Table S2) and found that except for cN0, there was no significant difference between the two groups. On the contrary, in patients with pN1 disease, there was no significance between the two groups in relation to RFS ($p = 0.5656$) (Fig. 2b).

Moreover, we checked the difference in recurrence site between the two groups (Fig. 3a), and this indicated that recurrence of the PET N (+) group has significantly occurred in LNs more often than other recurrence sites in comparison with the PET N (−) group ($p = 0.0345$) (Fig. 3b). The hazard ratio forest plot [PET N (+)/PET N (−)] for LN metastasis indicated a similar tendency among subcategories (Fig. 3c). These results suggest that PET N (+) might detect aggressive occult LN metastasis of BTC.

DISCUSSION

In the present study, we validated the role of FDG-PET diagnosis for LN metastasis in BTC and its prognostic value, and evaluated in detail its meaning in the
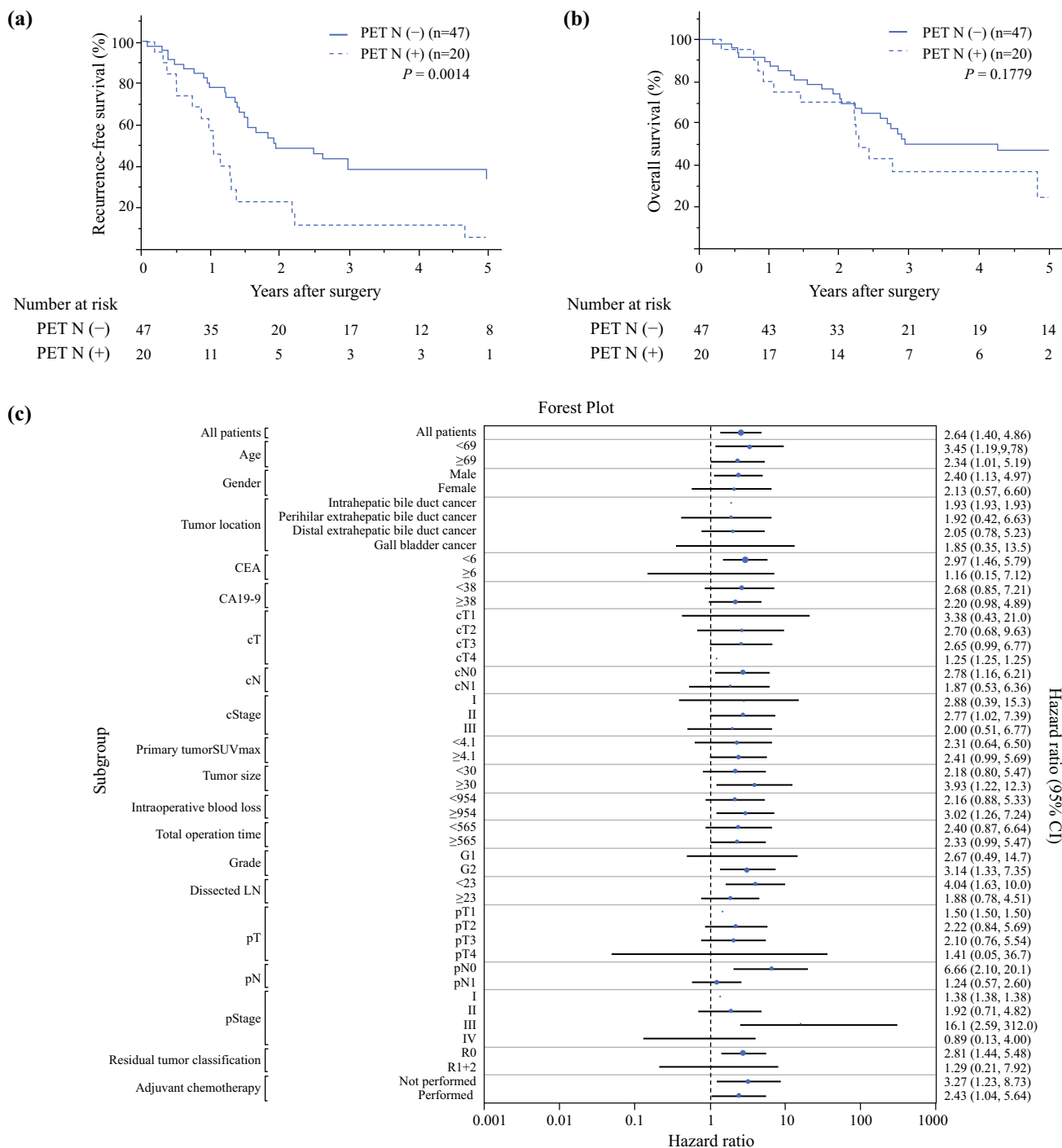
FIG. 1 Clinical impact of FDG-PET-positive LNM [PET N (+)] and FDG-PET-negative LNM [PET N (−)] in BTC. (**a**) Recurrence-free survival and (**b**) overall survival curve of patients with BTC divided by PET N. (**a**) The PET N (+) group showed significantly shorter recurrence-free survival rates, and (**b**) there was no significant difference in overall survival between the PET N (+) and PET N (−) groups. (**c**) Forest plot analysis of PET N for recurrence-free survival among the various subgroups. The figure shows a similar tendency of hazard ratio [PET N (+)/PET N (−)] for recurrence-free survival. *LNM* lymph node metastasis, *FDG-PET* F-18 fluorodeoxyglucose-positron emission tomography, *BTC* biliary tract cancer, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, SUV_{max} maximum standardized uptake value, *LN* lymph node, *CI* confidence interval

perioperative phase. Our previous study[12] used several SUV_{max} cut-off values, calculated using the receiver operating characteristic curve or mean + SD at

pathologically negative metastasis of LNs, and calculated the sensitivity, specificity, and accuracy for pN1. This revealed that PET N (+) [$SUV_{max} \geq 2.8$] was a significant

TABLE 3 Univariate and multivariate analysis of overall survival in patients with biliary tract cancers

		Univariate			Multivariate		
		HR	95% CI	P	HR	95% CI	P
Age, years	$\geq 69/< 69$	1.47	0.75–3.04	0.2694			
Gender	Male/Female	1.58	0.80–3.29	0.1874			
CEA, ng/mL	$\geq 6/< 6$	1.66	0.62–3.73	0.286	1.61	0.55–4.14	0.3595
CA19-9, U/mL	$\geq 38/< 38$	1.19	0.62–2.34	0.5972	0.95	0.45–1.96	0.8809
UICC, cT	$3 + 4/1 + 2$	1.91	0.97–3.97	0.0598	1.95	0.95–4.17	0.0697
UICC, cN	1/0	1.19	0.56–2.36	0.6336			
UICC, cStage	$III + IV/I + II$	1.31	0.66–2.53	0.4291			
FDG-PET SUV_{max} of primary tumor	$\geq 4.1/< 4.1$	1.02	0.53–2.01	0.9419	1.23	0.58–2.64	0.5822
FDG-PET SUV_{max} of lymph nodes	$\geq 2.8/< 2.8$	1.59	0.78–3.11	0.1929	1.33	0.61–2.80	0.2804
Adjuvant chemotherapy	Not performed / Performed	0.78	0.40–1.53	0.4689			

Values are expressed as mean±SD or number (%)

CA19-9 carbohydrate antigen 19-9, *CEA* carcinoembryonic antigen, *FDG-PET* F-18 fluorodeoxyglucose-positron emission tomography, *SUV* standard uptake value, *UICC* Union for International Cancer Control

and independent prognostic factor for 3-year survival in multivariate analysis. In this present study, we validated that PET N (+) [$SUV_{max} \geq 2.8$] was the preoperatively significant and independent prognostic risk factor for RFS; however, PET N (+) [$SUV_{max} \geq 2.8$] was not a significant risk factor for OS. The development of therapy after recurrence, including gemcitabine, S-1, cisplatin, and combination therapies (e.g. triplets of these agents,[15] KHBO 1401 [ESMO Sakai, ASCO Kobayashi]) might cause this difference between our previous report and the present report. Additionally, we analyzed the RFS and OS of our data set, excluding two patients who underwent strong chemotherapy consisting of GCS for adjuvant chemotherapy or therapy for recurrence (Supplementary Fig. S1). In these 64 patients, the analysis revealed that the PET N (+) group also had a significantly worse outcome than the PET N (−) group in relation to RFS ($p = 0.0064$) (Supplementary Fig. S2a). Moreover, the PET N (+) group tended to have worse OS than the PET N (−) group ($p = 0.0887$) (Supplementary Fig. S2b). Second, we evaluated the prediction ability of PET N (+) [$SUV_{max} \geq 2.8$] for pN1 in our new patient set. In our previous study, the sensitivity, specificity, accuracy, and positive predictive value were 37%, 97%, 86%, and 72%, respectively, which was similar to that of previous reports.[5–9] These rates for the new set of 67 patients were a little worse than those of our previous report.[12] It was considered the reason for this was that the number of patients in this current study was larger than that of the previous study; however, our new rates resembled those of previous reports.[5–9,12] Third, in BTC patients with pN0 disease, PET N (+) significantly

correlated with the poor RFS of these patients. We considered that PET N (+) might detect occult LN metastasis that eluded pathological diagnosis. These results suggested that preoperative FDG-PET diagnosis for LNs in BTC could detect occult metastasis and help with the treatment decision, including neoadjuvant chemotherapy.

Nowadays, FDG-PET is broadly utilized for the preoperative metastasis diagnosis of carcinomas. Moreover, the prognostic capability of FDG-PET was reported for several cancers. Lee et al. analyzed 723 patients with resectable lung adenocarcinoma and preoperative prognostic factors,[16] and demonstrated that high SUV_{max} (>9.5) of the primary tumor on FDG-PET was significantly associated with shorter OS and RFS in univariate analysis. Additionally, a high SUV_{max} was also one of the risk factors for OS in multivariate analysis. Moreover, Yamamoto et al. investigated the clinical usability of preoperative FDG-PET as a prognostic factor for resectable pancreatic adenocarcinoma.[3] They analyzed the relationship between the preoperative SUV_{max} of 128 patients' primary tumors and their prognosis, and demonstrated that $SUV_{max} \geq 6.0$ was a significant prognostic factor of early postoperative recurrence and poor survival. On the other hand, Song et al. assessed the relationship between the LN SUV_{max} in gastric cancer and prognosis.[4] They analyzed the data of 151 gastric cancer patients and demonstrated that preoperative nodal SUV_{max} was an independent prognostic factor for RFS and OS.

One possibility of the correlation of SUVmax and tumor progression is considered the involvement of glucose transporter 1 (GLUT-1). This molecule plays a crucial role
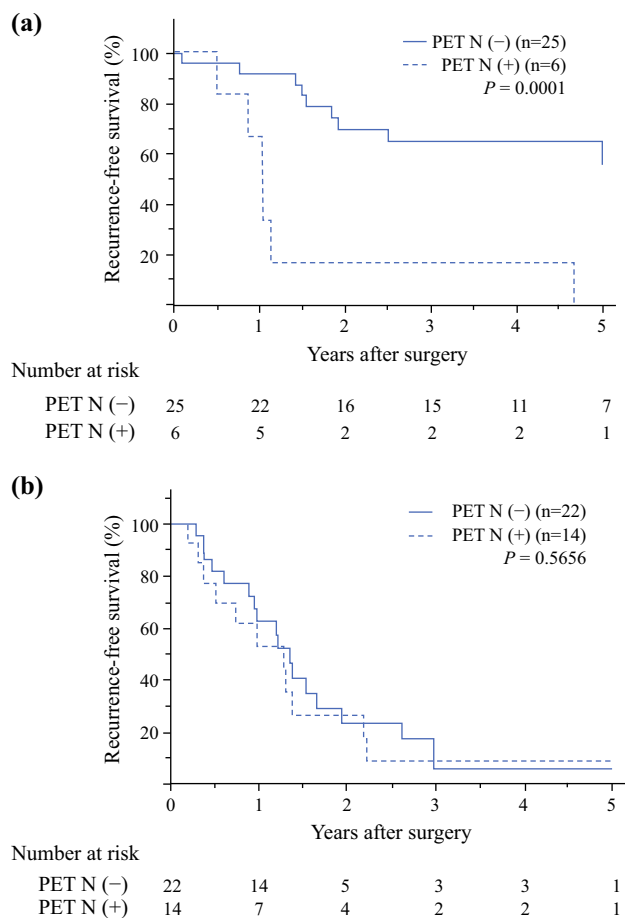
(a)

(b)

FIG. 2 Prognosis of patients (**a**) without or (**b**) with pathological LNM. (**a**) In patients without pathological LNM (pN0), survival analysis revealed that the FDG-PET-positive LNM [PET N (+)] group had a significantly worse recurrence-free survival outcome than the FDG-PET-negative LNM [PET N (−)] group. (**b**) In patients with pathological LNM (pN1), there was no significance in RFS between the two groups. *LNM* lymph node metastasis, *FDG-PET* F-18 fluorodeoxyglucose-positron emission tomography

in response to basal glucose uptake and ^{18}F-FDG uptake in FDG-PET. It was reported that GLUT-1 expression levels of the primary tumor correlated with poor prognosis in several cancers.[17–19] Song et al. discussed that the reason why the LN SUV_{max} correlates with poor prognosis of gastric cancer might depend on GLUT-1.[4] In BTC, Kubo et al. reported that high GLUT-1 expression of hilar cholangiocarcinoma correlated with poor RFS,[20] and analyzed that the high GLUT-1 expression was associated with LN metastasis. They also demonstrated that GLUT-1 inhibition for cholangiocarcinoma cells decreased their migration and invasion *in vitro*. Hence, it is considered that the SUV_{max} of LNs reflects BTC progression the same as GLUT-1 expression.

Therefore, it is considered that preoperative FDG-PET for BTC primary tumors might also be useful as a prognostic predictor; however, there are few reports of this

analysis because of difficulty in distinguishing high SUV_{max} between cholangiocarcinoma and cholangitis. Ma et al. reported that a primary tumor $SUV_{max} > 8$ was associated with RFS and OS in 66 patients with TNM stage I or II BTC.[21] This prognostic capability was limited in early-stage BTC. On the other hand, our strategy evaluating LN SUV_{max} was unlikely to be affected by cholangitis; therefore, we considered that the LN SUV_{max} might reflect BTC progression. We are preparing to perform further study regarding LN GLUT-1 expression in BTC and the relationship between expression and prognosis.

In this study, the PET N (+) group had a significantly worse outcome than the PET N (−) group in relation to RFS. Conversely, there was no significance between the two groups in relation to OS. Taking this into consideration, additional analysis of our data set without patients who underwent GCS combination chemotherapy as recurrence therapy suggested that this intense chemotherapy would be effective for BTC. Kanai et al. reported that GCS combination chemotherapy offered a survival benefit with manageable toxicity in patients with advanced BTC in a phase II study (KHBO 1002/UMIN000004468).[22] Our study validated the availability of FDG-PET for preoperative diagnosis of LN metastasis and could help in deciding whether or not to perform neoadjuvant chemotherapy for advanced BTC patients. At present, a phase II trial to investigate the efficiency of GCS combination neoadjuvant chemotherapy for resectable BTC patients diagnosed with cN1 disease by preoperative FDG-PET is now underway (KHBO1201/UMIN000009831). Our private unpublished retrospective analysis determined that neoadjuvant GCS had a survival benefit in patients with FDG-positive LNs ($SUV_{max} \geq 2.8$). Collectively, FDG-PET uptake at LNs would be useful for decisions regarding eligible criteria for neoadjuvant therapies. Additionally, a phase I/II trial to investigate the efficiency of neoadjuvant chemotherapy (GCS, or the combination of gemcitabine, cisplatin, and nab-paclitaxel) for BTC patients with metastatic LNs that are confirmed by preoperative FDG-PET and endoscopic ultrasound-guided fine-needle aspiration is also underway (jRC Ts051180178).

CONCLUSION

We validated that a higher LN SUV_{max} (≥ 2.8) was the preoperatively significant and independent prognostic risk factor for RFS in BTC. Moreover, our results indicated that preoperative FDG-PET for LNs could be helpful for clinical decision making regarding the perioperative treatment strategy, including neoadjuvant chemotherapy.
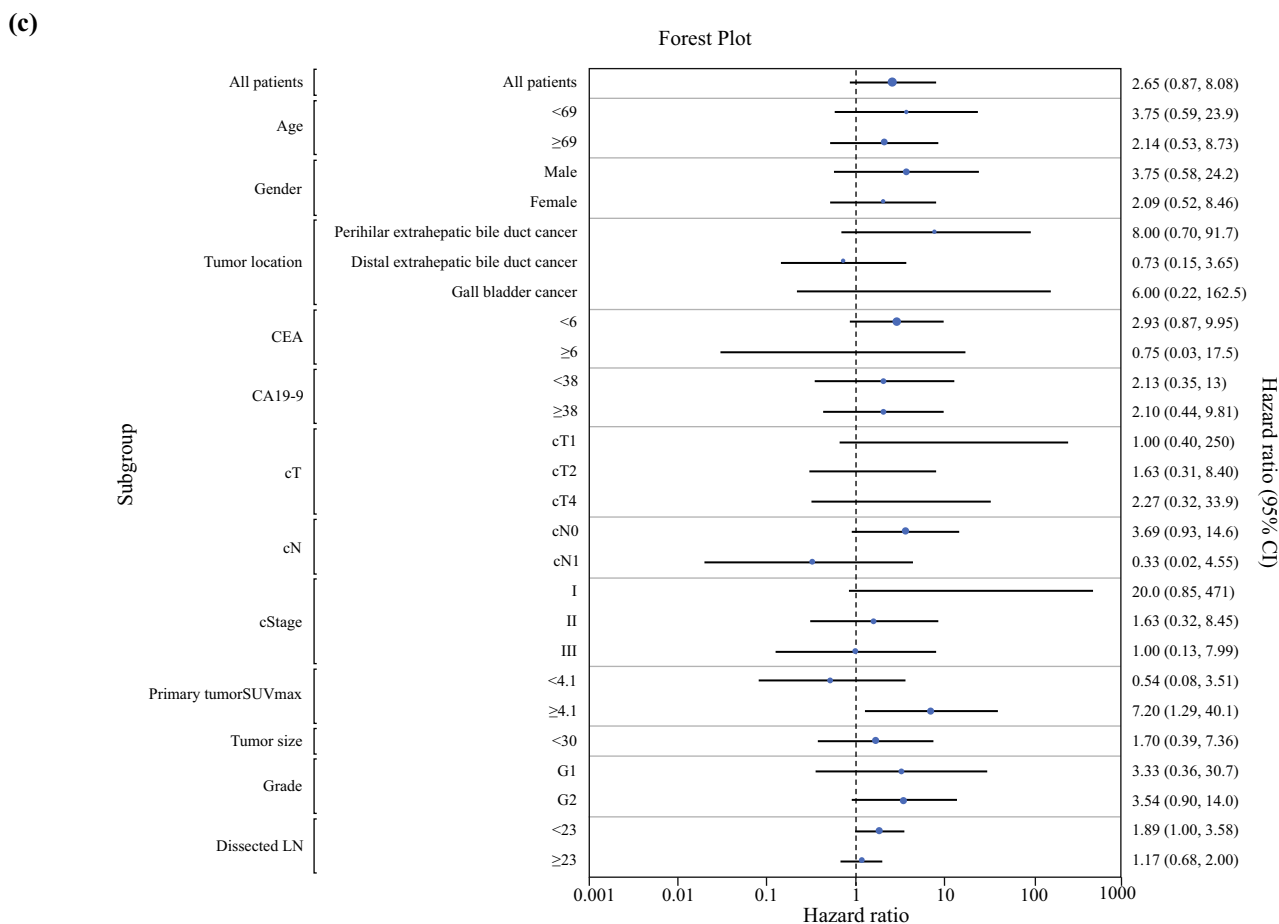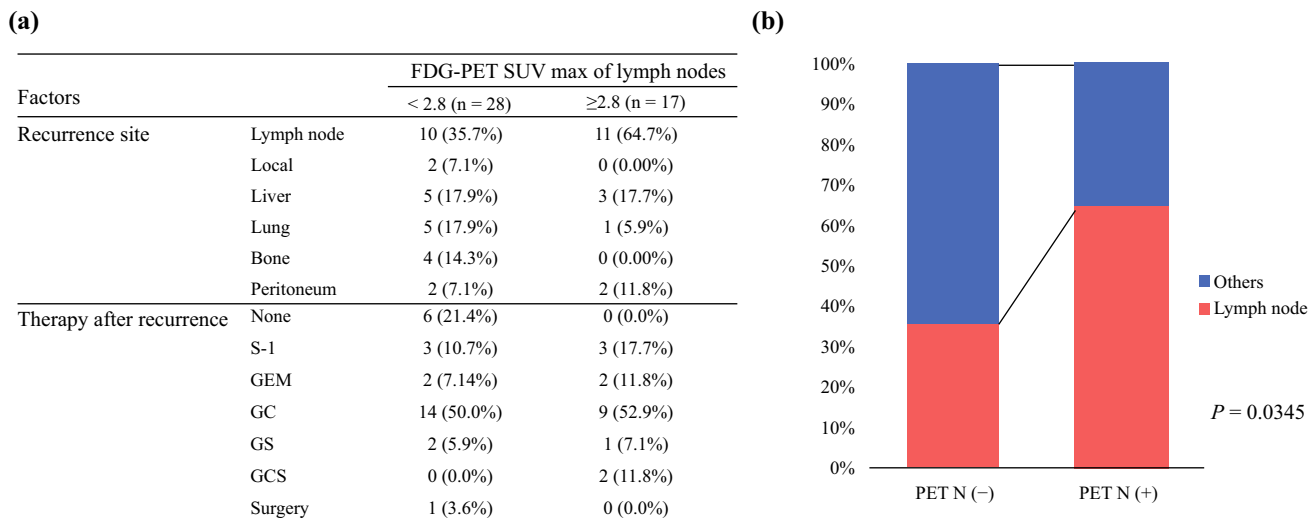
(a)

Factors		FDG-PET SUV max of lymph nodes	
		< 2.8 (n = 28)	≥2.8 (n = 17)
Recurrence site	Lymph node	10 (35.7%)	11 (64.7%)
	Local	2 (7.1%)	0 (0.00%)
	Liver	5 (17.9%)	3 (17.7%)
	Lung	5 (17.9%)	1 (5.9%)
	Bone	4 (14.3%)	0 (0.00%)
	Peritoneum	2 (7.1%)	2 (11.8%)
Therapy after recurrence	None	6 (21.4%)	0 (0.0%)
	S-1	3 (10.7%)	3 (17.7%)
	GEM	2 (7.14%)	2 (11.8%)
	GC	14 (50.0%)	9 (52.9%)
	GS	2 (5.9%)	1 (7.1%)
	GCS	0 (0.0%)	2 (11.8%)
	Surgery	1 (3.6%)	0 (0.0%)

(b)

(c)

FIG. 3 Differences in the recurrence sites and therapies, after recurrence, between the two groups. (**a**) List of recurrence sites and therapies after recurrence. (**b**) Ratio of lymph node recurrence, according to PET N (−) and (+). Recurrence in the FDG-PET-positive LNM group significantly occurred more often in lymph nodes than in other recurrence sites. (**c**) Forest plot analysis of PET N for LNM among the various subgroups. The figure shows a similar tendency of hazard ratio [PET N (+)/PET N (−)] for LNM. *GC* gemcitabine and cisplatin, *GCS* gemcitabine, cisplatin, and S-1, *GEM* gemcitabine, *GS* gemcitabine and S-1, *LN* lymph node. *FDG-PET* F-18 fluorodeoxyglucose-positron emission tomography, *LNM* lymph node metastasis, SUV_{max} maximum standardized uptake value, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *CI* confidence interval

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