Original article

Preoperative Diagnosis of Lymph Node Metastasis in Biliary and Pancreatic Carcinomas: Evaluation of the combination of multi-detector CT and serum CA19-9 Level

Atsushi Nanashima[1], Ichiro Sakamoto[2], Tomayoshi Hayashi[3], Syuuichi Tobinaga[1], Masato Araki[1], Masaki Kunizaki[1], Takashi Nonaka[1], Hiroaki Takeshita[1], Shigekazu Hidaka[1], Terumitsu Sawai[1], Toru Yasutake[1], Takeshi Nagayasu[1]

[1]Division of Surgical Oncology and Departments of [2]Radiology and [3]Pathology, Nagasaki University Hospital, 1-7-1 Sakamoto, Nagasaki, 852-8501 Japan

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*Correspondence to: A/Prof. Atsushi Nanashima, Division of Surgical Oncology, Department of Translational Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

Tel: +81-95-819-7304; Fax: +81-95-819-7306

E-mail: a-nanasm@nagasaki-u.ac.jp

Abstract

Background. It is difficult to diagnose lymph node metastasis in biliary and pancreas carcinomas before surgery.

Aim. To assess the utility of the combination of multi-detector computed tomographic (MDCT) findings and serum carbohydrate antigen (CA)19-9 level in the diagnosis of lymph node metastasis in biliary and pancreas carcinomas

Methods. The subjects were 139 patients with biliary and pancreas carcinomas who underwent surgical resection. We calculated the positive predictive values (PPV), sensitivities, specificities, positive likelihood ratios (PLR) and accuracies of diagnosis by MDCT alone, serum CA19-9 level alone, and their combination.

Results. The PPV and sensitivity were higher for node metastasis in hepatoduodenal ligament than in common hepatic artery (CHA) or para-aortic region (PAR). Specificity, accuracy and PLR were highest for CHA in biliary carcinoma. With pancreatic carcinoma, PLR was slightly higher in PAR compared to other regions. The sensitivity of CA19-9 for node metastasis was higher than that of MDCT, while the PPV, specificity, accuracy and PLR were low for both biliary and pancreas carcinoma. The combination of positive CT findings and high CA19-9 level had the highest positive rate for node metastasis for both types of carcinomas. Nodes around the supra-mesenteric vein could not be fully observed on CT.

Conclusion. The combination of high-resolution MDCT and CA19-9 is useful for the diagnosis of lymph node metastasis in biliary and pancreas carcinomas.

Word count: 222

Key words bile duct carcinoma, pancreas carcinoma, node metastasis, computed tomography, CA19-9

Introduction

Lymph node metastasis is a prognostic factor in patients with biliary or pancreas carcinoma who undergo surgical resection [1, 2]. Preoperatively, node status determined by image studies offers useful information for assessment of node metastasis and choice of radical surgery. However, preoperative image diagnosis does not always match the pathological findings. Several groups have reported that the diagnostic accuracy of imaging studies for lymph node metastasis remains unsatisfactory even with the application of multi-detector row computed tomography (MDCT) [3-5], magnetic resonance imaging (MRI) [6, 7] and positron emission tomography (PET) [8] in patients with pancreato-biliary carcinoma. Thus, in patients with lymphadenopathy detected by these imaging modalities, particularly the para-aortic lymph nodes, the choice of type and extent of surgery remains difficult due to the low positive predictive values (PPV), and the lymph node status can only be confirmed properly during laparotomy. On the other hand, serum tumor markers, such as carbohydrate antigen (CA)19-9, can be used as a sensitive diagnostic tool for cancer, and their levels are associated with advanced carcinoma including tumor extension and lymph node metastasis. [9, 10]. However, the accuracy of diagnosis of lymph node metastasis is also limited when such markers are used alone. Based on this background, we hypothesized in the present study that the combination of imaging studies and highly sensitive laboratory markers improves the accuracy of preoperative diagnosis of lymph node metastasis from pancreato-biliary carcinomas, and the selection of the most appropriate treatment approach. To test our hypothesis, we assessed first the diagnostic

accuracy of each of CT imaging and serum CA19-9, and then evaluated the combination of these two diagnostic modalities. We analyzed the CT findings and serum CA19-9 levels in consecutive patients with biliary and pancreatic carcinoma who had undergone surgical resection after 2000, and the diagnostic accuracy of each method was compared with the histopathological findings of regional lymph node metastasis **at a single cancer institute**.

Materials and Methods

Patients and preoperative assessment

Subjects comprised 139 consecutive patients (93 men, 46 women) with biliary or pancreas head carcinoma who underwent hepatectomy or pancreaticoduodenectomy between 2000 and 2008 at the Division of Surgical Oncology, Department of Translational Medical Sciences, Nagasaki University Hospital. The Ethics Review Board of our university approved the study protocol.

Between 2000 and 2008, multi-detector row CT was applied for the assessment and diagnosis of the extent of tumor spread and lymphadenopathy in the abdomen. Enhanced CT in the arterial and portal phases using contrast media was used in all cases. The apparatus was a MDCT with 4 detectors (Somatom Plus Volume Zoom; Siemens, Malvern, PA). After plain CT, a dual-phase enhanced CT was performed. Using an automatic infuser pump, 100 mL of non-ionized contrast media was injected intravenously at 3 mL/s. The arterial phase at 35 sec and delayed phase at 100-120 sec after injection were exposed. The beam width was 2.5 mm, slice width was 7 mm, and the interval of reconstruction ranged between 7 and 10 mm.

Positive nodes represented lymph nodes that could be detected on the enhanced CT. Lymph node metastasis was evaluated in 3 regions: 1) the hepato-duodenal ligament (#12); 2) the common hepatic artery (#8); and 3) the para-aortic region (#16) according to the *Classification of Biliary Tract Carcinoma* by the Japanese Society of Biliary Surgery and *Classification of Pancreatic Carcinoma* by the Japan Pancreas Society [11, 12]. An experienced radiologist (I.S.) reviewed the diagnosis of lymph

node metastasis by CT and measured the maximum size of the lymph node. On admission to the hospital, blood samples were obtained before the morning meal for measurement of serum CA19-9 (Elecsys® CA19-9 II; Roche Diagnostics, Indianapolis, IN). In patients with obstructive jaundice, blood samples was obtained when total bilirubin level was <2 mg/dl.

Evaluation of histopathological changes and serum CA19-9 levels

The surgically resected specimens were fixed in 10% formalin and the lymph nodes were sectioned serially at 5-mm intervals, stained with hematoxylin and eosin and examined microscopically. All histological slides were reviewed by an experienced pathologist (T.H.). The numbering of region of lymph nodes and T category (=Primary Tumor Invasion) were based on the *Classification of Biliary Tract Carcinoma* by the Japanese Society of Biliary Surgery and *Classification of Pancreatic Carcinoma* by the Japan Pancreas Society [11, 12]. The CT findings and serum CA19-9 levels were analyzed according to the histopathological findings. The cut-off level for abnormal serum CA19-9 was set at 37 U/ml (upper limit of normal range).

Statistical analysis

The Mann-Whitney U test was used for comparison of categorical data. PPV (%), sensitivity (%), specificity (%), accuracy, and positive likelihood ratio (PLR) were calculated using 2×2 tables. The impact of likelihood was considered "*large*" for >10, "*moderate*" for 5-10, "*small*" for 2-5, "*tiny*" for 1-2, and "*no change*" for 1. Continuous data were expressed as mean ± SD. Data of different groups were compared using

one-way analysis of variance (ANOVA) followed by Dunnet's multiple comparison test. A two-tailed *P* value of <0.05 was considered significant. Statistical analyses were performed using Statistica software (StatSoft, Tulsa, OK).

Results

The mean age of the 139 patients was 67±11 years (range, 30-87 years). Of the 139 patients, hilar bile duct carcinoma was present in 25 (18.0%), distal bile duct carcinoma in 29 (20.9%), ampullary carcinoma in 13 (9.4%), gallbladder carcinoma in 28 (20.1%), and pancreas head carcinoma in 44 (31.6%). We retrospectively reviewed data of these 139 patients, focusing on lymph node metastasis. In this cohort, 75 patients (33.1%) underwent pancreaticoduodenectomy, 46 (33.1%) had hepatic resection with or without resection of the extrahepatic bile duct, 7 (5.0%) underwent liver resection + pancreaticoduodenectomy, 5 (3.6%) underwent cholecystectomy, 4 (2.9%) had resection of the extrahepatic bile duct and 2 (1.4%) underwent probe laparotomy with lymph node biopsy. Postoperative tumor recurrence at 11 months of median follow-up period was observed in 23 patients (lymph node metastasis = 9, liver metastasis = 6, local recurrence = 3, and peritoneal carcinomatosis = 5) while 116 (83.5%) patients had no such recurrence. Five patients died during hospitalization and 5 others died of tumor-unrelated diseases.

Table 1 shows the correlation between CT findings and histologically-confirmed node metastasis in each region. The PPV and sensitivity were higher for node metastasis in the hepatoduodenal ligament compared to those in the common hepatic artery or para-aortic region. The specificity, accuracy and PLR were highest in the common hepatic artery among the 3 regions. However, the impact of PLR was not *large* or *moderate* in any region. When analyses were conducted for biliary and pancreas carcinoma separately (Table 2), the results for biliary carcinoma were similar to those

for the entire group. The impact of PLR in the common hepatic artery was *moderate* in biliary carcinomas. However, in pancreatic carcinoma, PLR was slightly higher (*small* impact) in the para-aortic region compared to the other two regions, although the specificity and accuracy were highest for the common hepatic region.

The sensitivity of serum CA19-9 level for node metastasis was higher than that of CT findings in each region (Table 3). However, the PPV, specificity, accuracy and PLR of serum CA19-9 level for node metastasis in each region were lower than those of CT findings. Similar tendencies were noted for both biliary and pancreas carcinoma (Table 4). However, the impact of PLR by CA19-9 level was *tiny* in all regions. Table 5 shows serum CA19-9 levels according to T category in biliary and pancreas carcinomas. Serum CA19-9 tended to be high in T3 and T4 categories but this was not significant in each carcinoma.

Table 6 shows the combination of CT findings and serum CA19-9 level for the diagnosis of lymph node metastases in each region. The combination of positive CT results and higher CA19-9 level had the highest positive rate for node metastasis compared to the other three combinations of CT findings and serum CA19-9 level. This tendency was similar in each node region for both biliary and pancreas carcinoma (Table 7).

Table 8 shows the regional distribution of unmatched node metastasis between the CT findings and histopathologically-confirmed node metastasis. In biliary carcinomas, pseudo-negative node metastasis on CT tended to be seen for nodes around the common hepatic artery, nodes around the bile duct and para-aortic nodes below the right renal vein. Pseudo-positive node metastases on CT tended to be seen for

para-aortic nodes below the right renal vein. In pancreatic carcinomas, pseudo-negative node metastasis tended to be marked in marginal nodes of the pancreatic head, nodes around the supra-mesenteric vein and para-aortic nodes below the right renal vein. No specific tendencies were identified for pseudo-positive node metastases on CT.

Discussion

Preoperative imaging assessment of regional lymph node metastasis in solid carcinomas is essential for making decisions about surgical indications and perioperative management [13]. In this regard, the diagnostic value of various imaging modalities including the high-powered CT, remains node limited at present. Several reports have examined the relationship between size or morphological structure of the lymph nodes on imaging and histopathologically-confirmed metastasis in hepatopancreatobiliary malignancies, but the accuracy of diagnosis using imaging studies remains unsatisfactory [3,4,6,14,15]. The first aim of this study was to clarify the status of the diagnostic accuracy for node metastasis in pancreato-biliary carcinomas in order to find related limitations or problems. In the next step, to improve the low diagnostic accuracy of node metastasis, we combined a surrogate marker with imaging studies. The size of lymph nodes detected by imaging is the most significant parameter for the diagnosis of metastasis [3, 6]. A size of 10 mm was applied as a cut-off level by Watadani et al. [15]. Noji et al. reported that PPV was only 31% for 10-mm in biliary carcinoma and a cut-off level of >16 mm was used to increase the PPV to >50% for diagnosis of node metastasis [3]. Thus, the accuracy of imaging studies increases with increased node size. In our series, we also examined node size using a cut-off of 10 mm; the specificity increased in nodes >10 mm compared with that in nodes <10 mm, similar to the report of Watadani et al. [15] (data not shown in the present study). However, the sensitivity and PPV were less than 50% in each regional lymph node using size >10 mm. Few lymph nodes measuring >16 mm were detected in

our series. Even in lymph nodes <10 mm in size, histopathologically-confirmed lymph node metastasis was common in our cohort. Noji et al. reported that approximately 30% of the lymph nodes were histopathologically positive at cut-off levels of 6, 8 and 10 mm [3]. In this regard, no correlation was reported between lymph node size and histopathological metastasis in other solid tumors [16, 17]. Therefore, we did not apply a cut-off size in the present study because such cut-off level of node size was probably not suitable for positive prediction based on the above studies. Other investigators have used the morphological characteristics or enhancement patterns using contrast media for the diagnosis of lymph node metastasis with biliary carcinoma [3,4,6,15,18]. Changes in the diagnostic accuracy might not be marked and heterogeneous findings in lymph nodes are rare [13, 18]. In our series, heterogeneous findings of lymph node detected by enhanced CT were also rare as well. Therefore, tumor size and morphology were considered not useful for improvement of the diagnosis of node metastasis.

The diagnostic accuracy may differ for each regional lymph node. Previous studies focused on the diagnosis of para-aortic lymph node metastasis [6, 14]. Confirmation of lymph node metastasis in the para-aortic region is important surgically with respect to the extent of surgical intervention for biliary and pancreatic carcinoma [13]. Noji et al. [14] reported a lower accuracy of node metastasis in this region compared to other regions. In our series, the diagnostic accuracy of node metastasis also differed according to the region and also according to the type of tumor (i.e., biliary and pancreatic carcinomas). The PPV for lymph node metastasis was lowest for the para-aortic region with biliary carcinomas, although the PPV of this region was similar to other regions with pancreatic carcinoma. In cases of pancreatic carcinoma, node

metastasis is more likely to occur due to the proximity of this organ, which might lead to higher PPV compared to biliary carcinoma. According to previous reports, the para-aortic lymph nodes are considered to be the neighboring regional lymph nodes for pancreatic carcinoma [19].

The PLR of a positive test tells us how well a positive test result does by comparing its performance when the disease is present compared with when it is absent. The PLR is a tool used to incorporate the sensitivity and specificity of a test into a single measure. Since the sensitivity and specificity are fixed characteristics of the test itself, the likelihood ratio is independent of the prevalence of the disease in the population. In the present result, the highest PLR was observed in the common hepatic arterial region compared to other regions, however, even the impact of PLR in this region was still statistically small, reflecting the low power of MDCT for the diagnosis of node metastasis. These results indicated that the diagnosis of node metastasis even by the advanced imaging modality is difficult at this stage.

The diagnostic accuracy of MDCT in the present study was similar to that reported previously [3,4,14,15]. PET and high-resolution MRI have been considered additional modalities to improve diagnostic accuracy [6-8, 20], although the PPV was similar to that of CT. Schwartz et al. [7] reported that the accuracy was similar for CT and MRI. Furukawa et al. [8] indicated the limitations of resolution of PET-CT imaging for lymph node metastasis. In our series, MRI and PET-CT were not always performed to gain more information of tumor spread. The diagnosis of lymph node involvement by these imaging modalities was not superior to that of CT in this study as well as previous

reports [6-8, 20], although precise analyses of the diagnostic power of CT and other modalities were not performed.

Recently, endoscopic ultrasound guided-fine needle aspiration (EUS-FNA) has been used for the diagnosis of solid tumors or lymphadenopathy around the digestive tract [21, 22]. This modality showed high sensitivity and predictive value over 80% for the diagnosis of malignancies [22]. This diagnostic accuracy is significantly higher than in the present study. The EUS-FNA is also a promising diagnostic tool for lymph node swelling in pancreato-biliary carcinomas. At this stage, however, the above procedures are not used routinely for the diagnosis of lymph node metastasis. Improvement of preoperative assessment by imaging studies is thus limited at this stage.

For preoperative assessment of tumor extension, tumor markers such as a serum CA19-9 level have been used in biliary and pancreas carcinomas [23, 24]. The diagnosis of lymph node metastasis using this marker alone is almost impossible. However, we hypothesized that the combination of image findings and serum tumor marker levels would increase the diagnostic accuracy of node metastasis, since CA19-9 level is related to malignant tumor behavior [25]. The results showed increase in PPV in cases with positive imaging results and levels of CA19-9 above the normal range. In the present study, we set up the cut-off level of CA19-9 to be >37 U/ml although the median CA19-9 value in our series was 49 U/ml. Marrelli et al. [26] reported that the use of a cut-off value of 90 U/ml selected based on receiver operating characteristic (ROC) analysis improved the diagnostic accuracy after biliary drainage. Thus, the use of a CA19-9 level higher than 37 U/ml might be necessary to determine the extent of malignant behavior. Further analysis in a large number of subjects would be necessary

to establish the most appropriate cut-off value for the diagnosis of node metastasis.

Brockmann et al. reported that CA19-9 correlated with lymph node status in gallbladder carcinoma [9]. The impact of PLR by measuring CA19-9 level was *tiny*, however, we hypothesized that this marker improves the diagnostic power of CT imaging for node metastasis because of its higher sensitivity than CT imaging in the present study. Previous studies indicated that CA19-9 levels were influenced by primary tumor spread and related cholangitis [9, 10, 27]. In our patients with obstructive jaundice, biliary drainage was preoperatively performed and biliary congestion or inflammation was controlled as much as possible. With respect to primary tumor extension, serum CA19-9 tended to be increased in advanced stages but was not significantly affected by category. In the present study, the correlation between node metastasis and CA19-9 was more significant compared to T category, although the influence of tumor extension or cholangitis could not be analyzed properly. **The lymph node metastasis may show the higher degree of malignant behavior in comparison with tumor extension in the biliary and pancreatic carcinomas. Therefore, CA 19-9 might be better correlated with node metastasis than T stage as described above. It is necessary to clarify these relationship between histological findings and the reliable tumor markers in the further study.**

The combination of high CA19-9 level and a positive node by MDCT increased the positive rate, indicating that CA19-9 level adds value in the diagnosis of lymph node metastasis in cases with imaging-positive lymphadenopathy. The combination of MDCT and CA19-9 level may be more useful for the diagnosis of node metastasis compared with that by MDCT alone. In the present study, CEA level was also examined

routinely but its sensitivity and PLR were lower than those of CA19-9 level (17-28% and <1.5, respectively). The diagnostic accuracy of other tumor markers have been reported recently [28, 29] and the most useful marker for the diagnosis of node metastasis need to be established. Improvement of diagnosis of lymph node metastasis should lead to changes in tumor management. At this stage, we have confirmed the accuracy of preoperative CT and high CA19-9 levels in the diagnosis of lymph node metastasis.

The present study showed the distribution of unmatched lymph node metastasis between imaging and histopathology. The results showed frequent involvement of the para-gastric lymph nodes and lymph nodes surrounding the supra-mesenteric artery (SMA). Although we did not focus on these regions in the present analysis, such node metastases could not be detected even by high-resolution MDCT in these cases. In fact, the prevalence of para-gastric lymph node metastasis is reported to be uncommon in these carcinomas [30]. In pancreatic carcinomas, lymphadenectomy of the lymph nodes surrounding the SMA is a key step in surgical resection.

In the present study, we could show a preliminary data regarding the diagnostic accuracy of lymph node metastasis at a single cancer institute and the further study in a larger cohort samples should be necessary to validate these results in the near future. In conclusion, our evaluation indicated that the combination of serum CA19-9 level and high-resolution MDCT is useful for the preoperative diagnosis of lymph node metastasis in biliary and pancreas carcinomas.

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Table 1 Comparison between image diagnosis and histological findings

CT findings	Histological findings			Results
	Node negative	Node positive		
All cases				PPV 69.8%
Node negative	51	35	86	Sensitivity 51.3%
Node positive	16	37	53	Specificity 76.1%
				Accuracy 63.3%
				PLR 2.2
	67	72		
Hepatoduodenal ligament				PPV 61.4%
Node negative	66	29	95	Sensitivity 48.2%
Node positive	17	27	44	Specificity 79.5%
				Accuracy 66.9%
				PLR 2.4
	83	56		
Common hepatic artery				PPV 50.0%
Node negative	106	17	123	Sensitivity 32.0%
Node positive	8	8	16	Specificity 93.0%
				Accuracy 82.0%
				PLR 4.6
	114	25		
Para-aorta				PPV 30.0%
Node negative	105	14	119	Sensitivity 30.0%
Node positive	14	6	20	Specificity 88.2%
				Accuracy 79.9%
				PLR 2.6
	119	20		

PPV, positive predictive value; PLR, positive likelihood ratio

Table 2 Comparison between image diagnosis and histopathological findings in biliary and pancreas carcinomas

Biliary carcinomas

CT findings	Histological findings			Results
	Node negative	Node positive		
All cases				PPV 67.5%
Node negative	37	18	55	Sensitivity 60.0%
Node positive	13	27	40	Specificity 74.0%
				Accuracy 67.4%
				PLR 2.3
All cases	50	45		
Hepatoduodenal ligament				PPV 57.6%
Node negative	42	20	62	Sensitivity 48.7%
Node positive	14	19	33	Specificity 75.0%
				Accuracy 64.2%
				PLR 2.0
All cases of hepatoduodenal ligament	56	39		
Common hepatic artery				PPV 54.5%
Node negative	72	12	84	Sensitivity 33.3%
Node positive	5	6	11	Specificity 93.5%
				Accuracy 82.1%
				PLR 5.1
All cases of common hepatic artery	77	18		
Para-aorta				PPV 21.4%
Node negative	72	9	81	Sensitivity 25.0%
Node positive	11	3	14	Specificity 86.7%
				Accuracy 78.9%
				PLR 1.9
All cases of Para-aorta	83	12		

Pancreas carcinomas

CT findings	Histological findings			Results
	Node negative	Node positive		
All cases				PPV 76.9%
Node negative	14	17	31	Sensitivity 37.0%
Node positive	3	10	13	Specificity 82.4%
				Accuracy 54.6%
				PLR 2.1
All cases	17	27		
Hepatoduodenal ligament				PPV 72.7%
Node negative	24	9	33	Sensitivity 47.1%
Node positive	3	8	11	Specificity 88.9%
				Accuracy 72.7%
				PLR 4.2
All cases of Hepatoduodenal ligament	27	17		
Common hepatic artery				PPV 40.0%
Node negative	34	5	39	Sensitivity 28.6%
Node positive	3	2	5	Specificity 91.9%
				Accuracy 81.8%
				PLR 3.5
All cases of common hepatic artery	37	7		
Para-aorta				PPV 50.0%
Node negative	33	5	38	Sensitivity 37.5%
Node positive	3	3	6	Specificity 91.7%
				Accuracy 81.8%
				PLR 4.5
All cases of para-aorta	36	8		

PPV, positive predictive value; PLR, positive likelihood ratio

Table 3 Comparison between serum CA19-9 and histopathological findings

Serum CA19-9	Histological findings			Results
	Node negative	Node positive		
All cases				PPV 64.1%
≤37 U/ml	44	31	75	Sensitivity 56.9%
>37 U/ml	23	41	64	Specificity 65.7%
				Accuracy 61.2%
				PLR 1.7
All cases	67	72		
Hepatoduodenal ligament				PPV 46.9%
≤37 U/ml	49	26	75	Sensitivity 53.6%
>37 U/ml	34	30	64	Specificity 59.0%
				Accuracy 56.8%
				PLR 1.3
All cases of hepatoduodenal ligament	83	56		
Common hepatic artery				PPV 25.0%
≤37 U/ml	66	9	75	Sensitivity 64.0%
>37 U/ml	48	16	64	Specificity 57.9%
				Accuracy 59.0%
				PLR 1.5
All cases of common hepatic artery	114	25		
Para-aorta				PPV 20.3%
≤37 U/ml	68	7	75	Sensitivity 65.0%
>37 U/ml	51	13	64	Specificity 57.1%
				Accuracy 58.3%
				PLR 1.5
All cases of para-aorta	119	20		

PPV, positive predictive value; PLR, positive likelihood ratio

Table 4 Comparison between serum CA19-9 level and histological findings in biliary and pancreas carcinomas

Biliary carcinomas

CT findings	Histological findings			Results
	Node negative	Node positive		
All cases				PPV 58.5%
≤37 U/ml	33	21	54	Sensitivity 55.3%
>37 U/ml	17	24	41	Specificity 66.0%
				Accuracy 60.0%
				PLR 1.6
All cases	50	45		
Hepatoduodenal ligament				PPV 46.3%
≤37 U/ml	34	20	54	Sensitivity 48.7%
>37 U/ml	22	19	41	Specificity 60.7%
				Accuracy 55.8%
				PLR 1.2
All cases of hepatoduodenal ligament	56	39		
Common hepatic artery				PPV 26.3%
≤37 U/ml	47	7	54	Sensitivity 61.1%
>37 U/ml	30	11	41	Specificity 61.0%
				Accuracy 61.1%
				PLR 1.6
All cases of common hepatic artery	77	18		
Para-aorta				PPV 19.5%
≤37 U/ml	50	4	54	Sensitivity 66.7%
>37 U/ml	33	8	41	Specificity 60.2%
				Accuracy 61.1%
				PLR 1.7
All cases of para-aorta	83	12		

Pancreas carcinomas

CT findings	Histological findings			Results
	Node negative	Node positive		
All cases				PPV 73.9%
≤37 U/ml	11	10	21	Sensitivity 63.0%
>37 U/ml	6	17	23	Specificity 64.7%
				Accuracy 63.6%
				PLR 1.8
All cases	17	27		
Hepatoduodenal ligament				PPV 47.8%
≤37 U/ml	15	6	21	Sensitivity 64.7%
>37 U/ml	12	11	23	Specificity 55.6%
				Accuracy 59.1%
				PLR 1.5
All cases of hepatoduodenal ligament	27	17		
Common hepatic artery				PPV 21.7%
≤37 U/ml	19	2	21	Sensitivity 71.4%
>37 U/ml	18	5	23	Specificity 51.4%
				Accuracy 54.6%
				PLR 1.5
All cases of common hepatic artery	37	7		
Para-aorta				PPV 21.7%
≤37 U/ml	18	3	21	Sensitivity 62.5%
>37 U/ml	18	5	23	Specificity 50.0%
				Accuracy 52.3%
				PLR 1.3
All cases of para-aorta	36	8		

PPV, positive predictive value; PLR, positive likelihood ratio

Table 5 Comparison between serum CA19-9 and stage of tumor extension.

	Serum CA19-9 level (U/ml)
Biliary carcinomas	
T1 (n=9)	12±7
T2 (n=25)	105±472
T3 (n=19)	81±102
T4 (n=42)	289±557
Pancreas carcinomas	
T2 (n=4)	12±2
T3 (n=10)	588±733
T4 (n=30)	721±1066

T-category (primary tumor invasion) was according to *Classification of Biliary Tract Carcinoma by the Japanese Society of Biliary Surgery* and *Classification of Pancreatic Carcinoma by the Japan Pancreas Society* [11, 12].

Table 6 Comparison between combination of CT findings and CA19-9, and histological findings

CT findings	Histological findings (%)			
	Node negative	Node positive		*P* value
All cases				
CT negative/CA19-9≤37	37	20 (35)	57	
CT negative/CA19-9>37	16	20 (56)	36	0.0034
CT positive/CA19-9≤37	7	10 (59)	17	
CT positive/CA19-9>37	7	22 (76)	29	
	67	72		
Hepatoduodenal ligament				
CT negative/CA19-9≤37	39	15 (28)	54	
CT negative/CA19-9>37	27	14 (34)	41	0.0040
CT positive/CA19-9≤37	9	11 (55)	20	
CT positive/CA19-9>37	8	16 (67)	24	
	83	56		
Common hepatic artery				
CT negative/CA19-9≤37	61	8 (12)	69	
CT negative/CA19-9>37	45	10 (19)	55	0.0009
CT positive/CA19-9≤37	5	1 (17)	6	
CT positive/CA19-9>37	3	6 (67)	9	
	114	25		
Para-aorta				
CT negative/CA19-9≤37	62	5 (8)	67	
CT negative/CA19-9>37	43	9 (17)	52	0.074
CT positive/CA19-9≤37	5	2 (29)	7	
CT positive/CA19-9>37	9	4 (31)	13	
	119	20		

Table 7 Comparison between combination of CT findings and CA19-9, and histological findings in biliary and pancreas carcinomas

Biliary carcinomas

CT findings	Histological findings			
	Node negative	Node positive		*P* value
All cases				
CT negative/CA19-9≤37	29	14 (33)	43	
CT negative/CA19-9>37	10	9 (47)	19	0.026
CT positive/CA19-9≤37	5	7 (58)	12	
CT positive/CA19-9>37	6	5 (71)	21	
	50	45		
Hepatoduodenal ligament				
CT negative/CA19-9≤37	27	12 (31)	39	
CT negative/CA19-9>37	15	8 (35)	23	0.11
CT positive/CA19-9≤37	7	8 (53)	15	
CT positive/CA19-9>37	7	11(61)	18	
	56	39		
Common hepatic artery				
CT negative/CA19-9≤37	45	7 (14)	52	
CT negative/CA19-9>37	27	6 (18)	33	0.0025
CT positive/CA19-9≤37	3	0 (0)	3	
CT positive/CA19-9>37	2	5 (71)	7	
	59	11		
Para-aorta				
CT negative/CA19-9≤37	46	3 (6)	49	
CT negative/CA19-9>37	26	6 (19)	32	0.27
CT positive/CA19-9≤37	4	1(20)	5	
CT positive/CA19-9>37	7	2 (22)	9	
	83	7		

Pancreas carcinomas

CT findings	Histological findings			
	Node negative	Node positive		*P* value
All cases				
CT negative/CA19-9≤37	8	6 (43)	14	
CT negative/CA19-9>37	6	11(65)	17	0.22
CT positive/CA19-9≤37	2	3 (60)	5	
CT positive/CA19-9>37	1	7 (88)	8	
	17	27		
Hepatoduodenal ligament				
CT negative/CA19-9≤37	12	3 (20)	15	
CT negative/CA19-9>37	12	6 (33)	18	0.038
CT positive/CA19-9≤37	2	3 (60)	5	
CT positive/CA19-9>37	1	5 (80)	6	
	27	17		
Common hepatic artery				
CT negative/CA19-9≤37	16	1 (6)	17	
CT negative/CA19-9>37	18	4 (18)	22	0.29
CT positive/CA19-9≤37	2	1 (33)	3	
CT positive/CA19-9>37	1	1 (50)	2	
	37	7		
Para-aorta				
CT negative/CA19-9≤37	16	2 (11)	18	
CT negative/CA19-9>37	17	3 (15)	20	0.19
CT positive/CA19-9≤37	1	1 (50)	2	
CT positive/CA19-9>37	2	2 (50)	4	
	36	8		

Table 8 Distribution of node metastasis in patients with inconsistent results.

A) Negative in image but node positive

Node number	Bile duct carcinoma	Pancreas carcinoma	All case
6		4	4
7		1	1
8a	10	4	14
8p	1		1
9	1	1	2
11		2	2
12b	8	1	9
12p	4		4
12a	1		1
13	4	7	11
14		5	5
15		1	1
16a2	4		4
16b1	7	5	12
17	2	5	7

B) Positive in image but node negative

Node number	Bile duct carcinoma	Pancreas carcinoma	All case
8a	2	2	4
12b	4	1	5
12a	1		1
13	2		2
14		1	1
16b1	7	2	9

Station number of regional lymph node was according to *Classification of Biliary Tract Carcinoma by the Japanese Society of Biliary Surgery* and *Classification of Pancreatic Carcinoma by the Japan Pancreas Society* [11, 12].

6; infra-pyloric, 7; left gastric artery, 8a; anterior hepatic artery, 8p; posterior hepatic artery, 9; celiac artery, 11; splenic artery, 12b; bile

duct, 12p portal vein, 12a; hepatic artery, 13; retro-pancreatic head, 14; supra-mesenteric artery, 15; middle colic artery, 16a2; inferior para-aorta (supra-right renal vein), 16b1; middle para-aorta (infra-right renal vein), 17; anterior pancreatic head.