HOKKAIDO UNIVERSITY

Title	CT evaluation of paraaortic lymph node metastasis in patients with biliary cancer.
Author(s)	Noji, Takehiro; Kondo, Satoshi; Hirano, Satoshi; Tanaka, Eiichi; Ambo, Yoshiyasu; Kawarada, Yo; Morikawa, Toshiaki
Citation	Journal of Gastroenterology, 40(7), 739-743 https://doi.org/10.1007/s00535-005-1618-8
Issue Date	2005-07
Doc URL	http://hdl.handle.net/2115/15862
Rights	The original publication is available at www.springerlink.com
Type	article (author version)
File Information	JG-40-7.pdf

<u>**Original article**</u>

CT evaluation of para-aortic lymph node metastasis in biliary cancer patients

Takehiro Noji, MD, Satoshi Kondo, MD, Satoshi Hirano, MD, Eiichi Tanaka,

MD,Yoshiyasu Ambo, MD, Yo Kawarada, MD,　Toshiaki Morikawa, MD,

Department of Surgical Oncology

Hokkaido University Graduate School of Medicine

N15 W7, Kita-ku, Sapporo 060-8638, Japan

Corresponding author and reprint request:

Satoshi Kondo, MD

Department of Surgical Oncology

Hokkaido University Graduate School of Medicine

N15 W7, Kita-ku, Sapporo 060-8638, Japan

Phone: +81-11-706-7714

Fax: +81-11-706-7158

Email: kondows@med.hokudai.ac.jp

Abstract

Objectives

The extent of para-aortic lymph nodes (PANs) metastasis is equivalent to distant metastases in patients with biliary carcinoma. Accurate preoperative assessment of PANs metastasis has a crucial impact on surgical indication. In this retrospective study, we evaluated whether computed tomography (CT) scans were useful for diagnosing PANs metastases and excluding patients with PANs metastases from surgical indication.

Methods

Between March 1999 and November 2003, 57 patients with biliary carcinoma underwent radical lymphadenectomy or surgical biopsy of PANs, nine of whom was diagnosed as having positive PANs microscopically. All patients had undergone abdominal CT scans before surgery. To diagnose PANs metastases, we used the following diagnostic criteria. 1) Size: when lymph nodes were greater than 12 mm, 10 mm, 8 mm or 6mm in diameter in long or short axis diameter, the nodes were considered metastatic. 2) Shape and size: when the axial ratio of a lymph node was greater than 0.5, 0.7, 1.0, and the maximum diameter in the long or short axis was greater than 12 mm, 10 mm, 8 mm, or 6mm the node was considered metastatic. 3) Internal structure: if the internal structure of a PANs was heterogeneous, the node was

2

considered metastatic.　 The positive predictive value was calculated for each included criterion when patients numbered 10 or more.

Results

Positive predictive values using these criteria range from 13% to 36%. Only one patient had PANs with heterogeneous internal structures.

Conclusion

We were unable to determine surgical indication based on the morphological criteria revealed by a CT scan.

Key words: Computed tomography, biliary carcinoma, para-aortic lymph nodes

Introduction

The extent of lymph node metastasis is one of the most important factors affecting prognosis in patients with biliary carcinoma. Previous studies showed that para-aortic lymph node (PAN) metastasis influenced poor prognosis in a manner equivalent to that of distant, hepatic metastasis or peritoneal carcinomatosis in gallbladder carcinoma and intrahepatic cholangiocarcinoma (1-2). Similarly poor prognosis has been shown in patients with hilar cholangiocarcinoma (3). Thus, the accurate preoperative assessment of PAN metastasis has a crucial impact on surgical indication, especially in patients with biliary carcinoma. Preoperative laparoscopic examination is thought to be useful in finding hepatic metastasis or peritoneal carcinomatosis in some cases, but not for finding PAN metastasis (4-5).

In diagnosing lymph node metastasis, some authors have emphasized that the size and shape of lymph nodes demonstrated by computed tomography (CT) scans is useful for analyzing abdominal tumors. Using this method, when the size is over 10 mm and not flat, the node is considered metastatic. When using these criteria for detecting PAN metastasis in biliary carcinoma, however, the specificity was very low. Furthermore, no study has addressed whether CT imaging was actually useful for diagnosis of PAN metastasis. Therefore, for biliary carcinoma patients, we usually do

surgical pick up biopsy or lymphadenectomy of PANs at first, and then intraoperative frozen section is used to diagnose PAN metastasis. When metastatic PANs would be appeared in intraoperative frozen section, we would not do radical resection. If these PANs metastasis could be detected by using CT scan or other modality, theses patients would not be done unnecessary laparotomy.

Because the purpose of this study was to determine whether useful information could be gathered by CT scans for avoiding unnecessary laparotomy, we used only positive predictive values to assess evaluation.

In this retrospective study, we compared PAN findings obtained by CT imaging with the results of pathologic examination of patients with biliary carcinoma who underwent radical lymphadenectomy or surgical biopsy of PANs.

Patients and method

Patients

From March 1999 to November 2003, 107 patients had been operated upon for biliary carcinoma. Among the 107 patients, 50 patients did not undergo lymphadenectomy or surgical biopsy of PANs because they had liver metastases or peritoneal carcinomatosis (11 patients), or they were of high age or had other complications (39 patients). Thus,

57 patients were included in our study. Forty-two patients underwent radical

lymphadenectomy and 15 patients underwent surgical biopsy of PANs.

There were 31 men and 26 women with a mean age of 63.2 years (range 40 to 77).

Radiological analysis and diagnosis criteria

Prior to surgery, all patients had undergone abdominal CT scans. CT of the abdomen

was performed at our institute using Aquillion (Toshiba) or Somatom Plus 4 (Simens).

All of the patients underwent three phase (arterial and portal dominant, venous phase)

spiral CT. Scanning was performed at 120kVp and 280 mAs. We injected 90ml of

nonionic contrast material iopromide at 300mg I/ml using an automated injector (Zto

Enhance A-50; Nemoto Kyorindo Co., Tokyo, Japan) at a rate of 3.5ml/s. Scanning in

the arterial, portal venous and venous phase was started 25s, 60s, and 100sec

respectively. Images were reconstructed at 5-mm interval. We reviewed these data

retrospectively. All PANs between the levels of the celiac artery and inferior mesenteric

artery were detected and measured on their long and short axes. We also noted if lymph

nodes had ring and heterogeneous enhancement. To diagnose PAN metastasis, we used

the following criteria. 1) Size: Metastasis of PANs was evaluated by size in diameter of

long axis or that of short axis. 2) Shape and size: Metastasis of PANs was evaluated by

size in diameter of long axis, that of short axis, and axial ratios of lymph nodes were

considered. 3) Internal structure: if the internal structure of PANs was heterogeneous, the nodes were considered metastatic. It is difficult to measure the true lymph node size of the vertical direction on abdominal CT scan. So, the long axis and short axis of the lymph node on the horizontal plane was measured on CT scan and evaluated instead of the true value of each axis, assuming that measured value were similar to true value. The largest and/or inhomogeneously stained lymph node was selected and defined as metastatic lymph node when multiple lymph nodes in the paraortic region were detected preoperatively on CT scan. The size and the location of the lymph node which was resected operatively was confirmed to be consistent with that on CT scan basis. Thus, in our study, lymph node detected on CT scan was exactly corresponding to what was pathologically examined.

Surgical procedure

Complete lymphadenectomy was performed as follows: the para-aortic connective tissue containing lymph nodes between the levels of the celiac artery and inferior mesenteric artery was resected. The left renal vein and right renal artery were skeletonized, concentrating especially on the area between the aorta and the inferior vena cava. The specimens from the para-aortic region were resected as en bloc packets containing multiple lymph nodes in complete lymphadenectomy. To obtain lymph node

materials for surgical biopsy, 3-10 large PANs between the levels of the celiac artery

and inferior mesenteric artery were resected.

Pathologic diagnosis and lymph node analysis

Materials were fixed in 10% formaldehyde, embedded in paraffin, and stained with

hematoxylin and eosin. The nodes were counted, after preparation, with a slide gauge.

Pathologists microscopically analyzed all dissected lymph nodes for metastatic

infiltration. Pathologic results were designated positive or negative for each patient

based on the presence or absence of PAN metastases (on a per-case basis rather than

per-lymph node).

Results

Of the 57 patients, there were 9 cases of intrahepatic cholangiocarcinoma, 17 cases of

hilar cholangiocarcinoma, 5 cases of distal cholangiocarcinoma, 25 cases of gallbladder

carcinoma, and 1 case of papilla of Vater carcinoma. Among these patients, 9 patients

had PAN metastasis (six cases of gallbladder carcinoma, one case of hilar

cholangiocarcinoma, and two cases of distal cholangiocarcinoma: Table 1).

A total of 158 lymph nodes were detected by CT scan (mean of 3.8±2.3 lymph nodes

per case) and 522 were resected from 42 patients (mean 12.4±9.1 lymph nodes per case)

who had undergone radical lymphadenectomy. In the 15 patients who had undergone surgical biopsy, 55 lymph nodes were detected by CT scan (mean 3.7±2.4 lymph nodes per case) and 48 lymph nodes were resected (mean 3.2±3.3 lymph nodes per case).

Diagnostic results are reported in Tables 2 and 3, which were created using the long or short axis diameter, respectively. As receiver operator characteristic analysis on each parameter did not show any usefulness of each parameter for predicting PAN metastasis, we evaluated it in combination of long or short axis diameter with axial ratios.

The strongest result is a 50% positive predictive value, using the criterion of >12mm in long axis diameter and an axial ratio equal to 1.0 (only one case matches this criterion). Positive predictive values using other criteria range from 13% to 36%.

We found only one patient with a ring-like, heterogeneously-enhanced lymph node. This case was a gallbladder carcinoma patient who had PAN metastases (diagnosed in the pathological examination) and had a lymph node measuring over 12 mm in the short axis diameter.

Discussion

In the present study, we attempted to use morphological criteria to detect PAN metastasis with biliary carcinoma. Though two criteria, using either size criteria over 12 mm in long axis diameter: positive predictive value was 36% (specifity was 87.2%,

sensitivity was 44.4% and accuracy was 78.9%) or over 6 mm and an axial ratio of 1.0 in

long axis diameter: positive predictive value was 35% (specifity was 64.6%, sensitivity

was 77.8% and accuracy was 66.7%), had relatively high results, we were unable to

determine surgical indication based on size and morphology.   And more, the strongest

result in specifity 97.9% is a criteria obtained when using over12mm in long axis

diameter and an axial ratio equal to 1.0 (only one case matches this criterion), but

Sensitivity is only 11.1 %.

The lack of correlation between lymph node size and metastatic infiltration has been

reported for other solid tumors. For example, a Gynecologic Oncology Group study

involving 264 patients found the sensitivity of a CT scan for identifying para-aortic

nodal metastasis to be only 34% for cervical carcinoma (8). In non-small cell lung

cancers, Prenzel *et al*. reported that the overall positive predictive value was 30.8%,

using 80 preoperative CT scans in the diagnosis of the involvement of mediastinal

lymph node metastasis. In this study, there was little correlation between metastasis and

lymph node size (9). This group had previously demonstrated that in patients with

gastric cancer, 55% of regional metastatic lymph nodes were less than 5 mm in diameter

(10). Similar data has been shown for colorectal carcinoma and esophageal carcinoma

(11-13).

A previous study of PANs in gallbladder carcinoma, on the other hand, demonstrated

a high positive predictive value (86%) using size and shape criteria. This study focused

on soft tissue masses with anterior-posterior dimensions of 10 mm or larger and

ring-like or heterogeneous contrast enhancement (6). The contrast between our studies

and previous studies is likely based on differences in patients' backgrounds. We found

only one case with a ring-like, heterogeneous contrast enhancement PAN. In the

previous study group, the number of patient with such lymph nodes was not determined,

so it is possible that there was a higher percentage than in our own study. Because our

institute is a tertiary referral hospital, patients with apparently metastatic PANs might

have been excluded as candidates for surgical treatment.

Analysis of PANs is not the only possible modality for the diagnosis of nodal

metastasis. Other authors have evaluated findings of 2-[^{18}F] fluoro-2-deoxy-D-glucose

(FDG) positron emission tomography (PET) for screening of regional lymph node

metastasis in biliary cancer patients. Kato *et al*. reported that the specificity of

FDG-PET was significantly higher than that of CT for detection of bile duct carcinoma

(14). In addition, the positive predictive value of their study was 100% (5/5) in regional

and PAN metastasis (calculated by our group based on their data). While the

sensitivity of their study was only 38%, it was concordant with another report (15). As

discussed in their report, the low sensitivity of FDG-PET might be caused by its limited spatial resolution compared to CT scans, which precludes the detection of microscopic metastases.

In diagnosis of PAN metastasis in cervical cancer, several studies demonstrated that positive predictive values of FDG-PET ranged 75% to 85.7% (16-17). Other groups reported mediastinal lymph node metastasis in non small-cell lung cancer. According to these studies, FDG-PET had slightly lower positive predictive values ranging from 56% to 70% (18-19). Finally, although no reports have been published regarding biliary carcinoma, high resolution MRI with lymphotropic super paramagnetic nanoparticles would be useful for detecting PAN metastases.

In a study of prostate carcinoma, Harisinghani *et al.* reported that the overall sensitivity, specifity, and positive predictive values for detecting PAN metastases per patient (using high resolution MRI with lymphotropic super paramagnetic nanoparticles) were 100%, 95.7%, 94.2%, respectively (20). In their study, the sensitivity, specifity, and positive predictive values for nodes with a short axis diameter of fewer than 5 mm were 41.4%, 98.1%, and 77.7%, respectively. This method allows the detection of small and otherwise undectable lymph node metastases and should detect micro metastases less than 2 mm in diameter.

Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) would also be useful for the diagnosis of PAN metastasis in biliary carcinoma. Chen *et al*. reported that the sensitivity, specificity, positive predictive value, and negative predictive value of EUS-FNA of lymph nodes were 98.3%, 100%, 100%, and 98.4%, respectively, and they therefore concluded that EUS-FNA was superior to lymph node echofeatures in evaluating mediastinal or peri-intestinal lymph adenopathy (21).

In conclusion, we were unable to determine surgical indication based on the morphological criteria revealed by CT scans. Other modalities, such as high resolution MRI with lymphotropic super paramagnetic nanoparticles, may provide more accurate information for biliary carcinoma.

References

(1) Kondo S, Nimura Y, Hayakawa N, Kamiya J, Nagino M, Uesaka K. Regional and para-aortic lymphadenectomy in radical surgery for advanced gallbladder carcinoma. Br J Surg. 2000 Apr; 87(4):418-22.

(2) T. Uenishi, K. Hirohashi, S. Kubo, T. Yamamoto, O. Yamazaki, H. Kinoshita. Clinicopathological factors predicting outcome after resection of mass-forming intrahepatic cholangiocarcinoma. Br J Surg. 2001 Jul; 88(7):969-74

(3) Kitagawa Y, Nagino M, Kamiya J, Uesaka K, Sano T, Yamamoto H, et al. Lymph node metastasis from hilar cholangiocarcinoma: audit of 110 patients who underwent regional and para-aortic node dissection. Ann Surg. 2001 Mar; 233(3):385-92.

(4) Weber SM, DeMatteo RP, Fong Y, Blumgart LH, Jarnagin WR. Staging laparoscopy in patients with extrahepatic biliary carcinoma. Analysis of 100 patients. Ann Surg. 2002 Mar; 235(3):392-9.

(5) D'Angelica M, Fong Y, Weber S, Gonen M, DeMatteo RP, Conlon K, et al. The role of staging laparoscopy in hepatobiliary malignancy: prospective analysis of 401 cases. Ann Surg Oncol. 2003 Mar; 10(2):183-9.

(6) Ohtani T, Shirai Y, Tsukada K, Muto T, Hatakeyama K. Spread of

gallbladder carcinoma: CT evaluation with pathologic correlation. Abdom Imaging. 1996 May-Jun; 21(3):195-201.

(7) Kokudo N, Makuuchi M, Natori T, Sakamoto Y, Yamamoto J, Seki M et al. Strategies for surgical treatment of gallbladder carcinoma based on information available before resection. Arch Surg. 2003 Jul; 138(7):741-50

(8) Heller PB, Maletano JH, Bundy BN, Barnhill DR, Okagaki T. Clinical-pathologic study of stage IIB, III, and IVA carcinoma of the cervix: extended diagnostic evaluation for para-aortic node metastasis Gynecologic Oncology Group study. Gynecol Oncol. 1990 Sep; 38(3):425-30.

(9) Prenzel KL, Monig SP, Sinning JM, Baldus SE, Brochhagen HG, Schneider PM, et al. Lymph node size and metastatic infiltration in non-small cell lung cancer. Chest. 2003 Feb; 123(2):463-7.

(10) Monig SP, Zirbes TK, Schroder W, Baldus SE, Lindemann DG, Dienes HP, et al. Staging of gastric cancer: correlation of lymph node size and metastatic infiltration. AJR Am J Roentgenol. 1999 Aug; 173(2):365-7.

(11) Monig SP, Baldus SE, Zirbes TK, Schroder W, Lindemann DG, Dienes HP, et al. Lymph node size and metastatic infiltration in colon cancer. Ann Surg Oncol 1999; 6,579-81

(12) Kotanagi H, Fukuoka T, Shibata Y, Yoshioka T, Aizawa O, Saito Y, et al. The size of lymph nodes does not correlate with the presence or absence of metastasis in lymph nodes in rectal cancer. *J* Surg Oncol 1993; 54,252-4

(13) Doi N, Aoyama N, Tokunaga M, Okamoto M, Hayashi M, Kameda Y, et al. Possibility of pre-operative diagnosis of lymph node metastasis based on morphology. Hepatogastroenterology. 1999 Mar-Apr; 46(26):977-80.

(14) Kato T, Tsukamoto E, Kuge Y, Katoh C, Nambu T, Nobuta A, et al. Clinical role of (18)F-FDG PET for initial staging of patients with extrahepatic bile duct cancer. Eur J Nucl Med Mol Imaging. 2002 Aug; 29(8):1047-54.

(15) Kluge R, Schmidt F, Caca K, Barthel H, Hesse S, Georgi P, et al. Positron emission tomography with [(18)F]fluoro-2-deoxy-D-glucose for diagnosis and staging of bile duct cancer. Hepatology. 2001 May;33(5):1029-35.

(16) Rose PG, Adler LP, Rodriguez M, Faulhaber PF, Abdul-Karim FW, Miraldi F. Positron emission tomography for evaluating para-aortic nodal metastasis in locally advanced cervical cancer before surgical staging: a surgicopathologic study. J Clin Oncol. 1999 Jan; 17(1):41-5.

(17) Lin WC, Hung YC, Yeh LS, Kao CH, Yen RF, Shen YY. Usefulness of 18F-fluorodeoxyglucose positron emission tomography to detect para-aortic lymph

nodal metastasis in advanced cervical cancer with negative computed tomography findings. Gynecol Oncol. 2003 Apr; 89(1):73-6

(18) Konishi J, Yamazaki K, Tsukamoto E, Tamaki N, Onodera Y, Otake T, et al. Mediastinal lymph node staging by FDG-PET in patients with non-small cell lung cancer: analysis of false-positive FDG-PET findings. Respiration. 2003 Sep-Oct; 70(5):500-6.

(19) Reed CE, Harpole DH, Posther KE, Woolson SL, Downey RJ, Meyers BF, et al; American College of Surgeons Oncology Group Z0050 trial. Results of the American College of Surgeons Oncology Group Z0050 trial: the utility of positron emission tomography in staging potentially operable non-small cell lung cancer.J Thorac Cardiovasc Surg. 2003 Dec; 126(6):1943-51.

(20) Harisinghani MG, Barentsz J, Hahn PF, Deserno WM, Tabatabaei S, van de Kaa CH, et al. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. N Engl J Med. 2003 Jun 19; 348(25):2491-9.

(21)Chen VK, Eloubeidi MA.Endoscopic ultrasound-guided fine needle aspiration is superior to lymph node echofeatures: a prospective evaluation of mediastinal and peri-intestinal lymphadenopathy. Am J Gastroenterol. 2004 Apr; 99(4):628-33.

Table 1 Patients characteristic: (n=57)

	Radical lymphdectomy (n=42)	Surgical biopsy (n=15)
GBC	20 (5)	7 (1)
HBDC	5 (2)	1 (0)
BDC	9 (1)	5 (0)
CCC	8 (0)	2 (0)
PVC	0	1 (0)

皆数はhistologycaly comfirmedされたPANs転移の患者数を示す

GBC:Galebladder carcinoma HBDC:Hilar cholangiocarcinoma BDC: Bile duct carcinoma CCC: Cholangio cell carcinoma PVC: Carciona of Varter

Table 2 Positive predictive value based upon long axis diameter and axial ratio

Long axis diameter (mm)	Total	Axial ratio		
		1	≧0.7	≧0.5
≧12	4/11 (36%)	1/2	1/3	1/7
≧10	4/20 (20%)	2/16 (13%)	3/10 (30%)	2/16 (13%)
≧8	6/37 (16%)	2/16 (13%)	4/18 (22%)	5/32 (16%)
≧6	9/48 (19%)	7/17 (35%)	8/35 (23%)	8/45 (18%)

Percentage indicate positive predictive value(number of patients true positive divided by number of patients positive using each diagnostic criterion based upon long axis diameter.)

Table 3 Positive predictive value based upon short axis diameter and axial ratio

Short axis diameter (mm)	Total	Axial ratio		
		1	$\geqq 0.7$	$\geqq 0.5$
$\geqq 10$	1/4	1/3	1/3	1/4
$\geqq 8$	3/12 (25%)	2/6	3/11 (27%)	3/12 (25%)
$\geqq 6$	8/29 (29%)	6/17 (29%)	7/26 (27%)	8/28 (29%)

Percentage indicate positive predictive value(number of patients true positive divided by number of patients positive using each diagnostic criterion based upon short axis diameter.)