Detection of Liver Metastases Secondary to Pancreatic Cancer:

Utility of Combined Helical Computed Tomography During Arterial Portography With Biphasic Computed Tomography-Assisted Hepatic Arteriography

Yoshiaki Ikuta[1], Hiroshi Takamori[1], Osamu Ikeda[2], Hiroshi Tanaka[1], Yasuo Sakamoto[1], Daisuke Hashimoto[1], Nobuyuki Ozaki[1], Osamu Nakahara[1], Satoshi Furuhashi[1], Shinya Abe[1], Toru Beppu[1], Shinya Shimada[3], Yasuyuki Yamashita[2], Hideo Baba[1]

Department of [1]Gastroenterological Surgery, [2]Diagnostic Radiology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Department of Surgery, Yatsushiro Social Insurance General Hospital, Kumamoto

Request for reprints: Professor Hideo Baba, Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Honjo 1-1-1, Kumamoto 860-8556, Japan. Phone: +81-96-373-5212; Fax: +81-96-373-5213;
E-mail address: hdobaba@kumamoto-u.ac.jp

Key Words: pancreatic cancer, liver metastasis, CTHA, CTAP

Abstract

Purpose: This study was designed to define the diagnostic advantage of computed tomography during arterial portography(CTAP) combined with computed tomography–assisted hepatic arteriography(CTHA) for preoperative detection of liver metastases secondary to pancreatic cancer compared with that of multidetector computed tomography (MDCT).

Methods: From January 2002 to December 2007, we retrospectively studied 197 consecutive patients with pancreatic cancer. MDCT was performed on 192 patients prior to preoperative visceral angiography. 153 patients underwent CTAP + CTHA at the time of preoperative angiography.

Results: Liver metastases were identified in 39 patients by means of MDCT. Of 129 patients who underwent CTAP + CTHA, 53 patients (41.1%) were diagnosed as having liver metastases, which could not be detected by MDCT. These tumors missed by MDCT ranged from 3 to 15 mm in size. On CTAP + CTHA, a solitary nodule in the liver was detected in 11 patients, 2 nodules in 6 patients, 3 lesions in 2 patient, and ≧ 4 lesions in 34 patients. The sensitivity and specificity of CTAP + CTHA versus MDCT were 94.2% versus 48.4% and 82.7% versus 97.9%, respectively.

Conclusions: The combination of CTAP and CTHA is useful to confirm liver metastases and can potentially offer more accurate staging of pancreatic cancer compared with MDCT.

INTRODUCTION

The prognosis of pancreatic adenocarcinoma still remains dismal, with a 5-year survival rate of 4%[1]. Despite improvements in imaging technology, under 20% of all patients will be potentially resectable at the time of initial diagnosis[1,2]. Complete pancreatic resection can yield actuarial 5-year survival rates of 15%–25% following pancreaticoduodenectomy [3-5]and 8%–14% following distal pancreatectomy[6,7]. Although surgery is the only curative treatment, even after curative resection of pancreatic carcinoma, most patients have a recurrence including approximately 62% of liver metastases[8,9]. A high recurrence rate of liver metastases in the early period after surgery might implicate that liver metastases are present at the time of operation but below the threshold (microscopic) of detection by current preoperative radiologic imaging and intraoperative examination. Therefore, more precise evaluation for hepatic lesions is necessary because accurate detection of liver metastases has major implications in guiding both appropriate treatment and defining prognosis.

We reported the effectiveness of computed tomography during arterial portography combined with computed tomography–assisted hepatic arteriography (CTAP + CTHA) detecting liver metastases from pancreatic cancer, previously [10]. This study included a large number of pancreatic cancer patients and was designed to evaluate the diagnostic advantage of CTAP + CTHA for preoperative detection of liver metastases compared with that of multidetector computed tomography (MDCT).

METHODS

We retrospectively studied 197 consecutive patients with pancreatic cancer from January 2002 to December 2007. Of the 197 patients, 192 underwent MDCT.

All CT scans were obtained with 4-slice MDCT (Lightspeed QXi; General Electric Medical System, Milwaukee, WI). Imaging parameters were established as a pitch of 3 with a table speed of 15.0 mm/rotation to visualize the arterial phase and portal venous phase. All phases were acquired in a cranial-to-caudal direction. An 18- or 20-gauge intravenous catheter was placed in the patients' antecubital vein. A total of 100–120 mL iopamidol 300 (Iopamiron; Nihon Schering, Osaka) was infused using a power injector at a rate from 3–4 mL/s. Thirty seconds after the start of infusion, entire liver imaging was performed during a breath-hold. Subsequently, the portal venous phase was obtained following 70 seconds of scan delay. Each image was reconstructed with contiguous 5-mm slice thickness.

CTAP + CTHA was performed at the time of preoperative angiography after no remote metastasis was confirmed on CT. All studies were performed with an IVR-CT system (Toshiba Medical Systems), which comprised a digital subtraction angiography system (KXO-80C/DFP-2000A; Toshiba Medical Systems) and helical CT scanner (X-Vision;

Toshiba Medical Systems). This equipment is capable of performing digital subtraction angiography and CT scanning with the patients in one position. A 5-French catheter was inserted via the right femoral artery with Seldinger technique, followed by positioning the tip of the catheter in the superior mesenteric artery, and testing the infusion capacity of the vessel. Subsequently, helical CT during the injection of the contrast medium into the superior mesenteric artery was performed for CTAP. CTAP was performed using 90 mL of contrast material (Optiray 160; Tyco Japan, Tokyo, Japan) injected at a rate of 2.5 mL/s. The CT scanning was performed 25 seconds after the start of the injection.

For CTHA, the tip of the catheter was placed in the common hepatic artery and the biphasic CT was performed during the injection of the contrast medium into this artery starting at 5 seconds after the start of the injection. CTHA was performed using 45 mL of Optiray 160 injected at a rate of 1.5 mL/s.

In all patients, MDCT and CTAP + CTHA studies were performed within 2 weeks.

All MDCT scans were reviewed by 2 experienced abdominal radiologists in consultation. At the MDCT reading, the readers knew that the patients had pancreatic carcinoma, but information about liver metastases was not given. They evaluated images of combination of plain, arterial phase, and portal venous phase images of

MDCT. CTAP + CTHA images were evaluated independently just after the examination by different experienced radiologists in consultation. Lesions, which were hypoattenuated on CTAP and enhanced on CTHA, were diagnosed as liver metastases. The presence of each lesion at diagnosis was defined as positive by histologic proof, intraoperative ultrasonography (IOUS), bimanual palpitation at operation, or enlargement of the lesions during the follow-up period on radiologic examinations. The absence of liver metastasis at diagnosis was proved by intraoperative findings for operative cases and/or follow-up radiologic examinations of more than 6 months.

RESULTS

The characteristics of the 192 patients are outlined in Table 1. There were 76 women and 116 men in this study. The average age of the patients was 64.5 years (range, 34–86). Of 192 patients, 182 were included in extrapancreatic diseases (29 in T3, 153 in T4) according to the General Rules for the Study of Pancreatic Cancer of the Japan Pancreas Society classification. Pancreatic tumor was limited to the pancreas in 10 patients (5 in T1, 5 in T2). The primary lesion of the pancreas was located in the head for 118 patients, in the body for 51, and in the tail for 23 patients (Table 1).

Figure 1 is a schematic diagram of diagnoses in preoperative liver metastases secondary to pancreatic cancer with MDCT and CTAP+CTHA in this study. Liver metastases were detected by MDCT in 39 patients (20.3%). Size of these lesions was ranging from 5 to 80mm (mean 28±20mm). Of the 39 patients, 25 underwent CTAP+CTHA. CTAP+CTHA could also detect these liver metastases in all the patients. Of the 153 patients who had no evidence of liver metastases on MDCT, 129 patients underwent CTAP+CTHA. Of the remaining 24 patients, 9 underwent surgery without being performed CTAP+CTHA. Of the 9 patients, 2 suffered from liver metastases 2 and 4 months after pancreatic resection, and one patient detected at surgery.

Of the 129 patients who underwent CTAP + CTHA, liver metastases were detected in 53 patients (41.1%). These liver metastases which could not be detected by MDCT, ranged from 3 to 15 mm (6.2±2.9mm) in size (Figure 2). Most of them were within 10 mm in diameter. A solitary nodule in the liver was detected in 11 patients, 2 nodules in 6 patients, 3 lesions in 2 patients, and multiple lesions in 34 patients by CTAP + CTHA. 4 out of 53 patients underwent laparotomy, and hepatic nodules were confirmed at the same site as detected by CTAP+CTHA. In figure 3, 5-mm hypoattenuated lesion was detected in segment2/3 of the liver by CTAP. This lesion was enhanced by CTHA but not detected by MDCT. This patient underwent pancreatectomy, and hepatic nodule was confirmed as liver metastasis from pancreatic cancer histologically.

We confirmed no liver metastastases by intraoperative findings in 55 patients. For the remaining 137 patients, follow-up radiological examination revealed the absence of liver metastases.

Of the 76 patients who detected no liver metastases by both MDCT and CTAP+CTHA, 42 underwent pancreatectomy. Only 2 patients of these 42 patients had liver metastases that were detected by MDCT within 6months after pancreatectomy. Among the remaining 34 patients, only 1 patient had liver metastases that were detected by MDCT within 6 months, therefore, of the 76 patients 73(96.1%) were considered to be “true negative”.

Table 2 summarizes comparison of the diagnostic accuracy of liver metastasis between MDCT and CTAP + CTHA. Of the 192 patients, 35 were excluded from analyses of diagnostic accuracy, because they died of advanced disease within 6 months. Of the 35 patients 2 underwent CTAP+CTHA. Of the 127 patients who had been performed CTAP + CTHA, 111 (87.4%) were diagnosed accurately. Of the 65 patients who were diagnosed as having no liver metastases by CTAP + CTHA, 3 suffer from liver metastases, and metastases could not be detected more than 6 months after surgery in the other 62 patients. On the other hand, of the 62 cases diagnosed as having liver metastases by CTAP + CTHA, metastases could not be detected within 6 months after the first CTAP + CTHA in 13 patients. The sensitivity and specificity of CTAP + CTHA versus MDCT were 94.2% (49 of 52) versus 48.4% (30 of 62) and 82.7% (62 of 75) versus 97.8% (93 of 95), respectively.

DISCUSSION

We had already reported that more than 50% of patients were diagnosed as having liver metastases by CTAP+CTHA, which could not detected by MDCT[10]. We concluded that the combination of CTAP + CTHA improve the detection of liver metastases secondary to pancreatic cancer previously[10], although it was small number study. Therefore we have analyzed a large number of patients with pancreatic cancer in this study. The major finding of this study is that the combination of CTAP and CTHA has sensitivity superior to that of MDCT for preoperative diagnosis in liver metastases from pancreatic cancer.

CTAP + CTHA have been the most sensitive nonsurgical imaging technique for the detection of hepatic metastases[11-14]. The sensitivity of CTAP + CTHA was 94.2% in this study, which is comparable with those in other trials (72-95.8%)[15-18].On the other hand, 48.4% of the sensitivity of MDCT was too low level. Bhattacharjya et al[15] reported that CTAP detected more lesions than MDCT but the difference was not statistically significant. However they also reported that MRI and CTAP were significantly better than MDCT in detecting multiple lesions. Satoi et al[18] reported that MDCT could detect liver metastases of pancreatic cancer than CTAP + CTHA.

These conclusion might be based on MDCT findings derived from 1.25mm VS 5mm thick contiguous slice. However their sensitivity of CTAP + CTHA was considerably low (72.0%) compared with other trials and contained only a small number (25 cases).

Disadvantages of CTAP + CTHA are low specificity, the need for technical experts in performing, cost and the relatively invasiveness[16,18]. CTAP and CTHA require larger quantity of contrast medium than MDCT. However, no patients experienced renal dysfunction after CTAP+CTHA. Therefore, CTAP+CTHA could be performed in all patients, although we should care patients' renal function.

In our hospital, we are trying the combination chemotherapy with intra-arterial 5-fluorouracil infusion combined with systemic gemcitabine for unresectable pancreatic cancer patients, and the result is well tolerated and seemed to be effective[19]. In this study, the false positive rate was 21% (13 out of 62). This is relatively high rate. The specificity of CTAP + CTHA is relatively low, because CTAP+CTHA regards some chronic liver damage or intrahepatic arterio-portal shunt as the presence of liver metastases. Also, we thought that it was because all these 13 patients received chemotherapy after diagnosis. These patients received systemic administration of gemcitabine combined with arterial continuous infusion of 5-fluorouracil. Therefore, some metastases might disappear because chemotherapy was effective during follow up period.

In this study, 41.1% of liver metastases, which could not be detected by MDCT, could be detected by CTAP + CTHA. Sizes of these metastatic lesions were within 15 mm, and most of these lesions were within 10 mm in diameter. Liver metastases secondary to pancreatic cancer have often been detected as multiple and small lesions, especially when within 10 mm in diameter. Bhattacharjya et al[15] reported that CTAP can detect smaller metastases (<1 cm) than CT and MRI. Jimenez et al[20] reported that more than 40% of cases predicted to be resectable by CT were not resectable during surgical laparotomy because of small metastases of the liver and peritoneal dissemination lesions missed in most cases. From this point of view, the combination of CTAP+CTHA is well qualified for preoperative evaluation of the existence of liver metastases from pancreatic cancer.

US is the noninvasive and relatively inexpensive examination for the detection of liver metastases. However, the sensitivity of US for detecting small metastases (<1 cm) is difficult to establish[21].

Superparamagnetic iron oxide (SPIO)–enhanced MRI has not only improved tumor detection but also allowed characterization of liver lesions[22]. Strotzer et al[22] reported that spiral CTAP cannot be replaced by SPIO-enhanced MRI because CTAP has higher sensitivity, although its specificity is relatively low. Vogl et al[23] and Bhattacharjya et al[15] reported that the diagnostic efficacy of SPIO-enhanced MRI is similar to that of CTAP. Tanimoto et al[16] also reported that the diagnostic efficacy of SPIO-enhanced MRI is similar to that of CTAP+CTHA. In this study, the patients were not performed MRI, so we could not compare MRI with MDCT and CTAP+CTHA.

Recently, Gd-EOB-DTPA-MRI (gadolinium-ethoxybenzyl-dietylenetriamine pentaacetic acid enhanced magnetic resonance imaging) is known to be useful modality of detecting liver tumor[24-27]. Akai et al[24] reported that Gd-EOB-DTPA-MRI is as useful as MDCT for detecting liver lesions. Hammerstingl et al[25] reported that Gd-EOB-DTPA-MRI is superior in the diagnosis of focal liver lesions compared with MDCT. Recent multicenter studies reported that Gd-EOB-DTPA-MRI is of clinical benefit relative to unenhanced MRI and spiral CT[26,27]. However, the majority of the patients were HCC patients in these reports. Therefore, further studies are needed to compare CTAP+CTHA with Gd-EOB-DTPA-MRI to detect liver metastases.

In conclusion, the combination of CTAP and CTHA is useful to confirm liver metastases before operation for resectable pancreatic cancer because it has higher sensitivity for the detection of liver metastases compared with MDCT.

REFERENCES

1 Kern S, Hruban R, Hollingsworth MA, Brand R, Adrian TE, Jaffee E et al.: The product of a pancreas cancer think tank. Cancer Res 2001;61:4923-4932.

2 Li D, Xie K, Wolff R, Abbruzzese JL: Pancreatic cancer. Lancet 2004;363:1049-1057.

3 Baumel H, Huguier M, Manderscheid JC, Fabre JM, Houry S, Fagot H: Results of resection for cancer of the exocrine pancreas: A study from the french association of surgery. Br J Surg 1994;81:102-107.

4 Sohn TA, Yeo CJ, Cameron JL, Koniaris L, Kaushal S, Abrams RA et al.: Resected adenocarcinoma of the pancreas-616 patients: Results, outcomes, and prognostic indicators. J Gastrointest Surg 2000;4:567-579.

5 Richter A, Niedergethmann M, Sturm JW, Lorenz D, Post S, Trede M: Long-term results of partial pancreaticoduodenectomy for ductal adenocarcinoma of the pancreatic head: 25-year experience. World J Surg 2003;27:324-329.

6 Dalton RR, Sarr MG, van Heerden JA, Colby TV: Carcinoma of the body and tail of the pancreas: Is curative resection justified? Surgery 1992;111:489-494.

7 Brennan MF, Moccia RD, Klimstra D: Management of adenocarcinoma of the body and tail of the pancreas. Ann Surg 1996;223:506-511; discussion 511-502.

8 Griffin JF, Smalley SR, Jewell W, Paradelo JC, Reymond RD, Hassanein RE et al.: Patterns of failure after curative resection of pancreatic carcinoma. Cancer 1990;66:56-61.

9 Sperti C, Pasquali C, Piccoli A, Pedrazzoli S: Recurrence after resection for ductal adenocarcinoma of the pancreas. World J Surg 1997;21:195-200.

10 Takamori H, Ikeda O, Kanemitsu K, Tsuji T, Chikamoto A, Kusano S et al.: Preoperative detection of liver metastases secondary to pancreatic cancer: Utility of combined helical computed tomography during arterial portography with biphasic computed tomography-assisted hepatic arteriography. Pancreas 2004;29:188-192.

11 Soyer P, Bluemke DA, Hruban RH, Sitzmann JV, Fishman EK: Hepatic metastases from colorectal cancer: Detection and false-positive findings with helical ct during arterial portography. Radiology 1994;193:71-74.

12 Li L, Wu PH, Mo YX, Lin HG, Zheng L, Li JQ et al.: Ct arterial portography and ct hepatic arteriography in detection of micro liver cancer. World J Gastroenterol 1999;5:225-227.

13 Inaba Y, Arai Y, Kanematsu M, Takeuchi Y, Matsueda K, Yasui K et al.: Revealing hepatic metastases from colorectal cancer: Value of combined helical ct during arterial portography and ct hepatic arteriography with a unified ct and

angiography system. AJR Am J Roentgenol 2000;174:955-961.

14 Furukawa H, Iwata R, Moriyama N: Is ct during arterial portography useful for the preoperative evaluation of liver metastases from pancreatic carcinoma? Pancreas 2001;22:200-202.

15 Bhattacharjya S, Bhattacharjya T, Baber S, Tibballs JM, Watkinson AF, Davidson BR: Prospective study of contrast-enhanced computed tomography, computed tomography during arterioportography, and magnetic resonance imaging for staging colorectal liver metastases for liver resection. Br J Surg 2004;91:1361-1369.

16 Tanimoto A, Wakabayashi G, Shinmoto H, Nakatsuka S, Okuda S, Kuribayashi S: Superparamagnetic iron oxide-enhanced mr imaging for focal hepatic lesions: A comparison with ct during arterioportography plus ct during hepatic arteriography. J Gastroenterol 2005;40:371-380.

17 Matsuo M, Kanematsu M, Inaba Y, Matsueda K, Yamagami T, Kondo H et al.: Pre-operative detection of malignant hepatic tumours: Value of combined helical ct during arterial portography and biphasic ct during hepatic arteriography. Clin Radiol 2001;56:138-145.

18 Satoi S, Yamamoto H, Takai S, Tanigawa N, Komemushi A, Yanagimoto H et al.: Clinical impact of multidetector row computed tomography on patients with

pancreatic cancer. Pancreas 2007;34:175-179.

19 Takamori H, Kanemitsu K, Tsuji T, Tanaka H, Chikamoto A, Nakahara O et al.: 5-fluorouracil intra-arterial infusion combined with systemic gemcitabine for unresectable pancreatic cancer. Pancreas 2005;30:223-226.

20 Jimenez RE, Warshaw AL, Rattner DW, Willett CG, McGrath D, Fernandez-del Castillo C: Impact of laparoscopic staging in the treatment of pancreatic cancer. Arch Surg 2000;135:409-414; discussion 414-405.

21 Robinson PJ: Imaging liver metastases: Current limitations and future prospects. Br J Radiol 2000;73:234-241.

22 Strotzer M, Gmeinwieser J, Schmidt J, Fellner C, Seitz J, Albrich H et al.: Diagnosis of liver metastases from colorectal adenocarcinoma. Comparison of spiral-ctap combined with intravenous contrast-enhanced spiral-ct and spio-enhanced mr combined with plain mr imaging. Acta Radiol 1997;38:986-992.

23 Vogl TJ, Schwarz W, Blume S, Pietsch M, Shamsi K, Franz M et al.: Preoperative evaluation of malignant liver tumors: Comparison of unenhanced and spio (resovist)-enhanced mr imaging with biphasic ctap and intraoperative us. Eur Radiol 2003;13:262-272.

24 Akai H, Kiryu S, Takao H, Tajima T, Shibahara J, Imamura H et al.: Efficacy of

double-arterial phase gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced liver magnetic resonance imaging compared with double-arterial phase multi-detector row helical computed tomography. J Comput Assist Tomogr 2009;33:887-892.

25 Hammerstingl R, Huppertz A, Breuer J, Balzer T, Blakeborough A, Carter R et al.: Diagnostic efficacy of gadoxetic acid (primovist)-enhanced mri and spiral ct for a therapeutic strategy: Comparison with intraoperative and histopathologic findings in focal liver lesions. Eur Radiol 2008;18:457-467.

26 Ichikawa T, Saito K, Yoshioka N, Tanimoto A, Gokan T, Takehara Y et al.: Detection and characterization of focal liver lesions: A japanese phase iii, multicenter comparison between gadoxetic acid disodium-enhanced magnetic resonance imaging and contrast-enhanced computed tomography predominantly in patients with hepatocellular carcinoma and chronic liver disease. Invest Radiol 2010;45:133-141.

27 Raman SS, Leary C, Bluemke DA, Amendola M, Sahani D, McTavish JD et al.: Improved characterization of focal liver lesions with liver-specific gadoxetic acid disodium-enhanced magnetic resonance imaging: A multicenter phase 3 clinical trial. J Comput Assist Tomogr 2010;34:163-172.

Figure legend:

Figure1.

Shematic diagram of dignoses in preoperative liver metastases secondary to pancreatic cancer by MDCT and CTAP+CTHA, Liver metastases were detected by MDCT in 39 patients (20.3%). Of the 153 patients who had no evidence of liver metastases on MDCT, 129 patients underwent CTAP+CTHA. Of the 129 patients who underwent CTAP + CTHA, liver metastases were detected in 53 patients (41.1%).

Figure 2.

Comparison of the size of the liver metastasis, Liver metastases were detected by MDCT in 39 patients. Sizes of these lesions were ranging from 5 to 80mm (mean 28±20mm). In 53 patients whose metastases could not be detected by MDCT, liver metastases could be detected by CTAP+CTHA. The sizes of these lesions were ranging from 3 to 15 mm (6.2±2.9mm) in size. Most of them were within 10 mm in diameter.

Figure3.

A 70-year old woman with liver metastasis from cancer of the body of the pancreas. A, MDCT shows the hypovascular mass in the body of the pancreas. B, MDCT could not detect liver metastasis. C, A 5-mm hypoattenuated lesion is noted on the CTAP scan in segment 3 (arrow). D, CTHA shows a focal enhancement lesion, which is the same place detected by CTAP (arrow).