

Recurrence 11 Years After Complete Response to Gemcitabine, 5-Fluorouracil, and Cisplatin Chemotherapy Followed by Radiotherapy in a Patient with Advanced Pancreatic Cancer: a Case Report

TOMOYUKI UCHIHARA^{1,2}, YO-ICHI YAMASHITA¹, WANG HUALIN^{1,3}, KAZUKI TAKEISHI¹,
SHINJI ITOH¹, NORIHUMI HARIMOTO¹, TOMOHARU YOSHIKUMI¹, SHINICHI AISHIMA⁴,
KEN SHIRABE¹, HIDEO BABA² and YOSHIHIKO MAEHARA¹

Departments of ¹Surgery and Science, and ³Anatomic Pathology, Pathological Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan;

²Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan;

⁴Department of Pathology and Microbiology, Faculty of Medicine, Saga University, Saga, Japan

Abstract. A 63-year-old man diagnosed with locally advanced pancreatic ductal adenocarcinoma (PDAC; stage IIa) was treated with chemotherapy (gemcitabine, 5-fluorouracil and cisplatin) followed by radiotherapy. He had complete response by imaging and relapse-free survival for 11 years. However, he subsequently presented with local tumor recurrence and underwent pancreaticoduodenectomy followed by chemotherapy; a partial response was achieved. As in liver metastasis of colonic cancer, complete response by imaging in PDAC may not mean pathological complete response. We would propose the importance of adjuvant surgery for a patient with PDAC with complete response by imaging after chemoradiotherapy.

Pancreatic ductal adenocarcinoma (PDAC) is a life-threatening disease causing 330,300 deaths per year worldwide (1). Eighty-five percent of patients with PDAC have advanced, unresectable disease, and the overall 5-year survival rate is reported to be only 4% (2). There have been reports of 23 studies involving 19 chemotherapy regimens, such as gemcitabine (GEM) alone, GEM plus cisplatin, and GEM plus irinotecan, for the treatment of unresectable PDAC (3). Recently, the potent FOLFIRINOX

regimen (fluorouracil, leucovorin, oxaliplatin, and irinotecan) was shown to significantly prolong survival in PDAC; the median progression-free survival in a phase II/III trial was 6.4 months in the FOLFIRINOX-treated group compared with 3.3 months in the GEM-treated group (4, 5). However, there have been no reports regarding long-term survival in patients with PDAC achieving complete response (CR) with chemoradiotherapy (CRT).

We, herein, report a case of tumor recurrence 11 years after CR with CRT against PDAC. It has been established that imaging CR may not mean pathological CR (pCR) in liver metastasis of colon cancer (6). However, as far as we are aware of, this case is the first report to demonstrate the importance of adjuvant surgery after imaging CR following CRT in patients with advanced PDAC.

Case Report

We report on a case of a 63-year-old man who was diagnosed with advanced PDAC 2.8 cm in size at the pancreatic head with invasion of the portal vein [stage IIa (7)] in January 2002 (Figure 1A). We proposed surgical resection, but the patient chose to receive CRT instead. He was treated with GEM combined with 5-fluorouracil and cisplatin [GFP regimen (8, 9)] and had CR after four cycles of chemotherapy (Figure 1B). To reduce the risk of residual tumor, he underwent radiation therapy (total 40 Gy), and uracil-tegafur chemotherapy after two years. Thereafter, he experienced 11 years of relapse-free survival.

The patient was seen at our Hospital in November 2013 with a chief complaint of anorexia. Blood tests showed abnormal

Correspondence to: Tomoyuki Uchihara, MD, Department of Gastroenterological Surgery, Kumamoto University Graduate School of Medical Sciences, 1-1-1 Honjo, Kumamoto-city, 860-8556 Japan, Tel: +81 963735212 Fax: +81 963714378, e-mail: tomoyuki.u.mikawa1@gmail.com

Key Words: Pancreatic cancer, complete response, recurrence, case report.

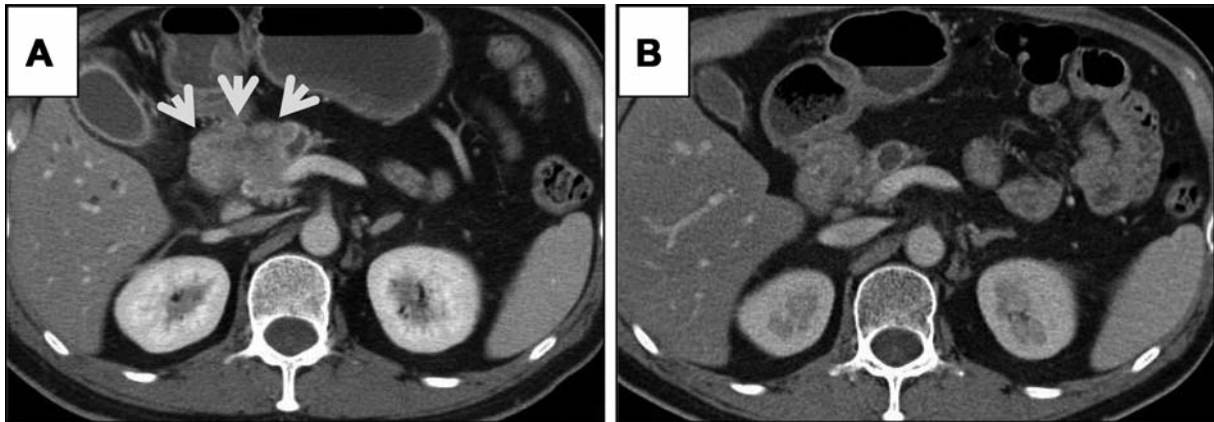


Figure 1. Computed tomography imaging at first diagnosis of pancreatic ductal adenocarcinoma. A: A low-density mass can be seen in the pancreatic head (arrows indicate). The mass was suspected to invade the portal vein. B: The mass disappeared after chemotherapy with gemcitabine, fluorouracil, and cisplatin.

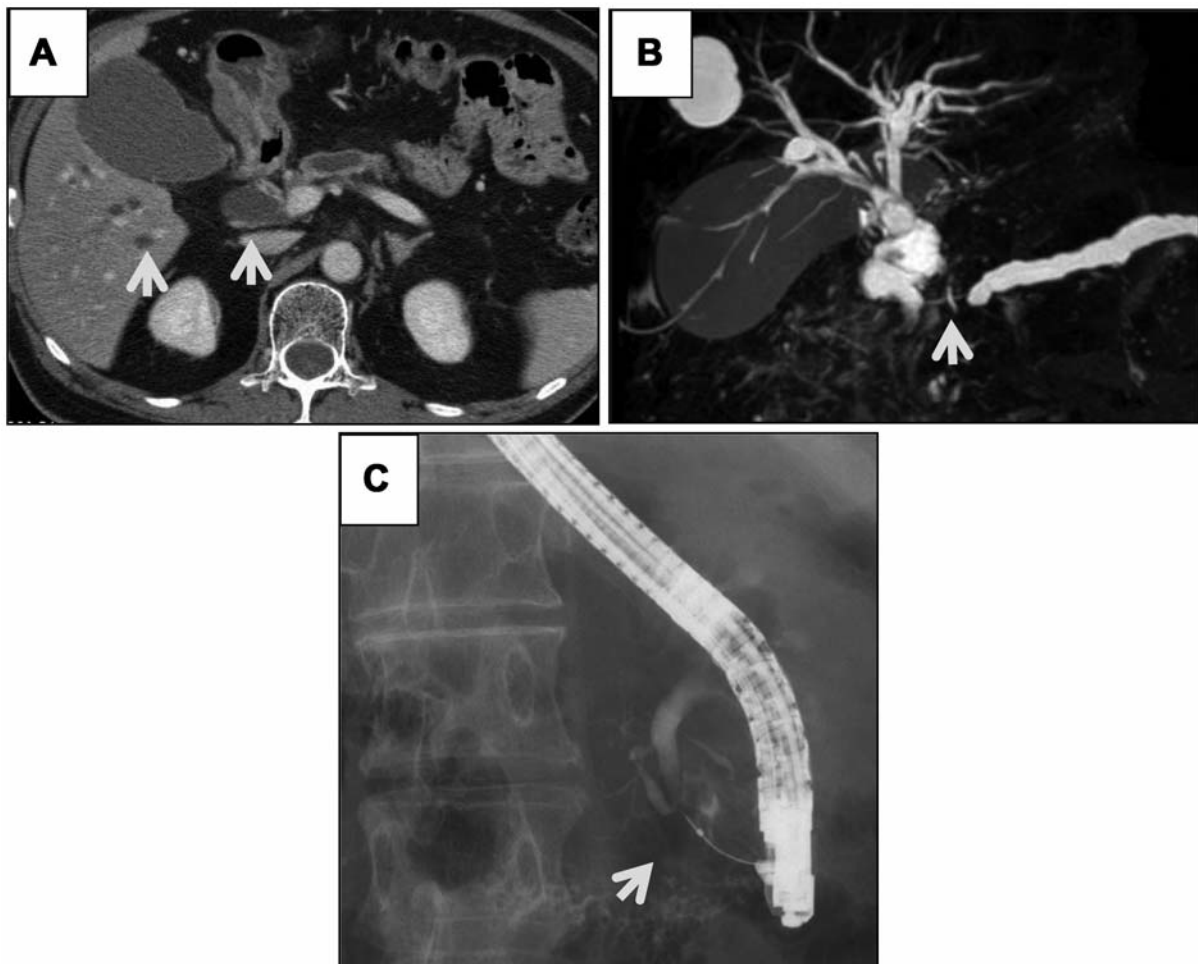


Figure 2. A: Preoperative computed tomographic imaging at recurrence of pancreatic ductal adenocarcinoma 11 years after clinical complete response to chemotherapy with gemcitabine, fluorouracil, and cisplatin. We found dilated intrahepatic bile and common bile duct ducts (arrows). However, we were unable to find any tumor. B: On magnetic resonance cholangiopancreatography, we found obstruction of the pancreatic duct at the pancreatic head (arrow). C: Endoscopic retrograde pancreatography showed obstruction of the main pancreatic duct (arrow).

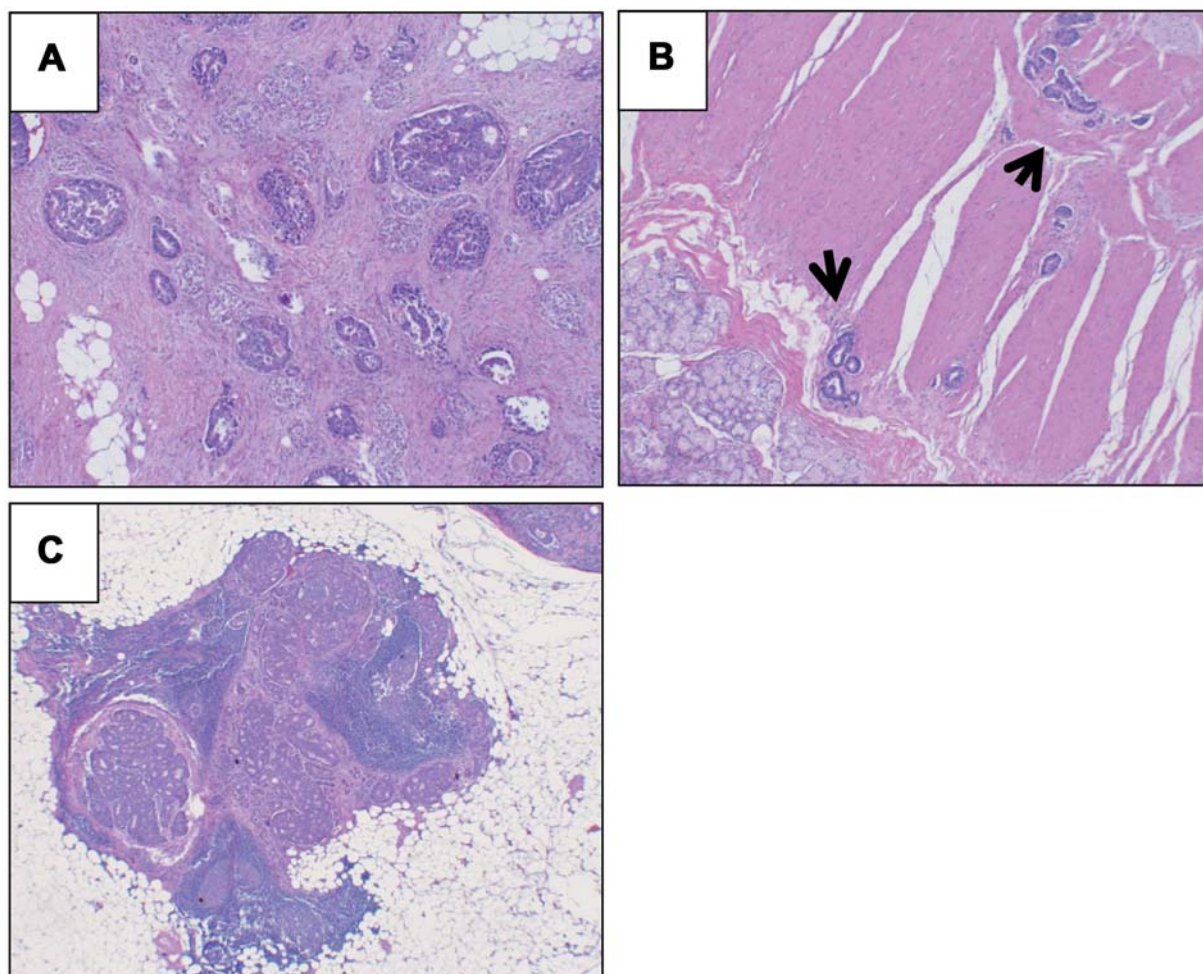


Figure 3. A: Pathological findings indicated the lesion was a well- to moderately-differentiated adenocarcinoma (hematoxylin and eosin staining, 100 \times). B: We found duodenal invasion by this tumor (arrows) (hematoxylin and eosin staining, 40 \times). C: We found metastasis to lymph node #13a (hematoxylin and eosin staining, 200 \times).

values as follows: total bilirubin 2.3 mg/dl, direct bilirubin 1.3 mg/dl, aspartate aminotransferase 693 U/l, alanine aminotransferase 1052 U/l, alkaline phosphatase 1021 U/l, and γ -glutamyl transpeptidase 1884 IU/l. Tumor markers were within normal limits, with levels of carcinoembryonic antigen (CEA; 1.2 ng/ml) and cancer antigen 19-9 (CA19-9; 21.9 U/ml) being almost the same as at the time of primary PDAC (CEA 2.1 ng/ml and CA19-9 54 U/ml). Imaging showed the dilatation of the common bile duct caused by obstruction of the lower bile duct; however, the presence of a tumor around the pancreatic head was not confirmed (Figure 2). We performed brushing cytology at the obstruction site of the lower bile duct during endoscopic retrograde cholangiography, and identified a class V adenocarcinoma. We, therefore, diagnosed recurrence of PDAC. We performed a sub-total stomach-preserving pancreaticoduodenectomy. During the operation, we identified localized peritoneal dissemination and two liver metastases. It

was not possible to perform R0 resection; however, we anticipated that we had the potential to improve the patient's prognosis through tumor volume reduction because these lesions would be slow growing and be sensitive to adjuvant chemotherapy. Pathological findings revealed that these tumors were well- to moderately-differentiated adenocarcinoma in the pancreatic head and metastases of the #13a, and #17 lymph nodes. We also found nerve, vein, and lymphatic vessel invasion (Figure 3).

After recovery following surgical resection, the patient received chemotherapy with GEM combined with S-1 (10). The treatment effect of this chemotherapy was judged as a partial response (PR) (11) because the sum of the longest diameter of the target lesion (liver metastasis) decreased from 120 mm at baseline to approximately 0 mm, but the size of the non-target lesion (peritoneal dissemination) stayed about the same at approximately 18 mm.

Discussion

It is very rare to obtain CR with CRT in PDAC. According to the report of Conroy *et al.* there was only one clinical CR among 171 patients treated with FOLFIRINOX chemotherapy (0.6%) and none among 171 patients who received gemcitabine (4). In contrast, a mean pathological CR rate of 24.4% has been reported for rectal cancer after neoadjuvant chemotherapy (NAC) (12). There have been certain reports of pathological CR with NAC, such as GEM- and fluorouracil-based regimens, in patients with PDAC, with rates of 7% (8/107 patients) (13) and 2.5% (11/442 patients) (14). Wang and Zhao reported that the median overall survival for patients with PDAC who obtained pathological CR with NAC was 31 months (0.6-194 months), and there was only one patient with more than 10 years' survival (14).

We are aware that a clinical CR with chemotherapy does not equate to pathological CR in patients with liver metastasis of colon cancer. Benoist *et al.* reported that 12 (26%) out of 66 patients with clinical CR had viable lesions at surgery on pathological examination (6). This finding may also apply to our case. We consider that a viable PDAC lesion could have existed in this patient for 11 years after achieving clinical CR, and that recurrence occurred by slow growth of these lesions. Therefore, to achieve a complete cure of malignancy, adjuvant surgery is also important for patients with PDAC who have clinical CR. In addition, it has been reported that adjuvant surgery is effective in cases of unresectable PDAC that are subsequently judged to be resectable following nonsurgical treatment. Opendro *et al.* (15) reported the importance of adjuvant surgery in PDAC for patients with clinical PR or CR with chemotherapy. They compared 15 patients (one CR and 14 PR) who underwent adjuvant surgery with 115 patients (23% of cases with CR or PR) who did not undergo surgical resection because of poor response to chemotherapy or performance status, and reported improved survival with adjuvant surgery; the median survival time with adjuvant therapy was 36 months, compared with 9 months without adjuvant surgery. Considering the tumor recurrence 11 years after a clinical CR was achieved with CRT in our own case, adjuvant surgery should be an important treatment strategy for patients with advanced PDAC with clinical CR. Data on the long-term survival of patients with PDAC after clinical or pathological CR are limited, and there were only five cases with survival durations of greater than 5 years (1.1%), and one case (0.2%) of greater than 10 years in a patient who was diagnosed with a pathological CR at surgery (14). We could not find any reports concerning long-term survival of patients with PDAC after clinical CR without adjuvant surgery.

We consider our case to be a recurrence of PDAC rather than a second primary PDAC because the location of the PDAC was almost the same as that of the tumor 11 years previously. However, it may not be possible to ultimately

distinguish between disease recurrence and a second primary PDAC in our case. We made the first diagnosis of PDAC based on only imaging studies 11 years prior. If we had obtained a biopsy sample of this tumor at the time of diagnosis, this sample would have helped us to correctly diagnose the later PDAC as recurrence or a second primary PDAC. Endoscopic ultrasound-guided fine-needle aspiration was first used for PDAC in Denmark in 1991 (16); however, it was not common at the time of this diagnosis in Japan.

In conclusion, this case suggests that in patients with PDAC, imaging CR after CRT may not mean that a pathological CR has been achieved. Therefore, adjuvant surgery is important for patients with PDAC.

Reference

- Bochatay L, Girardin M, Bichard P and Frossard JL: Pancreatic cancer in 2014: screening and epidemiology. *Rev Med Suisse* 10: 1582-1585, 2014.
- Vincent A, Herman J, Schulick R, Hruban RH and Goggins M: Pancreatic cancer. *Lancet* 378: 607-620, 2011.
- Gresham GK, Wells GA, Gill S, Cameron C and Jonker DJ: Chemotherapy regimens for advanced pancreatic cancer: a systematic review and network meta-analysis. *BMC Cancer* 14: 471, 2014.
- Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C and Ducreux M; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 364: 1817-1825, 2011.
- Conroy T, Gavaille C, Samalin E, Ychou M, and Ducreux M: The role of the FOLFIRINOX regimen for advanced pancreatic cancer. *Curr Oncol Rep* 15: 182-189, 2013.
- Benoist S, Brouquet A, Penna C, Julié C, El Hajjam M, Chagnon S, Mitry E, Rougier P, Nordlinger B: Complete response of colorectal liver metastases after chemotherapy: does it mean cure? *J Clin Oncol* 24: 3939-45, 2006.
- Sobin LH, Gospodarowicz M, and Wittekind C (eds.): International Union Against Cancer TNM Classification of Malignant Tumors (Seventh Edition). Wiley-Blackwell, 2009.
- Yamashita Y, Taketomi A, Itoh S, Harimoto N, Tsujita E, Sugimachi K, Gion T, and Maehara Y: Phase II trial of gemcitabine combined with 5-fluorouracil and cisplatin (GFP) chemotherapy in patients with advanced biliary tree cancers. *Jpn J Clin Oncol* 40: 24-28, 2010.
- Yamashita Y, Taketomi A, Fukuzawa K, Yoshizumi T, Uchiyama H, Simada M, Shirabe K, Wakasugi K, and Maehara Y: Gemcitabine combined with 5-fluorouracil and cisplatin (GFP) in patients with advanced biliary tree cancers: a pilot study. *Anticancer Res* 26: 771-775, 2006.
- Yanagimoto H, Ishii H, Nakai Y, Ozaka M, Ikari T, Koike K, Ueno H, Ioka T, Satoi S, Sho M, Okusaka T, Tanaka M, Shimokawa T, Kwon AH, and Isayama H: Improved survival with combined gemcitabine and S-1 for locally advanced pancreatic cancer: pooled analysis of three randomized studies. *J Hepatobiliary Pancreat Sci* 21: 761-766, 2014.

- 11 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, and Verweij J: New response evaluation criteria 365 in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 45: 228-247, 2009.
- 12 Martin ST, Heneghan HM, and Winter DC: Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. *Br J Surg* 99: 918-928, 2012.
- 13 Chun YS, Cooper HS, Cohen SJ, Konski A, Burtneess B, Denlinger CS, Astsaturov I, Hall MJ, and Hoffman JP: Significance of pathologic response to preoperative therapy in pancreatic cancer. *Ann Surg Oncol* 18: 3601-3607, 2011.
- 14 Wang H, and Zhao Q: Pathologic complete response to neoadjuvant therapy in patients with pancreatic ductal adenocarcinoma is associated with better prognosis. *Ann Diagn Pathol* 16: 427, 2012.
- 15 Opendro SS, Satoi S, Yanagimoto H, Yamamoto T, Toyokawa H, Hirooka S, Yamaki S, Inoue K, Matsui Y, and Kwon AH: Role of adjuvant surgery in initially unresectable pancreatic cancer after long-term chemotherapy or chemoradiation therapy: survival benefit? *J Hepatobiliary Pancreat Sci* 21: 695-702, 2014.
- 16 Vilmann P, Jacobsen GK, Henriksen FW, and Hancke S: Endoscopic ultrasonography with guided fine needle aspiration biopsy in pancreatic disease. *Gastrointest Endosc* 38: 172-173, 1992.

Received January 28, 2015

Revised February 17, 2015

Accepted February 18, 2015