Transcatheter Arterial Chemoembolization for Hepatic Recurrence after Curative Resection of Pancreatic Adenocarcinoma

Jin Hyoung Kim*, Eugene K. Choi[†], Hyun-Ki Yoon*, Gi-Young Ko*, Kyu-Bo Sung*, and Dong Il Gwon*

*Department of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea,

[†]Department of Radiological Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Background/Aims: Despite curative resection, hepatic recurrences cause a significant reduction in survival in patients with primary pancreatic adenocarcinoma. Transcatheter arterial chemoembolization (TACE) has recently been used successfully to treat primary and secondary hepatic malignancy. **Methods:** Between 2003 and 2008, 15 patients underwent TACE because of hepatic recurrence after curative resection of a pancreatic adenocarcinoma. The tumor response was evaluated based on computed tomography scans after TACE. The overall duration of patient survival was measured. **Results:** After TACE, a radiographically evident response occurred in six patients whose tumors demonstrated a tumor blush on angiography. Four patients demonstrated stabilization of a hypovascular mass. The remaining five patients demonstrated continued progression of hypovascular hepatic lesions. The median survival periods from the time of diagnosis and from the time of initial TACE were 9.6 and 7.5 months, respectively. **Conclusions:** TACE may represent a viable therapeutic modality in patients with hepatic recurrence after curative resection of pancreatic adenocarcinoma. (*Gut Liver* 2010;4:384-388)

Key Words: Pancreatic adenocarcinoma; Transcatheter arterial chemoembolization; Liver

INTRODUCTION

Pancreatic adenocarcinoma has poor prognosis with an overall five-year survival rate ranging from 0.4-4%.^{1,2}

Surgery resection represents the only form of curative therapy; however, only approximately 10% of pancreatic cancer patients are surgical candidates due to advanced disease at the time of diagnosis.³⁻⁵ Even with curative surgery, local recurrence and/or metastatic liver spread after curative resection is frequent and usually occur within one to two years after surgery.⁶⁻⁸ Most patients thereby qualify for palliative therapy, including systemic chemotherapy or radiation therapy. Such options, however, are of limited benefit, as pancreatic carcinomas respond poorly to such existing therapies.^{9,10}

Transcatheter arterial chemoembolization (TACE) is the mainstay of palliative therapy in patients with unresectable hepatocellular carcinoma (HCC).¹¹⁻¹³ Of late, studies have demonstrated successful application to a variety of secondary hepatic malignancies, including metastasis from neuroendocrine neoplasm, breast cancer, or sarcoma.¹⁴⁻¹⁷ To our knowledge, the use of TACE for the treatment of hepatic recurrence after curative surgery for pancreatic adenocarcinoma has yet to be reported. Therefore, the aim of the current study was to evaluate the clinical effectiveness of TACE in patients with hepatic recurrence after curative resection for pancreatic adenocarcinoma.

MATERIALS AND METHODS

1. Patient population

The study protocol was approved by our Institutional Review Board, and informed consent was obtained. Inclusion criteria of TACE in this study were recurrent hepatic metastasis from pancreatic adenocarcinoma, and

Correspondence to: Jin Hyoung Kim

Department of Radiology, Asan Medical Center, University of Ulsan College of Medicine, 388-1 Poongnap 2-dong, Songpa-gu, Seoul 138-736, Korea

Tel: +82-2-3010-4384, Fax: +82-2-476-0090, E-mail: mlfenew@hanmail.net

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Table 1. Summary of Data

Patient age/sex	Time interval: surgery and diagnosis of recurrence, mo	Recurrence pattern	Description of hepatic tumors	Tumor staining on angiography	TACE-related complications	No. of TACE treatments	Survival after recurrence, mo	Survival after initial TACE
70/M	1.5	Hepatic mets	Multiple nodules	Obscure	Nausea	1	9.6	8.2
68/F	3.7	Local and hepatic mets	Multiple nodules	Obscure	None	2	7	6
68/M	2	Local and hepatic mets	Multiple nodules	Yes	Nausea	3	13	12
53/M	1.6	Hepatic mets	Multiple nodules	Obscure	None	1	7.8	7.3
73/M	54	Hepatic mets	Solitary mass	Yes	Nausea	2	15	8.2
58/M	7	Hepatic mets	Two masses	Yes	Nausea, liver abscess	3	11.1	9.1
60/M	4	Hepatic mets	Multiple nodules	Obscure	Nausea	1	9.8	4.5
77/M	2	Hepatic mets	Multiple nodules	Yes	Nausea	1	12.4	11.3
61/F	4.7	Local and hepatic mets	Multiple nodules	Yes	Nausea	1	13.5	12.9
56/M	6.8	Local and hepatic mets	Multiple nodules	Obscure	None	1	3.4	2.1
42/M	3.4	Hepatic mets	Multiple nodules	Obscure	None	1	15	14
54/F	5	Hepatic mets	Multiple nodules	Yes	Nausea	1	8.4	7.5
77/F	1	Hepatic mets	Multiple nodules	Obscure	None	1	5.6	4.9
71/M	3.2	Hepatic mets	Multiple nodules	Obscure	None	2	6.6	4.6
63/F	4	Hepatic mets	Two masses	Obscure	Nausea, liver abscess	1	3.7	3

TACE, transcatheter arterial chemoembolization.

patients who were not suitable for radiofrequency ablation (because of tumor size/number/location). Exclusion criteria included any contraindication to an arterial procedure such as impaired clotting tests (platelet count $<50,000/\text{mm}^3$ or prothrombin activity $<50\%$), bacterial infection or renal failure, and patients with distant metastasis other than hepatic metastasis.

Retrospective review of our electronic medical data base from October 2003 to August 2008 revealed a total of 15 patients with recurrence after curative resection of pancreatic adenocarcinoma who had undergone TACE. Our study population consisted of a total of 15 patients (10 males, 5 females) with ages ranging from 42 to 77 years old (mean, $63.4 \text{ years} \pm 9.9$) (Table 1). All patients had undergone curative resection (Whipple surgery, $n=9$; pylorus-preserving pancreaticoduodenectomy, $n=4$; total pancreatectomy, $n=1$; distal pancreatectomy, $n=1$) for pancreatic adenocarcinomas. Recurrence was diagnosed on CT 1.5 to 54 months after surgery. Prior to TACE treatments, two patients underwent gemcitabine-based systemic chemotherapy, while the remaining 13 patients did not receive any other anticancer therapy. Contrast-enhanced computed tomography (CT) was performed on all patients prior to TACE to evaluate the characteristics of the tumor and the presence of extrahepatic metastasis.

2. Transcatheter arterial chemoembolization

Superior mesenteric and celiac arteriographies were initially performed to assess anatomy, tumor burden, vascularity, and portal vein patency. Cisplatin at a dose of 2 mg/kg was subsequently infused into the hepatic artery for 15 minutes without embolic particle administration. After selective catheterization of the feeding artery with a microcatheter, an emulsion of iodized oil (Lipiodol; Laboratoire Guerbet, Cedex, France) and cisplatin was infused into the feeding arteries until arterial flow stasis was achieved or iodized oil appeared in the portal branches. Embolization of the feeding arteries was then performed using 1-mm-diameter absorbable gelatin sponge particles (Gelfoam; Upjohn, Kalamazoo, MI, USA).

3. Follow-up

Tumor response was evaluated based on CT scans obtained 22-45 days (mean, $34 \text{ days} \pm 8.6$) after TACE and was classified into four grades according to the modified Response Evaluation Criteria in Solid Tumors (RECIST)¹⁸ as follows: complete response (the disappearance of any intratumoral enhancement in all target lesions); partial response (decrease $\geq 30\%$ in the sum of the greatest dimension of viable [enhancing] target lesions); progressive disease (increase $\geq 20\%$ in the sum of the greatest di-

mension of viable [enhancing] target lesions); and stable disease (not enough shrinkage or sufficient increase to qualify as a partial response or as progressive disease). All patients who underwent TACE were followed on a routine basis at one-month intervals. Repeat treatment was indicated when there were new tumors, tumor growth or when residual tumor was detected. Treatment was terminated if the patient could not tolerate the procedure because of a decline in clinical status or because of death.

Technical success was defined as successful catheter placement and administration of selected agents. Tumor response was categorized as regression, including complete response and partial response, or non-regression including stable and progressive disease.

Complications and related treatments were also evaluated. Using Kaplan-Meier method, the overall patient survival period was measured in months from the date of diagnosis of recurrence and from the time of the initial TACE. The survival period after TACE was compared in patients who showed tumor regression and in those who showed tumor non-regression using log-rank test.

RESULTS

A total of 22 chemoembolization procedures were performed in the 15 patients with three patients undergoing two sessions and two patients undergoing three sessions each. After the procedure, partial response was demonstrated in six patients whose tumors demonstrated an identifiable tumor blush on angiography (Fig. 1). Four patients demonstrated stabilization of a hypovascular mass. The remaining five patients demonstrated continued progression of hypovascular hepatic lesions with scant Lipiodol uptake. Therefore, six patients were classified as responders (40%) and nine as non-responders (60%) after TACE.

Overall, the procedure was well-tolerated. Nine patients reported limited nausea with or without vomiting that resolved within 5 days. Two patients (13%, 2/15) developed a liver abscess after embolization and was successfully managed with percutaneous drainage and antibiotic therapy.

All patients were followed until death. The median survival periods from the time of diagnosis and from the time of initial TACE were 9.6 (range, 3.4-15 months) and 7.5 months (range, 2.1-14 months), respectively. The survival rates after TACE were significantly higher in patients who showed an objective tumor response to TACE (median survival period, 11.3 months) compared to those who showed no response to TACE (median survival peri-

Fig. 1. A 68-year-old man with hepatic metastasis from recurrent pancreatic carcinoma after pylorus-preserving pancreaticoduodenectomy. (A) Contrast-enhanced computed tomography (CT) scan conducted 1 month prior to transcatheter arterial chemoembolization (TACE) shows multiple, well-defined enhancing nodular lesions (arrows) in both lobes of the liver. (B) Hepatic angiography demonstrating multiple, round tumor blushes (arrows) in both lobes of the liver. (C) Nonenhanced CT scan obtained 22 days after TACE demonstrating substantial lipiodol uptake by the tumor.

od, 4.9 months) ($p < 0.001$).

DISCUSSION

The prognosis for pancreatic adenocarcinoma remains dismal, with reported 5-year survival rates ranging from 13 to 25%.^{5,19-21} Local recurrence and/or metastatic liver spread despite curative resection represent two frequent

patterns of recurrence that is largely resistant to current mainstays of treatment, including chemotherapy and radiation.^{7,22,23} Compared to local recurrence, hepatic metastatic spread has worse prognosis, as it is associated with a shorter survival time (3 months vs 7 months).⁷ Therefore, effective control of hepatic metastasis is an important therapeutic goal for prolonging survival in these patients.

TACE has an important advantage over systemic chemotherapy in that it increases the regional concentration of chemotherapeutic agents and deprives the blood supply to cancer tissue by embolic occlusion in order to maximize killing of cancer cells while sparing healthy liver tissue and reducing systemic side effects.¹² Hypervascular hepatic tumor have a great chance of tumor response to TACE because a chemotherapeutic agent and embolic material can be much more effectively and selectively delivered after TACE.^{24,25}

Given the perception of pancreatic adenocarcinoma as a hypovascular tumor, the efficacy of TACE for hepatic metastasis from recurrent pancreatic adenocarcinoma remains in question. Given the increased angiogenesis and stromal volume in hepatic metastatic tumor than those of the primary tumor, some authors suggested that hepatic metastasis from hypovascular tumor (such as colon cancer, or pancreatic adenocarcinoma) can present with hypervascularity on arterial phase CT or US.^{26,27} Six of 15 patients in our study demonstrated tumor blush on angiography which thereby allowed for selective delivery of the chemotherapeutic agent and embolic material, resulting in subsequent tumor response.

In the present study, liver abscess occurred in 13% (2/15) of our study patients after TACE and this incidence rate was higher than that of liver abscess after TACE for hepatocellular carcinoma (0.2%).²⁸ Given that bilioenteric anastomosis prone to develop ascending biliary infection is most important predisposing factor to the development of liver abscess after TACE, TACE for hepatic metastasis after surgery for pancreatic adenocarcinoma should be carried out more carefully because the majority of these patients have bilioenteric anastomosis.

Our median survival period from the time of diagnosis of 9.6 months (range, 3.4-15 months) was substantially longer than the reported survival length of 3 months in those patients with conservative management of the hepatic recurrence.⁷ Given the ability of TACE to retard the progression of hepatic metastasis, in particular those that demonstrate tumor blush on angiography, TACE may be effective in prolonging survival in these patients.

In the current study, tumor response (complete or partial response) was not achieved in any patients with hep-

atic tumors that showed obscure tumor blush on angiography. Therefore, TACE for these hypovascular hepatic tumors is still questionable from the current study. Given its great effect on tumor necrosis, even for hypovascular tumor, radioembolization using 90Y may be an effective therapeutic option for these hypovascular hepatic tumors.²⁹

The principal limitation of this study was the small number of study patients and the lack of a control group. Nevertheless, we believe that our study elucidates a potential role for TACE in the management of hepatic metastasis from primary pancreatic carcinoma and provides support for prospective investigation. In conclusion, TACE is well tolerated and may prolong survival in patients with hepatic recurrence after curative resection of pancreatic adenocarcinoma when considering comparison to historically reported survival.

REFERENCES

1. Bramhall SR, Allum WH, Jones AG, Allwood A, Cummins C, Neoptolemos JP. Treatment and survival in 13,560 patients with pancreatic cancer, and incidence of the disease, in the west midlands: an epidemiological study. *Br J Surg* 1995;82:111-115.
2. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. *CA Cancer J Clin* 2007;57:43-66.
3. Nitecki SS, Sarr MG, Colby TV, van Heerden JA. Long-term survival after resection for ductal adenocarcinoma of the pancreas. Is it really improving? *Ann Surg* 1995;221:59-66.
4. Sener SF, Fremgen A, Menck HR, Winchester DP. Pancreatic cancer: a report of treatment and survival trends for 100,313 patients diagnosed from 1985-1995, using the National Cancer Database. *J Am Coll Surg* 1999;189:1-7.
5. Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg* 2000;4:567-579.
6. Griffin JF, Smalley SR, Jewell W, et al. Patterns of failure after curative resection of pancreatic carcinoma. *Cancer* 1990;66:56-61.
7. Sperti C, Pasquali C, Piccoli A, Pedrazzoli S. Recurrence after resection for ductal adenocarcinoma of the pancreas. *World J Surg* 1997;21:195-200.
8. Westerdahl J, Andrén-Sandberg A, Ihse I. Recurrence of exocrine pancreatic cancer--local or hepatic? *Hepatogastroenterology* 1993;40:384-387.
9. Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;15:2403-2413.
10. Tepper J, Nardi G, Sutt H. Carcinoma of the pancreas: review of MGH experience from 1963 to 1973. Analysis of surgical failure and implications for radiation therapy. *Cancer* 1976;37:1519-1524.
11. Brown DB, Cardella JF, Sacks D, et al. Quality improve-

- ment guidelines for transhepatic arterial chemoembolization, embolization, and chemotherapeutic infusion for hepatic malignancy. *J Vasc Interv Radiol* 2006;17(2 Pt 1):225-232.
12. Liapi E, Geschwind JF. Transcatheter and ablative therapeutic approaches for solid malignancies. *J Clin Oncol* 2007;25:978-986.
13. Kim JH, Yoon HK, Kim SY, et al. Transcatheter arterial chemoembolization vs. chemoinfusion for unresectable hepatocellular carcinoma in patients with major portal vein thrombosis. *Aliment Pharmacol Ther* 2009;29:1291-1298.
14. Ruutinen AT, Soulen MC, Tuite CM, et al. Chemoembolization and bland embolization of neuroendocrine tumor metastases to the liver. *J Vasc Interv Radiol* 2007;18:847-855.
15. Rajan DK, Soulen MC, Clark TW, et al. Sarcomas metastatic to the liver: response and survival after cisplatin, doxorubicin, mitomycin-C, Ethiodol, and polyvinyl alcohol chemoembolization. *J Vasc Interv Radiol* 2001;12:187-193.
16. Buijs M, Kamel IR, Vossen JA, Georgiades CS, Hong K, Geschwind JF. Assessment of metastatic breast cancer response to chemoembolization with contrast agent enhanced and diffusion-weighted MR imaging. *J Vasc Interv Radiol* 2007;18:957-963.
17. Park YS, Kim JH, Kim KW, et al. Primary hepatic angiosarcoma: imaging findings and palliative treatment with transcatheter arterial chemoembolization or embolization. *Clin Radiol* 2009;64:779-785.
18. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010;30:52-60.
19. 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.
20. Matsuno S, Egawa S, Fukuyama S, et al. Pancreatic Cancer Registry in Japan: 20 years of experience. *Pancreas* 2004;28:219-230.
21. Cleary SP, Gryfe R, Guindi M, et al. Prognostic factors in resected pancreatic adenocarcinoma: analysis of actual 5-year survivors. *J Am Coll Surg* 2004;198:722-731.
22. Hishinuma S, Ogata Y, Tomikawa M, Ozawa I, Hirabayashi K, Igarashi S. Patterns of recurrence after curative resection of pancreatic cancer, based on autopsy findings. *J Gastrointest Surg* 2006;10:511-518.
23. Katsumata K, Tomioka H, Sumi T, et al. Liver metastasis of pancreatic cancer managed by intra-arterial infusion chemotherapy combined with degradable starch microspheres. *Int J Clin Oncol* 2003;8:110-112.
24. Kim JH, Yoon HK, Sung KB, et al. Transcatheter arterial chemoembolization or chemoinfusion for unresectable intrahepatic cholangiocarcinoma: clinical efficacy and factors influencing outcomes. *Cancer* 2008;113:1614-1622.
25. Kim JH, Yoon HK, Ko GY, et al. Nonresectable combined hepatocellular carcinoma and cholangiocarcinoma: analysis of the response and prognostic factors after transcatheter arterial chemoembolization. *Radiology* 2010;255:270-277.
26. Noda A, Inaba K, Sakuragi S, et al. Hypervascular liver metastasis from hypovascular ductal cell carcinoma of the pancreas. *Intern Med* 2001;40:227-231.
27. Murphy-Lavallee J, Jang HJ, Kim TK, Burns PN, Wilson SR. Are metastases really hypovascular in the arterial phase? The perspective based on contrast-enhanced ultrasonography. *J Ultrasound Med* 2007;26:1545-1556.
28. Song SY, Chung JW, Han JK, et al. Liver abscess after transcatheter oily chemoembolization for hepatic tumors: incidence, predisposing factors, and clinical outcome. *J Vasc Interv Radiol* 2001;12:313-320.
29. Jakobs TF, Hoffmann RT, Dehm K, et al. Hepatic yttrium-90 radioembolization of chemotherapy-refractory colorectal cancer liver metastases. *J Vasc Interv Radiol* 2008;19:1187-1195.