J Hepatobiliary Pancreat Surg (2008) 15:603–607
DOI 10.1007/s00534-007-1323-5

Journal of HBP Surgery

Long-term outcomes of extended radical resection combined with intraoperative radiation therapy for pancreatic cancer

Hiroshi Takamori, Takehisa Hiraoka, Keiichiro Kanemitsu, Tatsuya Tsuji, Hiroshi Tanaka, Akira Chikamoto, Kei Horino, Toru Beppu, Masahiko Hirota, and Hideo Baba

Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8556, Japan

Abstract
Background/Purpose. Systemic and/or local recurrence often occurs even after curative resection for pancreatic cancer (PC). To prevent local relapse we adopted an extended radical resection combined with intraoperative radiation therapy in patients with PC, and all the patients were followed for more than 5 years.
Methods. We assessed the long-term outcomes of 41 patients who underwent this combined therapy. The cumulative survival curve in this series was depicted using the Kaplan-Meier method. Statistical analyses were performed using the log-rank test.
Results. The actual 5-year survival rate was 14.6%, with a median survival time of 17.6 months. Six patients have been 5-year survivors. Local recurrence occurred in only 2 patients (5.0%). Cancer-related death occurred in 32 patients, 18 of whom had liver metastases. The patients with liver metastases had a significantly shorter survival time than those with other cancer-related causes of death. Patients with n3 lymph node involvement, extrapancreatic nerve plexus invasion, and stage IV disease had significantly poorer prognoses than patients without these characteristics.
Conclusions. Our combined therapy for patients with PC contributed to local control; however, it provided no survival benefit, because of liver metastases.

Key words Pancreatic cancer · Actual 5-year survival · Extended radical resection · Intraoperative radiation therapy · Multimodality treatment

Introduction

Pancreatic cancer (PC) remains a lethal disease, in which the annual incidence is approximately equal to the annual deaths.[1] Surgical resection offers the only chance for cure, but even after curative resection there is a high probability of systemic and/or local relapses. Local recurrence occurs in 71.8%–73% of the patients.[2,3] One reason is that even when small tumors are located in the head or neck of the pancreas, they are frequently in close proximity to the superior mesenteric artery (SMA) or the celiac axis (CA), often yielding surgical margins measured in millimeters or less. A second reason is that the invasion of periarterial nerve sheaths could mean that there is a positive resection margin.[4] Actually, autopsies of patients who had standard resections for PC showed that local recurrence occurred in the soft tissue around the SMA and CA.[5] Therefore local control is one of the most crucial points of treatment for PC.

We applied intraoperative radiation therapy (IORT) in 1969[6] and first utilized IORT combined with resection in 1976[5,7] for PC. The rationale for the use of IORT is to maximize the dose of radiation delivered to the tumor bed and around the aorta (where cancer cells might invade) and to minimize the radiation dose to surrounding normal tissues. Studies regarding the involvement of lymph nodes have confirmed that patients undergoing the standard Whipple procedure have positive nodes outside the dissection.[8]

We adopted extended radical resection combined with IORT for PC in 1984. All patients who underwent this combined therapy have been followed more than 5 years after surgery. Our aim in this study was to assess the long-term outcomes of this combined therapy for PC.

Patients and methods

Patients and surgical technique

Between December 1984 and December 1999 at Kumamoto University, 41 patients underwent extended

Offprint requests to: H. Takamori
Received: October 12, 2007 / Accepted: December 7, 2007

radical pancreatectomy combined with IORT. Written informed consents were obtained from all the patients before the treatment.

This combined therapy involves the dissection of the juxta-paraaortic and regional lymph nodes together with the connective tissue and nervous plexus around the aorta, extending from the diaphragm above to the inferior mesenteric artery below. Following dissection, a dose of 30 Gy with 9- to 12-Mev electron-beam radiation was administered to the operative field, using a special variable pentagon applicator which could change the radiation field depending on the body size and the area of the tumor bed, including the paraaortic area from the diaphragm above to the inferior mesenteric below, as described previously.[5]

Histopathological examination and outcomes analyzed

We evaluated histological characteristics according to classification of PC defined by the Japan Pancreas Society.[9]

Local recurrence and/or distant metastases were defined as the detection of apparent mass formation on imagings. For the evaluation of recurrences, all patients were evaluated every 3 months for the first year after surgery, every 4 months the second year, and every 6 months subsequently, by chest and abdominal computed tomography (CT). Cytology or histological confirmation of recurrent disease was not required. The first site of recurrent disease was documented for the outcome analyses. Hospital death was defined as death during hospitalization.

Statistical analysis

The Kaplan-Meier method was used to analyze survival, and levels of significance were tested with the log-rank test. Differences were considered to be significant at $p < 0.05$.

Results

Patient characteristics

The study subjects included 17 women and 24 men. The median age of the patients was 60 years (range, 37 to 76 years). The primary pancreatic lesion was located in the head in 32 patients, in the body in 8, and in the tail in 1. We performed a pylorus-preserving pancreaticoduodenectomy in 14, a Whipple resection in 17, a distal pancreatectomy in 7, and a total pancreatectomy in 3. Histological examination could be performed in 40 patients. The histological characteristics are listed in Table 1. Of the 40 patients, 27 (67.5%) were affected by stage IV disease. The median tumor size was 3.0 cm (range, 1.1 to 12.0 cm). Lymph node metastases (n) were identified in 33 (82.5%) patients. Portal vein invasion (pv) was found in 14 (35.0%) patients. As to residual tumor (R), an R0 resection was performed in 26 (65.0%) patients, an R1 resection in 10, and an R2 resection in 4. Extrapancreatic nerve plexus invasion (pl) was found in 18 (45.0%) patients.

Table 1. Histological characteristics

No. of patients	40
Stage	
II	1
III	12
IVa	15
IVb	12
Tumor size (cm)	
1.0–2.0	3
2.1–4.0	27
4.1<	10
Nodal involvement	
n0	7
n1	17
n2	12
n3	4
Residual tumor	
R0	26
R1	10
R2	4
Portal vein invasion	
Present	14
Absent	26
Extrapancreatic nerve plexus invasion	
Present	18
Absent	22

Outcomes

Figure 1 shows the cumulative survival curve for patients with the combined therapy. The actual 5-year survival rate was 14.6%, with a median survival time of 17.6 months. Two patients are still alive without recurrence, 95.4 and 254.5 months after surgery, respectively. Six patients survived for more than 5 years. The characteristics of the 5-year survivors are outlined in Table 2. One patient was in stage II, two in stage III, and two in stage IVa. One patient had n0, four had n1+, and one had n2+. Three patients died of cancer relapses more than 5 years after the surgery.

The outcomes of all the patients are summarized in Table 3. Cancer-related death was observed in 32 patients, 18 of whom had liver metastases. Local recurrence was observed in only 2 patients (5.0%), although autopsies disclosed microscopic local recurrence in 4 (28.6%) of the 14 patients without liver metastases. Of the 32 patients who died of cancer-related causes, the 18 (56.3%) who suffered from liver metastases died within 30 months after surgery. On the other hand, the

Table 2. Characteristics of the 5-year survivors

	Age (years)	Sex	T category	N category	Stage	Outcome
1.	60	Female	t3	n1	III	Dead (61.0 months; local recurrence)
2.	58	Male	t4	n1	IVa	Dead (61.0 months; pleural dissemination)
3.	71	Female	t3	n1	III	Alive (95.4 months)
4.	66	Male	t3	n2	IVa	Dead (97.9 months; lung metastases)
5.	56	Female	t3	n1	III	Dead (164 months; renal failure)
6.	37	Female	t2	n0	II	Alive (254.5 months)

Table 3. Outcomes after extended radical resection combined with IORT for patients with pancreatic cancer

	No.	Survival time in months; median (range)
Cancer-related death	32	
Liver metastases	18	14.3 (5.6–30)
Without liver metastases	14	28.4 (10.8–97.7)
Lung metastases	3	
Peritoneal dissemination	6	
Pleural dissemination	1	
Recurrence in remnant pancreas	2	
Local recurrence	2	
Non-cancer-related death	7	
Hospital death (intraperitoneal bleeding)	4	2.2 (1.6–8.3)
Non-hospital death	3	32 (8.3–164)
Malnutrition	1	
Cardiac failure	1	
Renal failure	1	
Alive	2	

IORT, intraoperative radiation therapy

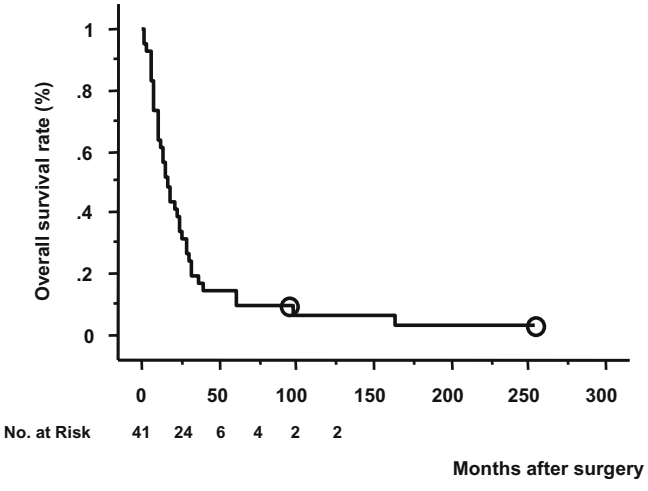

Fig. 1. The cumulative survival curve in this series is depicted; the curve was constructed using the Kaplan-Meier method

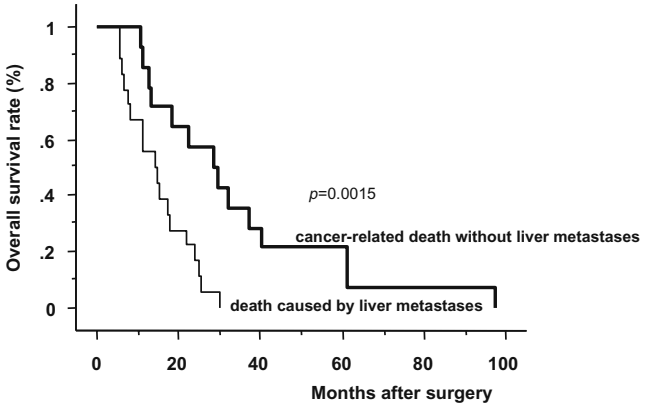

Fig. 2. Survival rates in the 32 patients who died of cancer-related causes, comparing patients with liver metastases and patients with other recurrences

14 patients without liver metastases died between 10.8 and 97.7 months after the surgery. Hospital death caused by intraabdominal bleeding occurred from 1.6 to 8.3 months after surgery in 4 patients (9.8%). The patients who experienced liver metastases had a median survival time of 14.3 months, and they had a significantly worse prognosis than those with other cancer-related causes of death (median survival time, 28.4 months; Fig. 2). The patients with stage IV disease had a significantly worse prognosis than those with stage II or III (Fig. 3). R0 resection did not contribute to survival benefit compared with R1-2. The pl (+) group had a significantly poorer prognosis compared with the pl (–) group

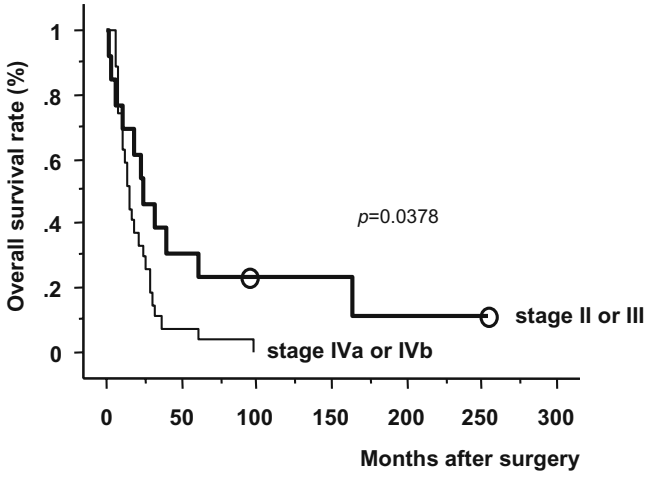

Fig. 3. Kaplan-Meier analysis of survival according to stage

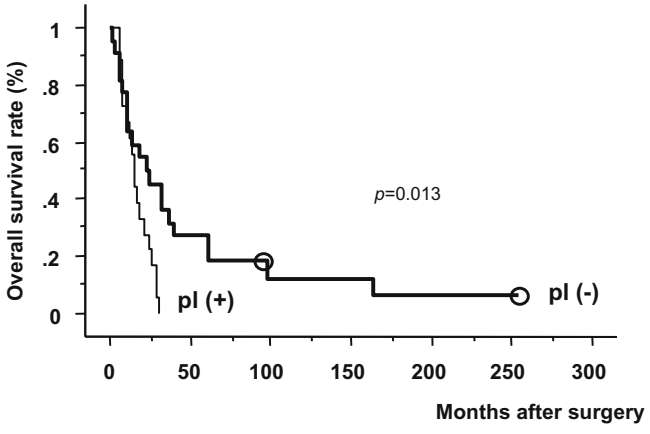

Fig. 4. Kaplan-Meier analysis of survival according to extrapancreatic nerve plexus invasion (*pl*)

(Fig. 4). No significant difference in survival was observed between the pv (+) and pv (–) groups. The patients with n3 had a significantly worse prognosis than the others (Fig. 5), although there was no significant difference in survival between the n (–) and n (+) groups, or between the n0-1 and n2-3 groups.

Discussion

Several studies have revealed that pancreatic resection can yield actual 5-year survival rates of 15% to 25% following pancreaticoduodenectomy and 8%–14% following distal pancreatectomy for PC. The patients with PC who received the combined therapy in the present study had an actual 5-year survival rate of 14.6%, and the therapy provided no survival benefit. Two randomized trials have shown that there was no survival benefit from extended surgery compared with a standard operation,[10,11] although several retrospective reports from Japan showed that extended surgery might have a survival benefit for patients with operable PC.[12–14] On the other hand, Pawlik et al.[15] stated that adequately powered randomized trials to address the potential benefit of extended lymphadenectomy would not be feasible, because these would require a prohibitively large sample size.

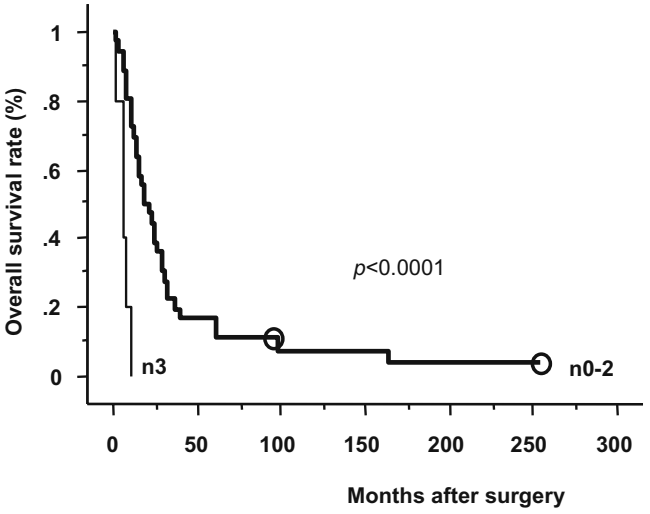

Fig. 5. Kaplan-Meier analysis of survival according to lymph node metastases (*n*)

We have reported previously that the combined therapy we have described here diminished local relapses, compared with standard resections alone, although it has not contributed to improving survival.[5,6] Other studies have also shown that IORT has little impact on survival, compared with surgery alone.[16–18] In the present long-term follow-up study, local recurrence was observed in only 2 patients (5.0%), although autopsies disclosed microscopic local recurrence in 4 (28.6%) of the 14 patients. The usefulness of imaging studies for the diagnosis of local relapse may be limited, because, in some cases, cancer cells may infiltrate the retroperitoneal soft tissue in the radiation field without the formation of a mass.[18] In the present study, we found that, histologically, these microscopic local relapses consisted of small numbers of cancer cells within surrounding thick connective tissue at autopsy (data not shown). These local recurrences seem to be a direct cause of death, as Hishinuma et al.[18] have mentioned previously.

One of our interesting findings was that the patients who died of liver metastases had a significantly worse prognosis than those who had other recurrence patterns. In an analysis of the cumulative survival curve of PC, we reported that the early postoperative phase reflected the poor prognosis of patients who died of hepatic metastases.[19] Raut et al.[4] have mentioned that

subclinical metastases are present in most patients at the time of diagnosis, even when imaging studies are normal. Therefore, more precise diagnostic tools for liver metastases and a strategy to prevent the formation of liver metastases are required to improve the survival of PC patients with resectable disease. We have proposed the diagnostic advantage of computed tomography during arterial portography, combined with computed tomography-assisted hepatic arteriography (CTAP + CTHA) for the preoperative detection of liver metastases secondary to PC.[20] CTAP + CTHA should be performed to select resectable PC before surgery.

In the present study, the pl (+) and n3 groups had significantly poorer prognoses than the other patients. These conditions may have reflected systemic spread rather than localized disease, because pl (+) was reported to be one of the most powerful predictive factors of liver metastases.[21] Several reports have shown that the R factor is one of the highly significant prognostic factors after resection for PC.[22–24] Interestingly, in the present study, the R1 and R2 groups did not have significantly poorer survival compared with the R0 group. It is unclear whether pv is a prognostic factor after surgery.[25] Our results showed no significant difference in survival between the pv (+) and pv (−) groups.

In conclusion, the combined therapy used in the present study improved local control; however, it provided no survival benefit for resectable PC, because of liver metastases. This combined therapy might be reassessed, if a strategy to prevent liver metastases is to be established in future.

References

1. Rockhart AC, Rothenberg ML, Berlin JD. Treatment for pancreatic cancer: current therapy and continued progress. Gastroenterology 2005;128:1642–54.
2. Griffin JF, Smally 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.
3. Sperti C, Pasquali C, Piccoli A, Pedrazzoli S. Recurrence after resection for ductal adenocarcinoma of the pancreas. World J Surg 1997;21:195–200.
4. Raut CP, Evans DB, Crane CH, Pisters PW, Wolff RA. Neoadjuvant therapy for pancreatic cancer. Surg Oncol Clin N Am 2004;13:639–61.
5. Hiraoka T, Kanemitsu K. Treatment using combined modalities. In: Howard JM, editor. Surgical diseases of the pancreas. Bartimore: Williams & Wilkins; 1988. p. 605–11.
6. Hiraoka T, Nakamura I, Tashiro S, Miyauchi Y. Intraoperative radiation therapy for pancreatic cancer in Japan. In: Dobelbower RR Jr, Abe M, editors. Intraoperative radiation therapy. Boca Raton, Florida: CRC; 1989. p. 181–93.
7. Hiraoka T, Watanabe E, Mochinaga M, Tashiro S, Miyauchi Y, Nakamura I, et al. Intraoperative radiation combined with radical resection for cancer of the head of the pancreas. World J Surg 1984;8:766–71.
8. Cubilla AL, Fortner J, Fitzgerald PJ. Lymph node involvement in carcinoma of the head of the pancreas. Cancer 1978;41:880–7.
9. Japan Pancreas Society. Classification of pancreatic cancer. Second English ed. Tokyo: Kanehara; 2003. p. 4–12.
10. Pedrazzoli S, DiCarlo V, Dionigi R, Mosca F, Pederzoli P, Pasquali C, et al. Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study. Lymphadenectomy Study Group. Ann Surg 1998;228:508–7.
11. Yeo CJ, Cameron JL, Sohn TA, Coleman J, Sauter PK, Hruban RH, et al. Pancreaticoduodenectomy with or without extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma: comparison of morbidity and mortality and short-term outcome. Ann Surg 1999;229:613–24.
12. Ishikawa O, Ohhigashi H, Sasaki Y, Kabuto T, Fukuda I, Furukawa H, et al. Practical usefulness of lymphatic and connective tissue clearance for the carcinoma of the pancreas head. Ann Surg 1988;208:215–20.
13. Manabe T, Ohshio G, Baba N, Miyashita T, Asano N, Tamura K, et al. Radical pancreatectomy for ductal cell carcinoma of the head of the pancreas. Cancer 1989;64:1132–7.
14. Hiraoka T, Uchino R, Kanemitsu K, Toyonaga M, Saitoh N, Nakamura I, et al. Combination of intraoperative radiation with resection of cancer of the pancreas. Int J Pancreatol 1990;7: 201–7.
15. Pawlik TM, Abdolla EK, Barnett CC, Ahmad SA, Cleary KR, Vauthey JN, et al. Feasibility of a randomized trial of extended lymphadenectomy for pancreatic cancer. Arch Surg 2005;140: 584–91.
16. Wagman R, Grann A. Adjuvant therapy for pancreatic cancer. Current treatment approaches and future challenges. Surg Clin North Am 2001;81:667–81.
17. Sumanura M, Kobari M, Lozonschi L, Egawa S, Matsuno S. Intraoperative radiotherapy for pancreatic adenocarcinoma. J Hepatobiliary Pancreat Surg 1998;5:151–6.
18. Hishinuma S, Ogata Y, Matsui J, Ozawa I. Results of surgery and adjuvant radiotherapy for pancreatic cancer. J Hepatobiliary Pancreat Surg 1998;5:143–50.
19. Takamori H, Hiraoka T, Kanemitsu K, Tsuji T, Hamada C, Baba H. Identification of prognostic factors associated with early mortality after surgical resection for pancreatic cancer. Under analysis of cumulative survival curve. World J Surg 2006;30:213–8.
20. 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;29:188–92.
21. Takamori H, Hiraoka T, Kanemitsu K, Tsuji T. Pancreatic liver metastases after curative resection combined with intraoperative radiation for pancreatic cancer. Hepatogastroenterology 2004;51: 1500–3.
22. Yeo CJ, Cameron JL, Lillemore KD, Sitzmann JV, Hruban RH, Goodman SN, et al. Pancreaticoduodenectomy for cancer of the head of the pancreas: 201 patients. Ann Surg 1995;221:721–33.
23. Millikan KW, Deziel DJ, Silverstein JC, Kanjo TM, Christein JD, Doolas A, et al. Prognostic factors associated with resectable adenocarcinoma of the head of the pancreas. Am Surg 1999; 65:618–23.
24. Benassai G, Mastrorilli M, Quarto G, Cappiello A, Giani U, Forestieri P, et al. Factors influencing survival after resection for ductal adenocarcinoma of the head of the pancreas. J Surg Oncol 2000;73:212–8.
25. Nakagohri T, Kinoshita T, Konishi M, Inoue K, Takahashi S. Survival benefits of portal vein resection for pancreatic cancer. Am J Surg 2003;186:149–53.